Socioeconomic determinants of cancer risk, detection, and outcome in the Netherlands since 1990

Mieke Aarts

COLOPHON

Copyright © Mieke Aarts, 2012

Socioeconomic Determinants of Cancer Risk, Detection, and Outcome in the Netherlands since 1990

Sociaaleconomische determinanten van kankerrisico, –detectie en –uitkomst in Nederland sinds 1990

Proefschrift

ter verkrijging van de graad van doctor aan de
Erasmus Universiteit Rotterdam
op gezag van de
rector magnificus

Prof.dr. H.G. Schmidt

en volgens besluit van het college voor Promoties.

De openbare verdediging zal plaatsvinden op
dinsdag 19 juni 2012 om 13.30 uur

door
Maria Josepha Aarts
geboren te Oploo

ERASMUS UNIVERSITEIT ROTTERDAM

Promotiecommissie

Promotor:	Prof.dr. J.W.W. Coebergh
Overige leden:	Dr. F.J. van Lenthe
	Prof.dr. V.J.M. Pop
	Prof.dr. C.C.D. van der Rijt
Copromotor:	Dr. W.J. Louwman

Contents

DECISION

CURATIVE

ROLE

SINCE 1990

data

DETERMINANTS

CATEGORY

HOUSING

RECOGNISING

OUTCOME

BRACHYTHERAPY

INTERVAL CANCER

material resources

CHARLSON

health seeking behaviour

METASTASIS

CONTRIBUTION

socioeconomic position

RADIOTHERAPY

COVERAGE

estimated annual percent change

axillary staging

EAPC

SMOKING

statistical

STUDIES

GP

staging

lifestyle

central nervous system

Comprehensive Cancer Centre South

HOSPITAL

intelligence

education

hazard ratio

VISITS

ATTENDANCE

EXPLANATION

SOCIAL SUPPORT

Eindhoven Cancer Registry

dementia

RISK FACTORS

DIAGNOSIS

SEP

stage

HORMONAL THERAPY

ADVANCED

FEAR

HYPERTENSION

mastectomy

diagnostics

colorectal

distribution

CARDIOVASCULAR DISEASE

therapy

HIGH

MENTAL

MAMMOGRAPHY

UPBRINGING

ENVIRONMENT

incidence

prostatectomy

p-value

QUESTIONNAIRE

HEALTH BEHAVIOUR

SF-36

GLOBE

PHYSICAL

socioeconomic status

SOCIOEC

occupation

NEIGHBOURHOOD EXPOSURE

LOW

value of housing

physical activity

REVIEW

colorectal cancer screening

comorbidities

CHEMORADIATION

INVITATION

INTERMEDIATE

TUBERCULOSIS

concomitant disease

VARIATION

logistic regression

ACCESS TO CARE

CONSULTATION

INVASIVE

numbers

CONTACTS

gap

LOCALISED

WORK

SCREEN-DETECTED TUMOUR

ASSETS

PSA

income

percentages

ALCOHOL CONSUMPTION

THE NETHERLANDS

HEALTH INSURANCE

health awareness

HOUSEHOLD

search

DETECTIO

DISCUSS

Chapter 1

Introduction

survival
opportunistic screening
sentinel node biopsy
understanding
GENETICS
mortality
selection
HEALTH LITERACY CHARACTERISTICS
OESOPHAGUS option
KNOWLEDGE
INEQUALITIES
rates screening PREFERENCES
watchful waiting
LUNG HR BREAST CONSERVING SURGERY
SOCIAL STRATIFICATIONS
INFORMATION
lymph node dissection
SEX
TUMOURS
postal code
CANCER
NETHERLANDS CANCER REGISTRY
CONOMIC
BCC quality of life DEPRIVATION PROGNOSIS MELANOMA PATIENTS
SUNNY opportunities CHEMOTHERAPY COPD TNM studies
95%CI IKZ CCCS
chi-square test PROSTATE breast conserving surgery HETEROGENEITY analyses referral
BREAST tumour size TRENDS MONITOR RISK chances social class
AGE (IN)EVITABILITY odds ratio OR palliative Cox regression
N population-based REPORTING SYMPTOMS
disparities
WARNING SIGNS

The subject of this thesis is the association between socioeconomic status (SES) and cancer detection and outcome in the Netherlands. Both a description of and explanation for variation in incidence, detection, staging, treatment, survival and health-related quality of life of cancer by SES are given. The studies reported in this thesis can be placed both within the broader framework of research on socioeconomic inequalities in health as well as within the narrower framework of research on socioeconomic inequalities in cancer. The methods and study settings are described, followed by the aims of this thesis.

SOCIOECONOMIC INQUALITIES IN HEALTH

Our society is characterised by heterogeneity, due to unequal distribution of knowledge, material and other resources among the inhabitants. Classification of persons into groups based on shared socioeconomic conditions leads to social stratification. This relative position on the social hierarchy is referred to by 'socioeconomic status' (SES). Common indicators of SES are income, education, occupation and race, each referring to a different aspect of social stratification. Through SES indicators inequalities can be revealed.

People with a lower SES generally have poorer health status and higher mortality than people from higher socioeconomic groups.[1] This inverse association between SES and health has been found for nearly all measures of SES and nearly all health outcomes. For example, people with low SES have higher rates of morbidity and mortality from cardiovascular diseases,[2] have poorer self-rated health,[3] more fears[4] and live nearly 7 years less in The Netherlands.[5] Similar associations have been reported for the incidence, detection, treatment and outcome for a variety of cancer types.[6, 7] These will be discussed below.

SOCIOECONOMIC INEQUALITIES IN CANCER
Incidence

More or less consistent excess risks for tobacco-related and other lifestyle-related cancers (i.e. respiratory cancers, cancers of the head and neck and upper gastro-intestinal tract, liver and cervix uteri) have been reported for people from the lower social strata. The risk for cancers of the colon, breast and ovary and malignant melanoma are generally higher among people from higher socioeconomic groups.[7, 8] A differential distribution of known risk factors for specific neoplasms between socioeconomic groups seems to be a likely explanation for the above mentioned inequalities. For example, the prevalence of smokers has become higher among those in lower compared to higher socioeconomic classes,[9] resulting in higher rates of cancer of the lung, larynx, mouth, pharynx, oesophagus and bladder.[10] The socioeconomic distribution of the risk factors may change over time, e.g. the prevalence of smoking was highest among males with high SES until the 1960s, but shifted around that time towards lowest prevalence in high SES. In females, this shift occurred circa 10 years later.[11]

However, smoking is not only related to cancer, but also to chronic obstructive pulmonary diseases (COPD) and cardiovascular diseases.[12] This explains the high prevalence of specific co-morbidity among lung cancer patients.[13] Low SES may thus be associated with higher levels of co-morbidity among cancer patients, and thereby default treatment selection.

1

Detection

Generally, health awareness is better in high SES than in low SES,[14] which will often lead to healthier lifestyle and more health seeking behaviour.[15] This not only reduces risks of most cancers, it also enhances early detection. Indeed, lower stage at diagnosis has been reviewed for high SES cancer patients, although null associations were mentioned as well.[16] It seems likely that part of the socioeconomic differences in (early) cancer detection result from more health seeking behaviour in high SES.

Cancer screening programmes aim to reduce mortality rates through systematic approach to early cancer detection, explicitly aiming to reach everybody. To optimise the effectiveness of the current screening programmes it is especially important to reach men and women at high risk of advanced stage disease at diagnosis and concomitant lower survival rates, i.e. low SES groups. However, in many countries, the proportion of individuals participating in cancer screening programmes for breast and cervix uteri has been highest among those with high SES.[17] For screening mammograms, this association was independent of the presence of organised breast screening programmes.[18] For the Netherlands, a country with equal access to screening and care for all women, these data on the breast cancer screening programme were lacking.

Treatment

Treatment differences related to SES have been reported for several cancers. Pancreatic cancer patients with low SES were found to be less likely to undergo surgical treatment compared to high SES, for which the reasons were not known.[19] In addition, deprived women had higher mastectomy rates for breast cancer and lower rates of breast conserving surgery, while the odds of receiving radiotherapy after breast conserving surgery was not related to SES.[20, 21] For prostate cancer, higher rates of radical surgery and radiotherapy were reported in high SES, which were suggested to be related to presence of comorbidities.[22] Also in oesophageal cancer, patients in the high SES group received more invasive therapies compared to the low SES group, i.e. they more frequently undergo oesophagectomy and chemotherapy, which could not be explained by comorbidities.[23] The authors speculated that these differences resulted from more complete discussion of treatment options between doctors and patients with high SES, related to their similar (high) educational levels. Furthermore it was thought that treatment differences arose from the fact that high SES patients are more eager to explore all therapeutic options, even experimental.[23] If this holds true, new therapeutics are first introduced in high SES and only to low SES after a while. Thereby socioeconomic differences in treatment selection will first increase, and subsequently reduce over time. For example, breast conserving surgery, being less invasive compared to the traditional mastectomy, or brachytherapy, more invasive than external beam radiotherapy for prostate cancer, may have been differentially introduced to the SES groups.

The association between SES and cancer treatment, also taking into account the time factor, has not yet been studied for most cancers in the Netherlands, a country with equal access to care and virtually full health insurance coverage. However, socioeconomic disparities in referral were observed for pancreatic cancer surgery with a higher referral rate to university hospitals for patients with high SES.[24] Similarly, low SES patients received less often adjuvant

chemotherapy for colon cancer stage III,[25] and, as discussed above, less often oesophagectomy and chemotherapy in oesophageal cancer.[23] Therefore treatment disparities for other cancers might be also observed for other cancers within the Netherlands.

Survival

Cancer mortality rates are generally higher in low SES groups.[8] This may result from higher incidence rates and/or poorer survival rates in low SES. For most cancers, poor survival rates were reported in low SES.[26, 27] During the 1980s survival disparities were also reported in the South-eastern Netherlands.[28] Explanations for socioeconomic differences in cancer survival have been reviewed and are classified as factors related to the tumour (stage at diagnosis and biological characteristics), the patient (host factors, the effect of treatment and psychosocial factors) and/or health care (treatment received, medical expertise and screening).[16] However, in the Dutch study, most of the variation in cancer survival could not be explained by the differential distribution of stage, histological type and treatment across SES categories.[28] Furthermore, the introduction of the mass breast cancer screening programme in The Netherlands improved survival of all breast cancer patients, but less so for women from lower socioeconomic strata, leading to increasing socioeconomic differences in breast cancer survival.[29]

Health-related quality of life

Health-related quality of life (HRQL) of cancer patients can be markedly affected, both positively as well as negatively, by certain primary treatments. For example, having had chemotherapy for non-Hodgkin lymphoma or preoperative radiotherapy for rectal cancer was associated with worse HRQL among survivors.[30, 31] Physical HRQL in prostate cancer survivors was highest among those who underwent radical prostatectomy and worst in those who received hormonal therapy.[32] Since SES may be related to treatment selection, we expect that HRQL is related to SES as well. The group of long-term survivors is growing, and by measuring HRQL, SES-specific problems can be addressed. Besides only limited information on SES in relation to HRQL is available among cancer survivors. Therefore it is of utmost importance to study the association of SES and HRQL among this group.

The importance of studying socioeconomic inequalities in health

Thus, differences in cancer risk, stage, treatment selection and outcome in terms of survival and health-related quality of life were significantly related to SES in many other countries. Socioeconomic inequalities in health should be reduced for two reasons. Firstly, public health in general can gain a lot by improving health of those with low SES towards the level of those with high SES.[33] In the Netherlands, the healthy life expectancy without physical limitations is 14 years lower for males with low education compared to high educated; for females this is even 15 years.[5]

Secondly, socioeconomic inequalities are considered unjust, because poor health limits one's opportunities in life. However, some say that health inequalities should only be considered to be unjust if these result from unequal distribution of health determinants on which the individual has no control.[33] Over time the magnitudes of socioeconomic inequalities may vary, e.g. by the introduction of new diagnostic procedures or therapeutics, which

1

are generally first only available to and used by high SES, and to low SES only after a while. This will first lead to increasing and then reducing socioeconomic inequalities. In addition, magnitudes of socioeconomic inequalities may vary between countries, thereby suggesting that these may be (at least partly) modifiable, e.g. by comparing policies addressing SES and health.[34] Therefore, research is needed to find entry-points for policies and interventions to assess effects of socioeconomic health inequalities in the long run, to monitor changes, and finally, to reduce socioeconomic health inequalities.

The relevance of this thesis

Although socioeconomic inequalities in cancer have been studied for several countries, associations have only been limitedly explored in the Netherlands. This country has a rather unique situation, in which all inhabitants have a compulsory health insurance which covers all health care costs, and (supposedly) equal access to health care for every inhabitant. Furthermore, well trained general practitioners are broadly available, i.e. one per 2000 people on average. In addition, data from the Netherlands Cancer Registry and Eindhoven Cancer Registry enabled population-based studies.

METHODS, POPULATION AND SETTING

The studies in this thesis were based on data from the Eindhoven Cancer Registry, the Netherlands Cancer Registry and the GLOBE study. The proxies of SES were from Statistics Netherlands, The Netherlands Institute for Social Research and the GLOBE study.

Eindhoven Cancer Registry

The Eindhoven Cancer Registry (ECR) started in 1955 as part of a programme for nationwide cancer registration. Data on all new cancer patients were collected directly from pathology reports and medical records, sometimes through emerging hospital discharge registries. The registry started in three hospitals in Eindhoven and gradually expanded to include the province of North Brabant and the northern part of the province of Limburg (Figure 1).

The area in the population-based ECR now hosts 2.4 million inhabitants, 10 general hospitals at 16 locations and is served by 6 regional pathology laboratories, two large radiotherapy institutes and one neurosurgical centre.[35] The region is characterised by good access to medical care without financial obstacles. The distance to a hospital has always been less than 30 kilometres. The population in the area is markedly aging due to longer life expectancy and a decreasing amount of newborns.

Netherlands Cancer Registry

The regional registries, other than the ECR, had discontinued their activities, until a successful nationwide programme was re-established since 1984. Since 1989 the whole Dutch population was covered by nine regional cancer registries (and eight from 2008), which established the Netherlands Cancer Registry. Since 2011 the other seven Comprehensive Cancer Centres have merged into Comprehensive Cancer Centre Netherlands (IKNL). IKNL and IKZ collaborate in the nationwide Netherlands Cancer Registry.

1

The cancer registries get notifications of all newly diagnosed malignancies by the automated pathology archive (PALGA). Additional sources are the national registry of hospital discharge, haematology departments and radiotherapy institutes. Completeness is estimated to be at least 95%.[36] Trained registration clerks actively collect data on diagnosis, topography, histology, stage and information about initial treatment (delivered within 6 months from diagnosis) from hospital medical records. The medical record is generally regarded as the most complete source of information on the patient's past and current health status.[37] Information on the vital status of the patients was initially obtained from the municipal registries and since 1995 onwards from the nationwide population registries network. These municipal registries provide virtually complete coverage of all deceased citizens of the Netherlands.

Figure 1. *The current area of the Eindhoven Cancer Registry of the Comprehensive Cancer Centre South.*

1

The GLOBE study

Data from the ECR were linked to respondents of the prospective GLOBE study. The GLOBE study started in 1991 and aimed to investigate in depth the contribution of explanatory factors to socio-economic inequalities in health. A detailed description of the purpose and design of the GLOBE study is presented elsewhere.[38] In short, a sample of 27,020 non-institutionalised Dutch persons, between 15 and 75 years of age, living in or near the city of Eindhoven was approached to fill out a postal questionnaire in 1991. The extensive questionnaires included measures of SES, self-reported health and factors such as health-related behaviour, material circumstances and psychosocial characteristics, health-care utilisation and childhood circumstances.

Socioeconomic status

In this thesis we used three different indicators of SES, as shown in Table 1. These proxies for SES are discussed in more detail in the following chapters.

Table 1. *Description of the proxies of socioeconomic status used in this thesis.*

Source of proxy for socioeconomic status	Area-based or individual level?	Based on	Data collection
The Netherlands Institute for Social Research (governmental organisation)	Area-based, 4-position of postal code (mean number of households=1765)	Income, employment and education	Private organisation performed telephone calls with one person per six-digit postal code area. This person was seen as representative for his/her area. These data were aggregated to four-digital postal code areas. (1995, 1998, 2002, 2006)
Statistics Netherlands (governmental organisation)	Area-based, 6-position of postal code (mean number of households=17)	Household income, economic value of housing	Fiscal data (household income: 1998 and economic value of the house/apartment: 2000)
Dutch GLOBE-study (cohort)	Individual level	Education	Questionnaires including questions on highest attained educational level in 1991

THIS THESIS

The research underlying this thesis aimed to contribute to the discussion on the role that SES plays in cancer risk, detection, and outcome, as depicted in Figure 2. More specifically, we aimed to measure the magnitude of socioeconomic inequalities in cancer risk and detection (referred to by number 1 in Figure 2) by means of incidence rates, uptake in screening programmes, stage at diagnosis, comorbidities at diagnosis, as well as socioeconomic inequalities in cancer outcome (numbers 2 in Figure 2) via treatment selection, survival and

quality of life in The Netherlands. We described the (trends in) levels of inequality and tried to explain inequalities in risk, detection, and outcome of cancer for a variety of tumours. The main objectives of the studies described in this thesis were to provide insight into:

1.   The association of SES and the risk and (determinants of) detection of cancer in a large population-based setting
2.   The association of SES and the outcomes of cancer in terms of (determinants of and trends in) treatment, survival, and long-term health-related quality of life
3.   Entry points for interventions to reduce the socioeconomic inequalities as assessed via abovementioned measures.

As "introduction" to this thesis, the multiple associations between SES and the incidence, detection and treatment of, survival and mortality from colorectal cancer have been reviewed in **chapter 2**.

In **chapter 3.1** the trends in the incidence of several tumours have been studied according to SES group. For basal cell carcinomas, further analyses were performed for age groups and sublocalisations (**chapter 3.2**). Attendance to mass breast cancer screening was investigated as determinant of detection, and thus consequences for stage at diagnosis and survival were studied in **chapter 3.3**.

Subsequently, the prevalence of comorbid conditions (possibly also affecting detection) at cancer diagnosis and the consequences for survival have been described (**chapter 4.1**). We explored the use of therapies according to SES for breast cancer patients in a nationwide study (**chapter 4.2**). In **chapter 4.3** we performed a comparable study for prostate cancer and included comorbidities to observe its effects on treatment as well as on survival. The impact of SES on the staging and treatment decisions in oesophageal cancer is described in **chapter 4.4**.The contribution of lifestyle factors on survival from cancer was based on data from GLOBE study linked to the ECR (**chapter 4.5**). As low SES individuals generally report poor health-related quality of life,[4] we investigated the association in long-term prostate cancer survivors (**chapter 4.6**). In the general discussion, the main results are summarised and future perspectives for research and clinical management are considered (**chapter 5**).
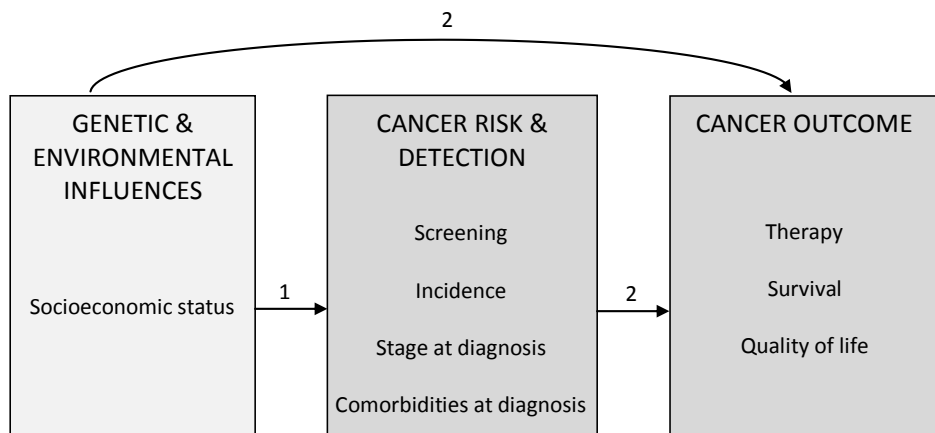
Figure 2. *Associations investigated in this thesis.*

1

REFERENCES

1. Mackenbach, J.P., Stirbu, I., Roskam, A.J., Schaap, M.M., Menvielle, G., Leinsalu, M. & Kunst, A.E. Socioeconomic inequalities in health in 22 European countries. *N Engl J Med* 358, 2468-81 (2008).

2. Lynch, J.W., Kaplan, G.A., Cohen, R.D., Tuomilehto, J. & Salonen, J.T. Do cardiovascular risk factors explain the relation between socioeconomic status, risk of all-cause mortality, cardiovascular mortality, and acute myocardial infarction? *Am J Epidemiol* 144, 934-42 (1996).

3. Mackenbach, J.P., Martikainen, P., Looman, C.W., Dalstra, J.A., Kunst, A.E. & Lahelma, E. The shape of the relationship between income and self-assessed health: an international study. *Int J Epidemiol* 34, 286-93 (2005).

4. Hoeymans, N., van Lindert, H. & Westert, G.P. The health status of the Dutch population as assessed by the EQ-6D. *Qual Life Res* 14, 655-63 (2005).

5. Bruggink, J.W. Ontwikkelingen in (gezonde) levensverwachting naar opleidingsniveau [in Dutch]. *Bevolkingstrends* 4e kwartaal (2009).

6. IARC. Social Inequalities and Cancer (eds. Kogevinas, M., Pearce, N., Susser, M. & Boffetta, P.) (Lyon, 1997).

7. Dalton, S.O., Schuz, J., Engholm, G., Johansen, C., Kjaer, S.K., Steding-Jessen, M., Storm, H.H. & Olsen, J.H. Social inequality in incidence of and survival from cancer in a population-based study in Denmark, 1994-2003: Summary of findings. *Eur J Cancer* 44, 2074-85 (2008).

8. Faggiano, F., Partanen, T., Kogevinas, M. & Boffetta, P. Socioeconomic differences in cancer incidence and mortality. *IARC Sci Publ*, 65-176 (1997).

9. Stronks, K., van de Mheen, H.D., Looman, C.W. & Mackenbach, J.P. Cultural, material, and psychosocial correlates of the socioeconomic gradient in smoking behavior among adults. *Prev Med* 26, 754-66 (1997).

10. Siemiatycki, J., Krewski, D., Franco, E. & Kaiserman, M. Associations between cigarette smoking and each of 21 types of cancer: a multi-site case-control study. *Int J Epidemiol* 24, 504-14 (1995).

11. Graham, H. Smoking prevalence among women in the European community 1950-1990. *Soc Sci Med* 43, 243-54 (1996).

12. Doll, R., Peto, R., Wheatley, K., Gray, R. & Sutherland, I. Mortality in relation to smoking: 40 years' observations on male British doctors. *Bmj* 309, 901-11 (1994).

13. Janssen-Heijnen, M.L., Schipper, R.M., Razenberg, P.P., Crommelin, M.A. & Coebergh, J.W. Prevalence of co-morbidity in lung cancer patients and its relationship with treatment: a population-based study. *Lung Cancer* 21, 105-13 (1998).

14. Robb, K., Stubbings, S., Ramirez, A., Macleod, U., Austoker, J., Waller, J., Hiom, S. & Wardle, J. Public awareness of cancer in Britain: a population-based survey of adults. *Br J Cancer* 101 Suppl 2, S18-23 (2009).

15. Fitzpatrick, P., Corcoran, N. & Fitzpatrick, J.M. Prostate cancer: how aware is the public? *Br J Urol* 82, 43-8 (1998).

16. Woods, L.M., Rachet, B. & Coleman, M.P. Origins of socio-economic inequalities in cancer survival: a review. *Ann Oncol* 17, 5-19 (2006).

17. Segnan, N. Socioeconomic status and cancer screening. *IARC Sci Publ*, 369-76 (1997).

18. Moser, K., Patnick, J. & Beral, V. Inequalities in reported use of breast and cervical screening in Great Britain: analysis of cross sectional survey data. *Bmj* 338, b2025 (2009).

19. Cheung, M.C., Yang, R., Byrne, M.M., Solorzano, C.C., Nakeeb, A. & Koniaris, L.G. Are patients of low socioeconomic status receiving suboptimal management for pancreatic adenocarcinoma? *Cancer* 116, 723-33 (2010).

20. Downing, A., Prakash, K., Gilthorpe, M.S., Mikeljevic, J.S. & Forman, D. Socioeconomic background in relation to stage at diagnosis, treatment and survival in women with breast cancer. *Br J Cancer* 96, 836-40 (2007).

21. Raine, R., Wong, W., Scholes, S., Ashton, C., Obichere, A. & Ambler, G. Social variations in access to hospital care for patients with colorectal, breast, and lung cancer between 1999 and 2006: retrospective analysis of hospital episode statistics. *Bmj* 340, b5479 (2010).

22. Fairley, L., Baker, M., Whiteway, J., Cross, W. & Forman, D. Trends in non-metastatic prostate cancer management in the Northern and Yorkshire region of England, 2000-2006. *Br J Cancer* 101, 1839-45 (2009).

23. van Vliet, E.P., Eijkemans, M.J., Steyerberg, E.W., Kuipers, E.J., Tilanus, H.W., van der Gaast, A. & Siersema, P.D. The role of socio-economic status in the decision making on diagnosis and treatment of oesophageal cancer in The Netherlands. *Br J Cancer* 95, 1180-5 (2006).

24. van Oost, F.J., Luiten, E.J., van de Poll-Franse, L.V., Coebergh, J.W. & van den Eijnden-van Raaij, A.J. Outcome of surgical treatment of pancreatic, peri-ampullary and ampullary cancer diagnosed in the south of The Netherlands: a cancer registry based study. *Eur J Surg Oncol* 32, 548-52 (2006).

25. Lemmens, V.E., van Halteren, A.H., Janssen-Heijnen, M.L., Vreugdenhil, G., Repelaer van Driel, O.J. & Coebergh, J.W. Adjuvant treatment for elderly patients with stage III colon cancer in the southern Netherlands is affected by socioeconomic status, gender, and comorbidity. *Ann Oncol* 16, 767-72 (2005).

26. Kogevinas, M. & Porta, M. Socioeconomic differences in cancer survival: a review of the evidence. *IARC Sci Publ*, 177-206 (1997).

27. Coleman, M.P., Babb, P., Sloggett, A., Quinn, M. & De Stavola, B. Socioeconomic inequalities in cancer survival in England and Wales. *Cancer* 91, 208-16 (2001).

28. Schrijvers, C.T., Coebergh, J.W., van der Heijden, L.H. & Mackenbach, J.P. Socioeconomic variation in cancer survival in the southeastern Netherlands, 1980-1989. *Cancer* 75, 2946-53 (1995).

29. Louwman, W.J., van de Poll-Franse, L.V., Fracheboud, J., Roukema, J.A. & Coebergh, J.W. Impact of a programme of mass mammography screening for breast cancer on socio-economic variation in survival: a population-based study. *Breast Cancer Res Treat* 105, 369-75 (2007).

30. Oerlemans, S., Mols, F., Nijziel, M.R., Lybeert, M. & van de Poll-Franse, L.V. The impact of treatment, socio-demographic and clinical characteristics on health-related quality of life among Hodgkin's and non-Hodgkin's lymphoma survivors: a systematic review. *Ann Hematol* (2011).

31. Thong, M.S., Mols, F., Lemmens, V.E., Rutten, H.J., Roukema, J.A., Martijn, H. & van de Poll-Franse, L.V. Impact of preoperative radiotherapy on general and disease-specific health status of rectal cancer survivors: a population-based study. *Int J Radiat Oncol Biol Phys* 81, e49-58 (2011).

32. Mols, F., van de Poll-Franse, L.V., Vingerhoets, A.J., Hendrikx, A., Aaronson, N.K., Houterman, S., Coebergh, J.W. & Essink-Bot, M.L. Long-term quality of life among Dutch prostate cancer survivors: results of a population-based study. *Cancer* 107, 2186-96 (2006).

33. Mackenbach, J. [Unhealthy differences. About social stratification and health in The Netherlands] (Van Gorcum, Assen, 1994).

34. Mackenbach, J., Judge, C.M., Navarro, C. & Kunst, A. in Tackling health inequalities in Europe: an integrated approach Eurothin (2007).

35. Coebergh, J.W.W., Janssen-Heijnen, M.L.G., Louwman, W.J. Cancer incidence, care and survival in the South of the Netherlands, 1955-1999, a report from the Eindhoven Cancer Registry with cross-border implications (Comprehensive Cancer Centre South (IKZ), Eindhoven, 2001).

36. Schouten, L.J., Hoppener, P., van den Brandt, P.A., Knottnerus, J.A. & Jager, J.J. Completeness of cancer registration in Limburg, The Netherlands. *Int J Epidemiol* 22, 369-376 (1993).

37. Kieszak, S.M., Flanders, W.D., Kosinski, A.S., Shipp, C.C. & Karp, H. A comparison of the Charlson comorbidity index derived from medical record data and administrative billing data. *J Clin Epidemiol* 52, 137-42 (1999).

38. van Lenthe, F.J., Schrijvers, C.T., Droomers, M., Joung, I.M., Louwman, M.J. & Mackenbach, J.P. Investigating explanations of socio-economic inequalities in health: the Dutch GLOBE study. *Eur J Public Health* 14, 63-70 (2004).

DECISION
ROLE
SINCE 1990
data
CURATIVE
CATEGORY
HOUSING
RECOGNISING
OUTCOME
BRACHYTHERAPY
DETERMINANTS
INTERVAL CANCER
health seeking behaviour
METASTASIS
CONTRIBUTION
CHARLSON
material resources
estimated
axillary
EAPC
staging
annual
percent
change
SMOKING
DISCUSS
statistical
socioeconomic position
RADIOTHERAPY
COVERAGE
GP
STUDIES
central nervous system
lifestyle
staging
HOSPITAL
socioeconomic status
Eindhoven Cancer Registry
dementia
Comprehensive Cancer Centre South
intelligence
education
hazard
ratio
RISK FACTORS
DIAGNOSIS
SEP
VISITS
ATTENDANCE
EXPLANATION
diagnostics
distribution
CARDIOVASCULAR DISEASE
stage
SOCIAL SUPPORT
HYPERTENSION
mastectomy
therapy
HIGH
HORMONAL THERAPY
ADVANCED
FEAR
MENTAL
MAMMOGRAPHY
colorectal
UPBRINGING
ENVIRONMENT
incidence
prostatectomy
p-value
QUESTIONNAIRE
HEALTH BEHAVIOUR
SF-36
GLOBE
PHYSICAL
SOCIOEC
NEIGHBOURHOOD
value of housing
ALCOHOL CONSUMPTION
EXPOSURE
LOW
socioeconomic status
physical activity
comorbidities
occupation
INTERMEDIATE
colorectal
cancer
REVIEW
CHEMORADIATION
INVITATION
TUBERCULOSIS
concomitant disease
screening
INVASIVE
CONTACTS
gap
VARIATION
logistic
regression
ACCESS TO CARE
CONSULTATION
ASSETS
numbers
PSA
LOCALISED
WORK
SCREEN-DETECTED TUMOUR
income
percentages
THE NETHERLANDS
HEALTH INSURANCE
health awareness
HOUSEHOLD
search
DETECTIO

Chapter 2

Socioeconomic status and changing inequalities in colorectal cancer? A review of the associations with risk, treatment and outcome

M.J. Aarts, V.E.P.P. Lemmens, M.W.J. Louwman, A.E. Kunst, J.W.W. Coebergh

ABSTRACT

Background
Upcoming mass screening for colorectal cancer (CRC) makes a review of recent literature on the association with socioeconomic status (SES) relevant, because of marked and contradictory associations with risk, treatment and outcome.

Methods
The Pubmed database using the MeSH terms 'Neoplasms' OR 'Colorectal Neoplasms' AND 'Socioeconomic Factors' for articles added between 1995 and October 1st 2009 led to 62 articles.

Results
Low SES groups exhibited a higher incidence compared with high SES groups in the US and Canada (range risk ratio (RR) 1.0-1.5), but mostly lower in Europe (RR 0.3-0.9). Treatment, survival and mortality all showed less favourable results for people with a lower socioeconomic status: Patients with a low SES received less often (neo)adjuvant therapy (RR ranging from 0.4 to 0.99), had worse survival rates (hazard ratio (HR) 1.3-1.8) and exhibited generally the highest mortality rates up to 1.6 for colon cancer in Europe and up to 3.1 for rectal cancer.

Conclusions
A quite consistent trend was observed favouring individuals with a high SES compared to those with a low SES that still remains in terms of treatment, survival and thus also mortality. We did not find evidence that the low/high SES gradients for treatment chosen and outcome are decreasing. To meet increasing inequalities in mortality from CRC in Europe for people with a low SES and to make mass screening successful, a high participation rate needs to be realised of low SES people in the soon starting screening program.

2

BACKGROUND

Socioeconomic inequalities in incidence and outcome have been reported for a variety of cancer types.[1-6] In general, cancer mortality is about 20-80% higher among individuals with a lower socioeconomic status (SES).[7] This disadvantage may be the result of a higher cancer incidence in some countries and/or lower cancer survival rates in most of them. A comprehensive review of studies published up to 1995 revealed an opposite trend for colorectal cancer (CRC)[7] – worldwide the 3rd most common type of cancer. For colon cancer low risks for individuals with a low SES were reported, both for mortality and incidence – in contrast to rectal cancer for which no consistent associations were observed.[7] However, CRC mortality appeared to be highest among people with a poor education across Europe during the 1990s.[8] On the eve of mass screening for colorectal cancer in the Netherlands a precise insight into the relationship with SES is even more relevant, since participation of high risk groups is crucial to obtain optimal screening results. We therefore conducted a systematic review of the relationship between SES and colorectal cancer incidence, treatment, survival and mortality.

MATERIALS AND METHODS

The electronic database of Pubmed was searched using the following strategy: ('Neoplasms'[Majr:NoExp] OR 'Colorectal Neoplasms'[Mesh]) AND ('socioeconomic factors'[Mesh]). Only articles in English added to Pubmed between January 1, 1995 and October 1, 2009 were included. All types of studies focusing on incidence, (determinants of) treatment and outcome (i.e. survival and mortality) were included, except reviews. All patients with colon or rectal cancer were included, independent of their characteristics (such as age, race, and place of residence). For treatment and mortality, we also included studies that did not distinguish between colon and rectal (i.e. colorectal cancer in general). If several ethnic groups were studied, only the results for Caucasians are presented here. Studies that used education, occupation, income, poverty or combinations of any of these as indicators of SES were included.

Articles were first screened by title for their contents, then by abstract. Full text was obtained for articles that met the above-mentioned inclusion criteria. After reading, these articles were judged and either included or excluded. Articles were excluded because of several reasons, i.e. since no abstract was available we should read the complete article; young age; focus only on spatial, rurality or race but not on education, occupation, income or poverty; or without distinction between colon and rectum. Furthermore, the reference lists of all included articles were screened for useful articles. Selection and abstraction were performed by one reviewer (MA). We extracted data on author, journal, year of publication, type of study, population at-risk, period of diagnosis, cancer (sub)site, SES indicators, results, suggested causes of inequalities and possible useful references from the included articles. The data is summarized in separate tables for incidence, treatment, survival and mortality. Data is presented as the odds of low versus high SES, calculated from the data in the articles.

RESULTS

The Pubmed search yielded 1808 articles, which were scanned by title (resulting in 232 abstracts) and then by abstract (resulting in 120 full-text articles). Of these, 55 were included

in this review. After scanning the reference lists, seven additional articles were included. Nineteen articles on incidence, 14 on survival, 20 on mortality and 14 on treatment were included; five studies concentrated on combinations of two of these, i.e. one on incidence and survival; one on incidence and mortality; and three on treatment and survival. Results are presented in tables 1 to 4; comprehensive tables can be found in Supplementary material.

Incidence

In the United States (US) and Canada (Table 1A) a lower social class was generally associated with higher risk of colon and rectal cancer, whereas European studies predominantly found lower risks (Table 1B).

Risk estimates among low SES groups in the US and Canada ranged from 1.0 to 1.6 if diagnosed before the mid-1990s (Table 1A),[9-15] whereas a study of patients diagnosed thereafter in the state of Alabama showed a lower risk (range 0.9-1.0).[16]

European relative risk estimates (Table 1B) ranged from 0.3 to 0.9 for low compared to a high SES in Italy,[17, 18] Finland,[1] Sweden,[19] Norway,[20] while no association[21] or increased risk was found in another Italian study,[21] and in France,[22] Denmark[23] and the Netherlands,[2] depending on the indicator used for measuring SES. In agreement with the majority of the results of European origin, Australian and South Korean studies reported a lower incidence among individuals with a low SES.[24-26]

Treatment

A lower chance of receiving curative treatment among colon cancer patients with a low SES was demonstrated consistently: odds ratios for surgery, (adjuvant) radiotherapy or (adjuvant) chemotherapy ranged from 0.4 to 0.99 for those with a low compared to a high SES (Table 2).[28-36]

Rectal cancer patients from low SES groups were less likely to receive radiotherapy and chemotherapy,[29, 36, 37] but this was not uniform. Furthermore, the risk of having a permanent stoma after surgery was higher among low SES patients (RR 1.4)[32] as well as the chance of undergoing abdomino-perineal excision of the rectum (APER).[32, 38, 39]

Survival

Both colon and rectal cancer patients from low SES groups consistently had worse survival rates compared to high SES patients (Table 3A and 3B); reported 5-year relative survival rates for low SES patients compared to high SES patients ranged from 0.5 to 0.9.[23, 32, 40] Furthermore, the risk of dying in the first five years after diagnosis was consistently elevated for patients with a low compared to a high SES (HR ranging from 1.1 to 1.8) (Table 3B).[31, 41-54] From 1986 to 1999, the survival disparities increased in England and Wales in both colon and rectal cancer patients.[55, 56]

Mortality

Mortality from colorectal cancer was generally highest among individuals with a low SES (Table 4A and 4B), also for the subsites colon and rectum separately. One US study showed

2

a transition from lower towards higher colorectal cancer mortality rates among those with a low SES since 1950 onwards (among men rate ratios increased from 0.4 to 1.3 for low vs. high SES between 1950 and 1998) (Table 4A),[61] but another US study showed this only for men (RR 0.96 and 1.2 for patients diagnosed in 1959-1972 and 1982-1996, respectively), but not women (RR 1.3 and 0.9)[62, 63] whereas in France the rate ratio was 2.5 for men diagnosed between 1968-1974, also for those diagnosed between 1990-1996 [64] (Table 4B).

In Europe, associations between SES and mortality from rectal cancer than for colon cancer when studied separately (rate ratios up to 3.1 for rectal cancer and up to 1.6 for colon cancer).[25, 65-69]

Table 1A. Associations between incidence of colon and rectal cancer and socioeconomic status in US and Canada.

Author, year	Study base	Indicators	Type of measurement	Risk of low versus high SES	
				Males	**Females**
Colon					
Gorey and Vena, 1995 [12]	US, 1979-1986	Poverty	RR[a] (95%CI)[b]	**1.39 (1.24-1.55)**[c]	**1.48 (1.33-1.65)**
Gorey et al., 1998 [11]	Canada, 1986-1993	Poverty	Standardised incidence rate ratio	**1.11 (1.02-1.20)**	0.99 (0.97-1.01)
Krieger et al., 1999 [10]	US, 1988-1992	% Working, professional, poverty, education	Incidence rate ratio	**1.3 (1.1-1.6)**	**1.3 (1.1-1.6)**
Mackillop et al., 2000 [9]	US, 1988-1992	Income	RR US	**1.08 (1.01-1.14)**	**1.10 (1.03-1.16)**
	Canada, 1989-1993		RR Canada	**1.20 (1.10-1.33)**	**1.15 (1.05-1.28)**
Shipp et al., 2005 [16]	US, 1996-1999	Education / Income / Poverty	RR	**0.91 (0.85-0.97)** *Both sexes* / 0.99 (0.98-1.01) *Both sexes* / 1.02 (0.93-1.09) *Both sexes*	
Mouw et al., 2008 [15]	US, 1995-1996	Education	RR	1.10 (0.94-1.29)	**1.37 (1.06-1.77)**
Rectal					
Gorey and Vena, 1995 [12]	US, 1979-1986	Poverty	RR	**1.36 (1.16-1.60)**	**1.64 (1.39-1.94)**
Gorey et al., 1998 [11]	Canada, 1986-1993	Poverty	Standardised incidence rate ratio	**1.25 (1.08-1.44)**	**1.04 (1.01-1.07)**
Mackillop et al., 2000 [9]	US, 1988-1992	Income	RR US	**1.19 (1.10-1.32)**	1.02 (0.98-1.05)
	Canada, 1989-1993		RR Canada	**1.23 (1.09-1.43)**	1.00 (0.94-1.08)
Mouw et al., 2008 [15]	US, 1995-1996	Education	RR	**1.50 (1.17-1.92)**	1.05 (0.68-1.62)

[a] RR: relative risk or risk ratio.
[b] 95%CI: 95% confidence interval.
[c] Values in bold are statistically significant.

2

2

Table 1B. Associations between incidence of colon and rectal cancer and socioeconomic status in Europe, Australia and South Korea.

Author, year	Study base	Indicators	Type of measurement	Risk of low versus high SES	
				Males	**Females**
Colon					
Van Loon et al., 1995 [2]	The Netherlands, 1986-1989	Education Occupation Social standing[d]	RR[a] (95%CI)[b]	1.00 (0.54-1.85) 1.41 (0.77-2.56) **0.38 (0.19-0.76)[c]**	1.14 (0.50-2.56) 1.39 (0.67-2.94) 1.22 (0.26-5.88)
Marshall et al., 1999 [22]	France, 1988-1992	Socioprofessional hierarchy Employee category	Odds ratio	2.4 (0.8-7.2) 1.2 (0.4-3.4)	
Tavani et al., 1999 [17]	Italy, 1985-1996	Education Social class (occupation)	Odds ratio	**0.41 (0.31-0.53)** **0.43 (0.34-0.55)**	0.78 (0.53-1.14) **0.75 (0.58-0.97)**
Pisa et al., 2000 [18]	Italy, 1992-1996	Education Occupation	Odds ratio	**0.26 (0.15-0.43)** **0.42 (0.26-0.67)**	**0.33 (0.18-0.63)** 0.77 (0.43-1.43)
Bouchardy et al., 2002 [27]	Switzerland, 1980-1993	Occupation		↑SES ↑risk	
Hemminki and Li, 2003 [19]	Sweden, 1961-1998	Education	Standardised incidence ratio	**1.11 (1.04-1.18)**	**0.90 (0.81-0.99)**
Braaten et al., 2005 [20]	Norway, 1991-2001	Education	RR		1.23 (0.70-2.20)
Weiderpass and Pukkala, 2006 [1]	Finland, 1971-1995	Education, occupation, industrial status, industry groupings	Standardised incidence ratio	**0.78 versus 1.37** **[RR=0.6]**[a]	0.92 versus 1.13 [RR=0.8]

Study	Country, period	SES indicator	Outcome measure	Period		
Egeberg et al., 2008 [23]	Denmark, 1994-2003	Education	Incidence rate ratio		0.93 (0.85-1.01)	1.02 (0.93-1.12)
		Disposable income			1.01 (0.94-1.08)	0.94 (0.88-1.01)
		Social class (occupation)			**0.70 (0.61-0.81)**	0.87 (0.67-1.14)
		Housing tenure			**1.19 (1.12-1.26)**	0.98 (0.93-1.05)
		Size of dwelling			**1.30 (1.10-1.52)**	0.86 (0.67-1.11)
Spadea et al., 2009 [21]	Italy, 1985-1999	Education	Relative risk	1985-1999	0.93 (0.83-1.04)	0.93 (0.80-1.07)
				1985-1989	**0.73 (0.60-0.90)**	0.79 (0.61-1.03)
				1990-1994	1.12 (0.90-1.38)	1.00 (0.77-1.30)
				1995-1999	1.00 (0.82-1.21)	1.04 (0.82-1.30)
Burnley, 1997 [25]	Australia, 1985-1991	Income Jarman index[d]	Pearson correlation		0.27 -0.21	
Pearce and Bethwaite, 1997 [26]	New Zealand, 1984-1987	Elley-Irving scale[d]	Incidence/100,000 person years		8.9 versus 12.9 [RR=0.7]	
Kim et al., 2008 [24]	South Korea, 2001	Income	Relative index of inequalities per 100,000 population		0.98 (0.61-1.57)	**0.69 (0.59-0.80)**
Rectal						
Tavani et al., 1999 [17]	Italy, 1985-1996	Education	Odds ratio		**0.41 (0.31-0.53)**	0.99 (0.60-1.64)
		Social class (occupation)			0.85 (0.63-1.16)	0.85 (0.61-1.19)
Pisa et al., 2000 [18]	Italy, 1992-1996	Education	Odds ratio		0.77 (0.42-1.43)	**0.31 (0.14-0.67)**
		Occupation			1.11 (0.67-2.00)	0.83 (0.38-2.0)
Bouchardy et al., 2002 [27]	Switzerland, 1980-1993	Occupation			No association	
Hemminki and Li, 2003 [19]	Sweden, 1961-1998	Education	Standardised incidence ratio		**0.83 (0.76-0.91)**	0.92 (0.80-1.06)

Table 1B continues on next page

2

Continuation of table 1B

Author, year	Study base	Indicators	Type of measurement		Risk of low versus high SES	
					Males	**Females**
Braaten et al., 2005 [20]	Norway, 1991-2001	Education	RR			0.63 (0.33-1.20)
Weiderpass and Pukkala, 2006 [1]	Finland, 1971-1995	Education, occupation, industrial status, industry groupings	Standardised incidence ratio		0.92 versus 0.98 [RR=0.9]	0.92 versus 1.10 [RR=0.8]
Egeberg et al., 2008 [23]	Denmark, 1994-2003	Education	Incidence rate ratio		1.02 (0.93-1.12)	1.12 (1.00-1.27)
		Disposable income			**1.09 (1.01-1.18)**	0.99 (0.90-1.07)
		Social class (occupation)			**0.83 (0.73-0.97)**	0.92 (0.60-1.07)
		Housing tenure			**1.17 (1.10-1.25)**	1.04 (0.96-1.13)
		Size of dwelling			1.16 (0.97-1.39)	1.07 (0.78-1.45)
Spadea et al., 2009 [21]	Italy, 1985-1999	Education	Relative risk	1985-1999	**1.27 (1.07-1.50)**	1.16 (0.94-1.43)
				1985-1989	0.94 (0.71-1.25)	1.09 (0.73-1.63)
				1990-1994	**1.57 (1.15-2.14)**	1.27 (0.88-1.84)
				1995-1999	**1.44 (1.09-1.91)**	1.08 (0.76-1.55)
Pearce and Bethwaite, 1997 [26]	New Zealand, 1984-1987	Elley-Irving scaled	Incidence/100,000 person years		9.3 versus 7.9 [RR=1.2]	
Kim et al., 2008 [24]	South Korea, 2001	Income	Relative index of inequalities per 100,000 population		0.97 (0.66-1.43)	1.29 (0.84-1.98)

[a] RR: relative risk or risk ratio [brackets represent relative risks calculated from the data].
[b] 95%CI: 95% confidence interval.
[c] Values in bold are statistically significant.
[d] Jarman index: elderly living alone, one parent families, unskilled, unemployment, overcrowding; Elley-Irving scale: occupation, income and education; social standing: based on an ordering of occupational titles according to social standing.

Table 2. Associations between treatment of colon, rectal and colorectal cancer and socioeconomic status.

Author, year	Study base	Indicators	Social scale	Stage	Therapy	Colon	Rectal	Colorectal
						Odds for receiving treatment for low versus high SES patients		
Roetzheim et al., 2000 [28]	US, 1994	Education (E) Income (I)	OR^a (95% CI)^b (I): change in odds of receiving therapy per increase in income category	I-IV	Surgery			E **0.68 (0.47-0.99)**^c
								I 0.93 (0.85-1.02)
					Radiotherapy	E 0.78 (0.55-1.10)	1.02 (0.49-2.15)	
						I **0.90 (0.83-0.98)**	**0.79 (0.67-0.93)**	
					Chemotherapy			E 0.84 (0.59-1.19)
								I 0.98 (0.90-1.06)
Schrag et al., 2001 [36]	US, 1992-1996	Income	OR	II-III	Any adjuvant radiotherapy		0.92 (0.63-1.33)	
					Adjuvant radiotherapy +chemotherapy		0.73 (0.51-1.06)	
Campbell et al., 2002 [30]	UK, 1995-1996	Carstairs index^d	OR	I-IV	Surgery			0.52 (0.14-1.87)
					Radiotherapy			0.85 (0.38-1.91)
					Chemotherapy			0.49 (0.22-1.10)
VanEenwyk et al., 2002 [35]	US, 1996-1997	Income	OR	II colon II-III rectum	Chance of NOT receiving adjuvant therapy	**2.0 (1.2-3.1)**	0.7 (0.4-1.3)	
Ayanian et al., 2003 [37]	US, 1996-1997	Income	OR	III colon II-III rectum	Adjuvant chemotherapy	0.8 (0.6-1.1)		
					Adjuvant radiotherapy		0.7 (0.4-1.4)	

Table 2 continues on next page

2

Continuation of table 2

Author, year	Study base	Indicators	Social scale	Stage	Therapy	Odds for receiving treatment for low versus high SES patients		
						Colon	Rectal	Colorectal
Hall et al., 2005 [57]	Australia, 1991-2001	Occupation, income, education, housing	OR	?	Likelihood of surgery			1.13 (0.88-1.45)
Lemmens et al., 2005 [34]	The Netherlands, 1995-2001	Housing and income	OR	III	Adjuvant chemotherapy	0.5		
McGory et al., 2006 [29]	US, 1994-2001	Poverty	OR	II	Chemotherapy	0.991 (0.988-0.995)	0.992 (0.986-0.998)	
				III			0.992 (0.986-0.997)	
				II	Radiotherapy		0.993 (0.987-0.999)	
				III			0.991 (0.986-0.996)	
Vulto et al., 2007 [58]	The Netherlands, 1996-2005	Housing and income	OR	I-IV	Radiotherapy > 6 months after diagnosis		1.1 (0.8-1.7)	
Byers et al., 2008 [31]	US, 1997	Combination of education and income	% treatment	Regional stage	Chemotherapy			50% versus 56% [RR=0.9]c

Study	Country, period	SES measure	Outcome[a,b]	Tumour stage	Treatment	% treatment / OR
Meulenbeld et al., 2008 [33]	The Netherlands, 1990-2004	Housing and income	% treatment	IV	Chemotherapy 1990-1994 1995-1999 2000-2002 2003-2004	11% versus 22% [RR=0.5] 15% versus 37% [RR=0.4] 30% versus 53% [RR=0.6] 47% versus 50% [RR=0.9]
Tilney et al., 2008 [38]	England, 1996-2004	Index of multiple deprivation	OR	?	APER abdomin-operineal excision of rectum)	**1.589 (1.449-1.744)**
Harris et al., 2009 [32]	UK, 2000-2007	Index of multiple deprivation[d]	% treatment	I-IV	Surgery / Surgery, of which permanent stoma	**79.2% versus 93% [RR=0.9]**[c] / 40.8% versus 30% [RR=1.4]
Tilney et al., 2009 [39]	Great Britain and Ireland, 2000-2005	Index of multiple deprivation	OR	I-III	APER abdomin-operineal excision of rectum)	**1.638 (1.362-1.969)**

[a] OR: odds ratio [brackets represent relative risks calculated from the data].
[b] 95%CI: 95% confidence interval.
[c] Values in bold are statistically significant.
[d] Carstairs index: overcrowding, employment, social class, car ownership; Index of multiple deprivation: income, employment, health and disability, education, skills and training, houses and services, living environment, crime.

2

Table 3A. Associations between survival (relative survival) from colon and rectal cancer and socioeconomic status.

Author, year	Study base	Indicators	Type of measurement	Survival of patients with low versus high SES	
				Male	Female
Colon					
Gorey et al., 1997 [40]	US and Canada, 1986-1992	Income	Survival rate ratio (95% CI)[b]		
			US 1 year **0.90 (0.86-0.94)**[c]		**0.94 (0.89-0.99)**
			US 5 year **0.78 (0.65-0.94)**		**0.82 (0.69-0.98)**
			Canada 1 year 0.97 (0.92-1.02)		**1.06 (1.01-1.12)**
			Canada 5 year 0.97 (0.84-1.11)		**1.33 (1.14-1.55)**
Shack et al., 2007 [59]	UK, 1996-2000	Scottish indices of multiple deprivation[d]	Absolute difference in 5-year relative survival	**-5.7**	**-6.1**
Egeberg et al., 2008 [23]	Denmark, 1994-2003	Education	5-year relative survival (%)	42% versus 46% [RR=0.9][a]	46% versus 49% [RR=0.9]
		Disposable income		40% versus 46% [RR=0.9]	**45% versus 55% [RR=0.8]**
		Social class (occupation)		49% versus 48% [RR=1.0]	42% versus 45% [RR=0.9]
		Housing tenure		**39% versus 46% [RR=0.8]**	47% versus 49% [RR=1.0]
		Size of dwelling		36% versus 49% [RR=0.7]	37% versus 51% [RR=0.7]
Mitry et al., 2009 [56]	England and Wales, 1986-1999	1986-1995 Carstairs deprivation index[d] 1996-1999 Index of multiple deprivation[d]	Average change every 5 years in *absolute* deprivation gap (low-high SES):		
			1-year relative survival	**-2.2 (-3.5, -1.0)**	**-1.4 (-2.5, -0.2)**
			5-year relative survival	**-1.9 (-3.4, -0.3)**	**-2.2 (-3.6, -0.8)**
Rectal					
Gorey et al., 1997 [40]	US and Canada, 1986-1992	Income	Survival rate ratio		
			US 1 year **0.88 (0.83-0.93)**		**0.89 (0.80-0.99)**
			US 5 year 0.87 (0.69-1.09)		0.80 (0.61-1.05)
			Canada 1 year 0.96 (0.89-1.03)		1.02 (0.89-1.17)
			Canada 5 year 0.90 (0.72-1.12)		1.05 (0.81-1.37)

2

Study	Country, period	SES measure	Outcome		
Shack et al., 2007 [59]	UK, 1996-2000	Scottish indices of multiple deprivation	Absolute difference in 5-year relative survival	-5.3	-8.0
Egeberg et al., 2008 [23]	Denmark, 1994-2003	Education	5-year relative survival (%)	44% versus 50% [RR=0.9]	51% versus 57% [RR=0.9]
		Disposable income		**41% versus 51% [RR=0.8]**	49% versus 58% [RR=0.8]
		Social class (occupation)		46% versus 56% [RR=0.8]	68% versus 72% [RR=0.9]
		Housing tenure		43% versus 48% [RR=0.9]	50% versus 55% [RR=0.9]
		Size of dwelling		41% versus 48% [RR=0.9]	**29% versus 59% [RR=0.5]**
Harris et al., 2009 [32]	UK, 2000-2007	Index of multiple deprivation	5-year survival (%): all patients	**33% versus 64% [RR=0.5]** *Both sexes*	
			: patients with resectional surgery	**50% versus 72% [RR=0.7]** *Both sexes*	
Mitry et al., 2009 [55]	England and Wales, 1986-1999	1986-1995 Carstairs deprivation index	Average change every 5 years in *absolute* deprivation gap (low-high SES):		
		1996-1999 Index of multiple deprivation	1-year relative survival	**-1.4 (-2.7, -0.1)**	-1.2 (-2.8, 0.3)
			5-year relative survival	**-2.4 (-4.1, -0.6)**	**-2.5 (-4.5, -0.5)**

a RR: relative risk or risk ratio [brackets represent relative risks calculated from the data].
b 95%CI: 95% confidence interval.
c Values in bold are statistically significant.
d Scottish index of multiple deprivation: income, employment, health, education, skills and training, housing, geographic access and crime; Carstairs index: overcrowding, employment, social class, car ownership; Index of multiple deprivation: income, employment, health and disability, education, skills and training, houses and services, living environment, crime.

2

34

Table 3B. *Associations between survival (risk of death) from colon, rectal and colorectal cancer and socioeconomic status.*

Author, year	Study base	Indicators	Type of measurement	Risk of death of patients with low versus high SES	
				Male	Female
Colon					
Auvinen et al., 1995 [42]	Finland, 1971-1985	Occupation	RR[a] (95% CI)[b]	1.04 (0.82-1.33)	1.22 (0.98-1.49)
Lemmens et al., 2005 [34]	The Netherlands, 1995-2001	Housing and income	Hazard ratio	1.0 *Both sexes*	
Zhang-Salomons et al., 2006 [41]	US, 1988-1992, Canada, 1989-1993	Income (I) Poverty (P)	RR (5-year)	US I: **1.36**[c] *Both sexes* P: **1.46** *Both sexes* Canada I: 1.07 *Both sexes* P: 1.05 *Both sexes*	
Hussain et al., 2008 [44]	Sweden, 1990-2004	Education	Hazard ratio	**1.23 (1.08-1.41)**	**1.33 (1.12-1.59)**
Le et al., 2008 [51]	US, 1994-2003	Education, income and occupation	Hazard ratio	**1.26 (1.20-1.32)** *Both sexes*	
Meulenbeld et al., 2008 [33]	The Netherlands, 1990-2004	Housing and income	Hazard ratio	1.02 (0.91-1.16)	
Yu et al., 2008 [53]	Australia, 1996-2000	Education and occupation	Relative excess risk of death	**1.14** *Both sexes*	

2

Rectal

Study	Country/period	SES measure	Effect measure	Value	
Auvinen et al., 1995 [42]	Finland 1971-1985	Occupation	RR	**1.54 (1.18-2.00)**	**1.79 (1.35-2.38)**
Dickman et al., 1998 [60]	Finland, 1977-1985	Occupational status	Excess risk of death	38% (28-47) Both sexes	
Zhang-Salomons et al., 2006 [41]	US, 1988-1992; Canada, 1989-1993	Income (I) Poverty (P)	RR (5-year)	US I: **1.61** Both sexes P: **1.57** Both sexes Canada I: 1.20 Both sexes P: 1.00 Both sexes	
Hussain et al., 2008 [44]	Sweden, 1990-2004	Education	Hazard ratio	1.15 (0.96-1.37)	1.20 (0.91-1.59)
Le et al., 2008 [51]	US, 1994-2003	Education, income and occupation	Hazard ratio	**1.33 (1.24-1.42)** Both sexes	
Yu et al., 2008 [53]	Australia, 1996-2000	Education and occupation	Relative excess risk of death	**1.11** Both sexes	

[a] RR: relative risk or risk ratio [brackets represent relative risks calculated from the data].
[b] 95%CI: 95% confidence interval.
[c] Values in bold are statistically significant.

2

Table 4A. Associations between mortality from colorectal cancer and socioeconomic status, US.

Author, year	Study base	Indicators	Type of measurement	Relative risk of dying, low versus high SES	
				Males	**Females**
Colorectal					
Singh et al., 2002 [61]	US, 1950-1998	Education, income, occupation, unemployment, housing, access to phone, households without plumbing	RR^a/100,000 (95% CI)^b 25-64 y: 1950 1998 >65 y: 1950 1990	**0.44 (0.38-0.51)**^{c} **1.26 (1.13-1.39)** **0.40 (0.36-0.45)** **0.78 (0.72-0.83)**	**0.56 (0.49-0.64)** **1.22 (1.07-1.36)** **0.58 (0.53-0.65)** **0.88 (0.83-0.94)** (1992)
Steenland et al., 2002 [62]	US, 1959-1972 and 1982-1996	Education	Mortality rate ratios 1959-1972 1982-1996	0.96 (0.86-1.08) 1.10 (0.97-1.25)	**1.27 (1.12-1.44)** **1.21 (1.01-1.40)**
Singh et al., 2003 [70]	US, 1995-1999	Poverty	Mortality rate/100,000	26.16 versus 25.54 [RR=1.0]^a	17.82 versus 18.14 [RR=1.0]
Steenland et al., 2004 [63]	US, 1984-1997	Occupation and Nam-Powers score^d	RR	**1.21 (1.16-1.27)**	**0.91 (0.86-0.96)**
Albano et al., 2007 [71]	US, 2001	Education	RR	**1.81 (1.73-1.89)**	**1.7 (1.63-1.82)**
Chu et al., 2007 [72]	US, 1990-2000	% below poverty	Mortality rate/ 100,000 1990-1994 1995-2000	27.8 versus 29.7 [RR=0.9] 25.8 versus 25.6 [RR=1.0]	18.8 versus 20.1 [RR=0.9] 17.5 versus 17.9 [RR=1.0]
Kinsey et al., 2008 [73]	US, 1993-2001	Education	RR/100,000 population	1993: **1.5 (1.4-1.6)** 2001: **2.0 (1.9-2.2)**	1993: **1.4 (1.3-1.6)** 2001: **1.9 (1.7-2.1)**

^{a} RR: relative risk or risk ratio [square brackets represent relative risks calculated from the data].
^{b} 95%CI: 95% confidence interval.
^{c} Values in bold are statistically significant.
^{d} Nam Powers score: income and education.

2

Table 4B. Associations between mortality from colon and rectal cancer and socioeconomic status, Europe, Japan and Australia.

Author, year	Study base	Indicators	Type of measurement	Relative risk of dying, low versus high SES	
				Males	**Females**
Colon					
Faggiano et al., 1995 [66]	Italy, 1981	Education	RR[a] (95% CI)[b]	0.62 (0.38-1.02)	**0.37 (0.20-0.69)**[c]
Smith et al., 1996 [65]	Australia, 1987-1991	Income, education, occupation	Odds ratio	1.05 (0.92-1.22)	1.15 (0.99-1.33)
Burnley et al., 1997 [25]	Australia, 1986-1993	Occupation (O) Income (I) Jarman index (J)[d]	Deaths/100,000 (O)		
				1986-1989 20.6 versus 32.1 [RR=0.6][a]	
				1990-1993 29.1 versus 41.8 [RR=0.7]	
			Standardized mortality rate (I)		
				1985-1991 **0.91** versus 1.04	
			Correlation with mortality rates (J)		
				-0.17	
Menvielle et al., 2005 [67]	France, 1975-1990	Education Occupational class	Relative index of inequality	0.9 (0.6-1.6)	1.0 (0.5-1.8)
				1.6 (1.0-2.7)	0.6 (0.3-1.4)
Lawlor et al., 2006 [68]	Sweden, 1970-2001	Parents' occupation	Hazard ratio	0.96 (0.80-1.16)	0.97 (0.80-1.18)
Puigpinós et al., 2009 [69]	Spain, 1992-2003	Education	Relative Index of inequality		
				1992-1994 1.25 (0.94-1.65)	0.94 (0.68-1.31)
				1995-1997 1.09 (0.84-1.41)	1.41 (1.00-1.97)
				1998-2000 1.01 (0.79-1.28)	1.19 (0.88-1.63)
				2001-2003 1.05 (0.82-1.34)	**1.47 (1.06-2.04)**
Rectal					
Faggiano et al., 1995 [66]	Italy, 1981	Education	Mortality rate ratio	0.52 (0.25-1.11)	1.69 (0.82-3.51)

Table 4B continues on next page

Continuation of table 4B

Author, year	Study base	Indicators	Type of measurement	Relative risk of dying, low versus high SES	
				Males	**Females**
Smith et al., 1996 [65]	Australia, 1987-1991	Income, education, occupation	Odds ratio	**0.78 (0.65-0.94)**	0.94 (0.75-1.19)
Menvielle et al., 2005 [67]	France, 1975-1990	Education Occupational class	Relative index of inequality	**2.9 (1.3-6.4)** **3.1 (1.4-6.8)**	1.0 (0.4-2.6) Not available
Puigpinós et al., 2009 [69]	Spain, 1992-2003	Education	Relative Index of inequality		
			1992-1994	1.44 (0.87-2.40)	1.28 (0.67-2.44)
			1995-1997	1.57 (0.96-2.57)	1.80 (0.95-3.43)
			1998-2000	**2.85 (1.76-4.60)**	1.40 (0.77-2.56)
			2001-2003	**1.66 (1.05-2.63)**	0.96 (0.53-1.73)
Colorectal					
Pollock and Vickers, 1997 [74]	UK, 1987-1992	Townsend deprivation score[d]	Standardized mortality ratio	104 versus 100 [RR=1.0] *Both sexes*	
Rosengren and Wilhelmsen, 2004 [75]	Sweden, 1970-1990	Occupation	Mortality/100,000 person years	51 versus 29 [RR=1.8]	
Shaw et al., 2006 [76]	Australia, 1981-1999	Income Education	Relative index of inequality	**1.72 (1.27-2.33)** 1.39 (0.94-2.06)	1.41 (1.0-1.98) 1.28 (0.95-1.74)
Menvielle et al., 2007 [64]	France, 1968-1996	Occupational class	Relative index of inequality		
			1968-1974	**2.53 (1.08-5.92)**	1.28 (0.67-2.44)
			1975-1981	**3.13 (1.29-7.57)**	1.80 (0.95-3.43)
			1982-1988	2.07 (0.81-5.28)	1.40 (0.77-2.56)
			1990-1996	**2.48 (1.06-5.82)**	0.96 (0.53-1.73)

2

Study	Location/period	SES indicator	Measure		
Ezendam et al., 2008 [77]	Poland: 2001-2003 Lithuania: 2000-2002 Estonia 1998-2002 Finland: 1990-2000 Sweden: 1990-2000	Education	Relative index of inequality	Poland **1.19 (1.11-1.28)** Lithuania **0.66 (0.52-0.83)** Estonia 0.91 (0.70-1.19) Finland 0.94 (0.81-1.09) Sweden **1.10 (1.01-1.20)**	Poland **1.12 (1.03-1.21)** Lithuania 1.16 (0.90-1.49) Estonia 0.83 (0.64-1.08) Finland 1.03 (0.88-1.21) Sweden **1.29 (1.17-1.41)**
Menvielle et al., 2008 [8]	12 European regions, 1990s	Education	Relative index of inequality (RII)	RII>1.0 in 9 out of 12 regions, range: 0.92 (0.69-1.24) to 1.58 (1.06-2.34)	RII>1.0 in 10 out of 12 regions, range: 0.77 (0.44-1.33) to 1.36 (1.00-1.84)
Nishi et al., 2008 [78]	Japan, 1980-2003	Education	Hazard ratio	1.14 (0.72-1.79)	0.71 (0.31-1.67)

[a] RR: relative risk or risk ratio [brackets represent relative risks calculated from the data].
[b] 95%CI: 95% confidence interval.
[c] Values in bold are statistically significant.
[d] Jarman index: elderly living alone, one parent families, unskilled, unemployment, overcrowding; Townsend deprivation score: unemployment, owning car, owning house, overcrowding.

DISCUSSION

A higher incidence of colorectal cancer was observed among low SES groups compared to high SES groups in the US and Canada, but not in Europe, where higher SES classes were at increased risk. Treatment, survival and mortality all showed less favourable results for people with a lower socioeconomic status: patients with a low SES had less chance of receiving (neo)adjuvant chemotherapy, had worse survival and mortality rates thus were highest in the lowest SES groups.

A high colon cancer incidence among individuals with a high SES had been demonstrated previously in articles published up to 1995.[7] We have now confirmed the higher incidence of both colon and rectal cancer among those with a high SES in Europe, Australia and South-Korea. In the US and Canada an inverse association was found with a lower incidence among patients with a high SES, although the results from the relatively small number of articles suggest that the incidence disparities in the US and Canada were narrowing over time. SEER data revealed no consistent pattern of poverty areas and CRC incidence from 1975 to 1999 but the inequalities decreased over time. Despite a previous report of this intercontinental discrepancy in CRC incidence,[7] exact causes remain unclear. Several mechanisms may play a role. Firstly, lifestyle (risk) factors may be related to SES in different ways and thereby affect incidence, e.g. physical activity and diet. As far as we know, there are no international studies that show different SES gradients for lifestyle factors between different continents.

Secondly, screening participation strongly vary across the continents. The compliance for colonoscopy in the German national screening program among inhabitants aged 55 and older was only 12%.[79] In contrast, 51% of the US population of 50 years and older underwent opportunistic endoscopy from 1995 to 2004.[80] This may have resulted in a decreasing incidence due to removal at a precancerous stage (i.e. polyps). This effect may be observed predominantly among those with a high SES, because higher screening rates were found for the higher social classes.[61, 67, 70, 71, 74, 81, 82] However, the use of screening may also result temporarily in a higher incidence. Therefore, the introduction of opportunistic screening (and thereby early detection) has possibly contributed to the changing patterns in incidence that were observed in the US and Canada.

Socioeconomic inequalities in treatment may result from differences in access to and use of medical care, as well as the quality and type of care.[61, 66, 71, 74, 81-86] A high SES was associated with earlier stage at diagnosis, largely resulting from greater health awareness and higher screening participation.[82, 87-89] Since treatment is also determined by stage at diagnosis, socioeconomic inequalities may arise in non stage-specific analyses of treatment disparities. In addition, the presence and severity of co-morbidity may influence treatment. Since a SES-gradient for the presence of co-morbidity has been observed (Louwman and colleagues, 2009), treatment may be influenced by SES through other concomitant diseases.

Survival rates were consistently worse among patients with a low SES, which has been demonstrated previously in a review including articles published up to 1996.[90] Suggested causes for the socioeconomic gradient in survival are related to stage at diagnosis, number of co-morbidities and treatment. The precise impact of these factors is difficult to assess,

because data from the studies included are often adjusted for different combinations of factors (see Supplementary material for comprehensive overview). One study reported that stage at diagnosis explained part of the survival inequalities,[70] while other studies reported a significant association with SES after adjustment for stage, co-morbidity and/or therapy.[43, 45, 46] Recently, improved survival from colon cancer was found to be related to better access to optimal treatment for those with a high SES;[56] this effect was remained after adjustment for stage at diagnosis in another study.[91] Co-morbidity and, to a lesser extent, lifestyle characteristics explained most of the excess risk of 30-day postoperative death among those with a low SES, whereas treatment and disease factors explained only a negligible part.[49, 92]

Socioeconomic gradients may change due to the upcoming programs for screening in Europe and Australia. Incidence will first rise and then decrease after several years of screening. Given the low incidence rates among low SES groups before the screening has started, incidence rates may increase among these persons. Detection will be advanced by screening and is indeed associated with earlier stage at diagnosis.[93] Subsequently survival will improve and lower mortality from colorectal cancer is expected.[94] Thus, the introduction of screening may improve the disadvantages for people with a low SES and may result in a narrowing of the socioeconomic gap in detection and outcomes of CRC. However, this is only the case if all SES groups participate equally in screening, although higher attendance rates have been observed among those with a high SES.[95] If uptake is not distributed equally, screening may even result in widening of the socioeconomic inequalities. Therefore, ensuring high uptake is very important, especially among those with a low SES. It is important to address barriers to CRC screening, i.e. lack of trust in doctors, lack of symptoms, lack of doctor's recommendation to participate, and fatalistic views of cancer.[96]

To conclude, we observed a quite consistent trend favouring individuals with a high SES compared to those with a low SES that still remains in terms of treatment, survival and thus also mortality. We did not find evidence that the low/high SES gradients for treatment chosen and outcome are decreasing. To meet increasing inequalities in colorectal cancer mortality from CRC in Europe for people with a low SES and to make mass screening successful, a high participation rate needs to be realised of low SES people in the, soon starting screening program.

ACKNOWLEDGEMENT

APPENDIX A. SUPPLEMENTARY MATERIAL
Supplementary data associated with this article can be found in the online version, at doi: 10.106/j.ejca.2010.04.026.

REFERENCES

1. Weiderpass, E. & Pukkala, E. Time trends in socioeconomic differences in incidence rates of cancers of gastro-intestinal tract in Finland. *BMC Gastroenterol* 6, 41 (2006).

2. van Loon, A.J., van den Brandt, P.A. & Golbohm, R.A. Socioeconomic status and colon cancer incidence: a prospective cohort study. *Br J Cancer* 71, 882-7 (1995).

3. Auvinen, A. Social class and colon cancer survival in Finland. *Cancer* 70, 402-9 (1992).

4. Coleman, M.P., Babb, P., Sloggett, A., Quinn, M. & De Stavola, B. Socioeconomic inequalities in cancer survival in England and Wales. *Cancer* 91, 208-16 (2001).

5. Dalton, S.O., Schuz, J., Engholm, G., Johansen, C., Kjaer, S.K., Steding-Jessen, M., Storm, H.H. & Olsen, J.H. Social inequality in incidence of and survival from cancer in a population-based study in Denmark, 1994-2003: Summary of findings. *Eur J Cancer* 44, 2074-85 (2008).

6. Schrijvers, C.T. & Mackenbach, J.P. Cancer patient survival by socioeconomic status in seven countries: a review for six common cancer sites [corrected]. *J Epidemiol Community Health* 48, 441-6 (1994).

7. Faggiano, F., Partanen, T., Kogevinas, M. & Boffetta, P. Socioeconomic differences in cancer incidence and mortality. *IARC Sci Publ*, 65-176 (1997).

8. Menvielle, G., Kunst, A.E., Stirbu, I., Strand, B.H., Borrell, C., Regidor, E., Leclerc, A., Esnaola, S., Bopp, M., Lundberg, O., Artnik, B., Costa, G., Deboosere, P., Martikainen, P. & Mackenbach, J.P. Educational differences in cancer mortality among women and men: a gender pattern that differs across Europe. *Br J Cancer* 98, 1012-9 (2008).

9. Mackillop, W.J., Zhang-Salomons, J., Boyd, C.J. & Groome, P.A. Associations between community income and cancer incidence in Canada and the United States. *Cancer* 89, 901-12 (2000).

10. Krieger, N., Quesenberry, C., Jr., Peng, T., Horn-Ross, P., Stewart, S., Brown, S., Swallen, K., Guillermo, T., Suh, D., Alvarez-Martinez, L. & Ward, F. Social class, race/ethnicity, and incidence of breast, cervix, colon, lung, and prostate cancer among Asian, Black, Hispanic, and White residents of the San Francisco Bay Area, 1988-92 (United States). *Cancer Causes Control* 10, 525-37 (1999).

11. Gorey, K.M., Holowaty, E.J., Laukkanen, E., Fehringer, G. & Richter, N.L. Association between socioeconomic status and cancer incidence in Toronto, Ontario: possible confounding of cancer mortality by incidence and survival. *Cancer Prev Control* 2, 236-41 (1998).

12. Gorey, K.M. & Vena, J.E. The association of near poverty status with cancer incidence among black and white adults. *J Community Health* 20, 359-66 (1995).

13. Wu, X., Cokkinides, V., Chen, V.W., Nadel, M., Ren, Y., Martin, J. & Ellison, G.L. Associations of subsite-specific colorectal cancer incidence rates and stage of disease at diagnosis with county-level poverty, by race and sex. *Cancer* 107, 1121-7 (2006).

14. Clegg, L.X., Reichman, M.E., Miller, B.A., Hankey, B.F., Singh, G.K., Lin, Y.D., Goodman, M.T., Lynch, C.F., Schwartz, S.M., Chen, V.W., Bernstein, L., Gomez, S.L., Graff, J.J., Lin, C.C., Johnson, N.J. & Edwards, B.K. Impact of socioeconomic status on cancer incidence and stage at diagnosis: selected findings from the surveillance, epidemiology, and end results: National Longitudinal Mortality Study. *Cancer Causes Control* 20, 417-35 (2009).

15. Mouw, T., Koster, A., Wright, M.E., Blank, M.M., Moore, S.C., Hollenbeck, A. & Schatzkin, A. Education and risk of cancer in a large cohort of men and women in the United States. *PLoS One* 3, e3639 (2008).

16. Shipp, M.P., Desmond, R., Accortt, N., Wilson, R.J., Fouad, M. & Eloubeidi, M.A. Population-based study of the geographic variation in colon cancer incidence in Alabama: relationship to socioeconomic status indicators and physician density. *South Med J* 98, 1076-82 (2005).

17. Tavani, A., Fioretti, F., Franceschi, S., Gallus, S., Negri, E., Montella, M., Conti, E. & La Vecchia, C. Education, socioeconomic status and risk of cancer of the colon and rectum. *Int J Epidemiol* 28, 380-5 (1999).

18. Pisa, F.E., Barbone, F., Montella, M., Talamini, R., La Vecchia, C. & Franceschi, S. Migration, socio-economic status and the risk of colorectal cancer in Italy. *Eur J Cancer Prev* 9, 409-16 (2000).

19. Hemminki, K. & Li, X. Level of education and the risk of cancer in Sweden. *Cancer Epidemiol Biomarkers Prev* 12, 796-802 (2003).

20. Braaten, T., Weiderpass, E., Kumle, M. & Lund, E. Explaining the socioeconomic variation in cancer risk in the Norwegian Women and Cancer Study. *Cancer Epidemiol Biomarkers Prev* 14, 2591-7 (2005).

21. Spadea, T., D'Errico, A., Demaria, M., Faggiano, F., Pasian, S., Zanetti, R., Rosso, S., Vicari, P. & Costa, G. Educational inequalities in cancer incidence in Turin, Italy. *Eur J Cancer Prev* 18, 169-78 (2009).

22. Marshall, B., Chevalier, A., Garillon, C., Goldberg, M. & Coing, F. Socioeconomic status, social mobility and cancer occurrence during working life: a case-control study among French electricity and gas workers. *Cancer Causes Control* 10, 495-502 (1999).

23. Egeberg, R., Halkjaer, J., Rottmann, N., Hansen, L. & Holten, I. Social inequality and incidence of and survival from cancers of the colon and rectum in a population-based study in Denmark, 1994-2003. *Eur J Cancer* 44, 1978-88 (2008).

24. Kim, C.W., Lee, S.Y. & Moon, O.R. Inequalities in cancer incidence and mortality across income groups and policy implications in South Korea. *Public Health* 122, 229-36 (2008).

25. Burnley, I.H. Disadvantage and male cancer incidence and mortality in New South Wales 1985-1993. *Soc Sci Med* 45, 465-76 (1997).

26. Pearce, N. & Bethwaite, P. Social class and male cancer mortality in New Zealand, 1984-7. *N Z Med J* 110, 200-2 (1997).

27. Bouchardy, C., Schuler, G., Minder, C., Hotz, P., Bousquet, A., Levi, F., Fisch, T., Torhorst, J. & Raymond, L. Cancer risk by occupation and socioeconomic group among men--a study by the Association of Swiss Cancer Registries. *Scand J Work Environ Health* 28 Suppl 1, 1-88 (2002).

28. Roetzheim, R.G., Pal, N., Gonzalez, E.C., Ferrante, J.M., Van Durme, D.J. & Krischer, J.P. Effects of health insurance and race on colorectal cancer treatments and outcomes. *Am J Public Health* 90, 1746-54 (2000).

29. McGory, M.L., Zingmond, D.S., Sekeris, E., Bastani, R. & Ko, C.Y. A patient's race/ethnicity does not explain the underuse of appropriate adjuvant therapy in colorectal cancer. *Dis Colon Rectum* 49, 319-29 (2006).

30. Campbell, N.C., Elliott, A.M., Sharp, L., Ritchie, L.D., Cassidy, J. & Little, J. Impact of deprivation and rural residence on treatment of colorectal and lung cancer. *Br J Cancer* 87, 585-90 (2002).

31. Byers, T.E., Wolf, H.J., Bauer, K.R., Bolick-Aldrich, S., Chen, V.W., Finch, J.L., Fulton, J.P., Schymura, M.J., Shen, T., Van Heest, S. & Yin, X. The impact of socioeconomic status on survival after cancer in the United States : findings from the National Program of Cancer Registries Patterns of Care Study. *Cancer* 113, 582-91 (2008).

32. Harris, A.R., Bowley, D.M., Stannard, A., Kurrimboccus, S., Geh, J.I. & Karandikar, S. Socioeconomic deprivation adversely affects survival of patients with rectal cancer. *Br J Surg* 96, 763-8 (2009).

33. Meulenbeld, H.J., van Steenbergen, L.N., Janssen-Heijnen, M.L., Lemmens, V.E. & Creemers, G.J. Significant improvement in survival of patients presenting with metastatic colon cancer in the south of The Netherlands from 1990 to 2004. *Ann Oncol* 19, 1600-4 (2008).

34. Lemmens, V.E., van Halteren, A.H., Janssen-Heijnen, M.L., Vreugdenhil, G., Repelaer van Driel, O.J. & Coebergh, J.W. Adjuvant treatment for elderly patients with stage III colon cancer in the southern Netherlands is affected by socioeconomic status, gender, and comorbidity. *Ann Oncol* 16, 767-72 (2005).

35. VanEenwyk, J., Campo, J.S. & Ossiander, E.M. Socioeconomic and demographic disparities in treatment for carcinomas of the colon and rectum. *Cancer* 95, 39-46 (2002).

36. Schrag, D., Gelfand, S.E., Bach, P.B., Guillem, J., Minsky, B.D. & Begg, C.B. Who gets adjuvant treatment for stage II and III rectal cancer? Insight from surveillance, epidemiology, and end results--Medicare. *J Clin Oncol* 19, 3712-8 (2001).

37. Ayanian, J.Z., Zaslavsky, A.M., Fuchs, C.S., Guadagnoli, E., Creech, C.M., Cress, R.D., O'Connor, L.C., West, D.W., Allen, M.E., Wolf, R.E. & Wright, W.E. Use of adjuvant chemotherapy and radiation therapy for colorectal cancer in a population-based cohort. *J Clin Oncol* 21, 1293-300 (2003).

38. Tilney, H.S., Heriot, A.G., Purkayastha, S., Antoniou, A., Aylin, P., Darzi, A.W. & Tekkis, P.P. A national perspective on the decline of abdominoperineal resection for rectal cancer. *Ann Surg* 247, 77-84 (2008).

39. Tilney, H., Lovegrove, R.E., Smith, J.J., Thompson, M.R. & Tekkis, P.P. The National Bowel Cancer Project: social deprivation is an independent predictor of nonrestorative rectal cancer surgery. *Dis Colon Rectum* 52, 1046-53 (2009).

40. Gorey, K.M., Holoware, E.J., Fehringer, G., Laukkanen, E., Moskowitz, A., Webster, D.J. & Richter, N.L. An international comparison of cancer survival: Toronto, Ontario, and Detroit, Michigan, metropolitan areas. *Am J Public Health* 87, 1156-63 (1997).

41. Zhang-Salomons, J., Qian, H., Holowaty, E. & Mackillop, W.J. Associations between socioeconomic status and cancer survival: choice of SES indicator may affect results. *Ann Epidemiol* 16, 521-8 (2006).

42. Auvinen, A., Karjalainen, S. & Pukkala, E. Social class and cancer patient survival in Finland. *Am J Epidemiol* 142, 1089-102 (1995).

43. Polednak, A.P. Poverty, comorbidity, and survival of colorectal cancer patients diagnosed in Connecticut. *J Health Care Poor Underserved* 12, 302-10 (2001).

44. Hussain, S.K., Lenner, P., Sundquist, J. & Hemminki, K. Influence of education level on cancer survival in Sweden. *Ann Oncol* 19, 156-62 (2008).

45. Du, X.L., Fang, S., Vernon, S.W., El-Serag, H., Shih, Y.T., Davila, J. & Rasmus, M.L. Racial disparities and socioeconomic status in association with survival in a large population-based cohort of elderly patients with colon cancer. *Cancer* 110, 660-9 (2007).

46. Desoubeaux, N., Herbert, C., Launoy, G., Maurel, J. & Gignoux, M. Social environment and prognosis of colorectal cancer patients: a French population-based study. *Int J Cancer* 73, 317-22 (1997).

47. Gomez, S.L., O'Malley C, D., Stroup, A., Shema, S.J. & Satariano, W.A. Longitudinal, population-based study of racial/ethnic differences in colorectal cancer survival: Impact of neighborhood socioeconomic status, treatment and comorbidity. *BMC Cancer* 7, 193 (2007).

48. Smith, J.J., Tilney, H.S., Heriot, A.G., Darzi, A.W., Forbes, H., Thompson, M.R., Stamatakis, J.D. & Tekkis, P.P. Social deprivation and outcomes in colorectal cancer. *Br J Surg* 93, 1123-31 (2006).

49. Frederiksen, B.L., Osler, M., Harling, H., Ladelund, S. & Jorgensen, T. The impact of socioeconomic factors on 30-day mortality following elective colorectal cancer surgery: a nationwide study. *Eur J Cancer* 45, 1248-56 (2009).

50. Kelsall, H.L., Baglietto, L., Muller, D., Haydon, A.M., English, D.R. & Giles, G.G. The effect of socioeconomic status on survival from colorectal cancer in the Melbourne Collaborative Cohort Study. *Soc Sci Med* 68, 290-7 (2009).

51. Le, H., Ziogas, A., Lipkin, S.M. & Zell, J.A. Effects of socioeconomic status and treatment disparities in colorectal cancer survival. *Cancer Epidemiol Biomarkers Prev* 17, 1950-62 (2008).

52. Robbins, A.S., Pavluck, A.L., Fedewa, S.A., Chen, A.Y. & Ward, E.M. Insurance status, comorbidity level, and survival among colorectal cancer patients age 18 to 64 years in the National Cancer Data Base from 2003 to 2005. *J Clin Oncol* 27, 3627-33 (2009).

53. Yu, X.Q., O'Connell, D.L., Gibberd, R.W. & Armstrong, B.K. Assessing the impact of socio-economic status on cancer survival in New South Wales, Australia 1996-2001. *Cancer Causes Control* 19, 1383-90 (2008).

54. Groome, P.A., Schulze, K.M., Keller, S. & Mackillop, W.J. Demographic differences between cancer survivors and those who die quickly of their disease. *Clin Oncol (R Coll Radiol)* 20, 647-56 (2008).

55. Mitry, E., Rachet, B., Quinn, M.J., Cooper, N. & Coleman, M.P. Survival from cancer of the rectum in England and Wales up to 2001. *Br J Cancer* 99 Suppl 1, S30-2 (2008).

56. Mitry, E., Rachet, B., Quinn, M.J., Cooper, N. & Coleman, M.P. Survival from cancer of the colon in England and Wales up to 2001. *Br J Cancer* 99 Suppl 1, S26-9 (2008).

57. Hall, S.E., Holman, C.D., Platell, C., Sheiner, H., Threlfall, T. & Semmens, J. Colorectal cancer surgical care and survival: do private health insurance, socioeconomic and locational status make a difference? *ANZ J Surg* 75, 929-35 (2005).

58. Vulto, J.C., Louwman, W.J., Lybeert, M.L., Poortmans, P.M., Rutten, H.J., Brenninkmeijer, S.J. & Coebergh, J.W. A population-based study of radiotherapy in a cohort of patients with rectal cancer diagnosed between 1996 and 2000. *Eur J Surg Oncol* 33, 993-7 (2007).

59. Shack, L.G., Rachet, B., Brewster, D.H. & Coleman, M.P. Socioeconomic inequalities in cancer survival in Scotland 1986-2000. *Br J Cancer* 97, 999-1004 (2007).

60. Dickman, P.W., Auvinen, A., Voutilainen, E.T. & Hakulinen, T. Measuring social class differences in cancer patient survival: is it necessary to control for social class differences in general population mortality? A Finnish population-based study. *J Epidemiol Community Health* 52, 727-34 (1998).

61. Singh, G.K., Miller, B.A. & Hankey, B.F. Changing area socioeconomic patterns in US cancer mortality, 1950-1998: Part II--Lung and colorectal cancers. *J Natl Cancer Inst* 94, 916-25 (2002).

62. Steenland, K., Henley, J. & Thun, M. All-cause and cause-specific death rates by educational status for two million people in two American Cancer Society cohorts, 1959-1996. *Am J Epidemiol* 156, 11-21 (2002).

63. Steenland, K., Hu, S. & Walker, J. All-cause and cause-specific mortality by socioeconomic status among employed persons in 27 US states, 1984-1997. *Am J Public Health* 94, 1037-42 (2004).

64. Menvielle, G., Leclerc, A., Chastang, J.F., Melchior, M. & Luce, D. Changes in socioeconomic inequalities in cancer mortality rates among French men between 1968 and 1996. *Am J Public Health* 97, 2082-7 (2007).

65. Smith, D., Taylor, R. & Coates, M. Socioeconomic differentials in cancer incidence and mortality in urban New South Wales, 1987-1991. *Aust N Z J Public Health* 20, 129-37 (1996).

66. Faggiano, F., Lemma, P., Costa, G., Gnavi, R. & Pagnanelli, F. Cancer mortality by educational level in Italy. *Cancer Causes Control* 6, 311-20 (1995).

67. Menvielle, G., Luce, D., Geoffroy-Perez, B., Chastang, J.F. & Leclerc, A. Social inequalities and cancer mortality in France, 1975-1990. *Cancer Causes Control* 16, 501-13 (2005).

68. Lawlor, D.A., Sterne, J.A., Tynelius, P., Davey Smith, G. & Rasmussen, F. Association of childhood socioeconomic position with cause-specific mortality in a prospective record linkage study of 1,839,384 individuals. *Am J Epidemiol* 164, 907-15 (2006).

69. Puigpinos, R., Borrell, C., Antunes, J.L., Azlor, E., Pasarin, M.I., Serral, G., Pons-Vigues, M., Rodriguez-Sanz, M. & Fernandez, E. Trends in socioeconomic inequalities in cancer mortality in Barcelona: 1992-2003. *BMC Public Health* 9, 35 (2009).

70. Singh, G.K., Miller, B.A., Hankey, B.F. & Edwards, B.K. in Area Socioeconomic Variations in US Cancer Incidence, Mortality, Stage, Treatment, and Survival, 1975-1999 (MD: National Cancer Institute, Bethesda, 2003).

71. Albano, J.D., Ward, E., Jemal, A., Anderson, R., Cokkinides, V.E., Murray, T., Henley, J., Liff, J. & Thun, M.J. Cancer mortality in the United States by education level and race. *J Natl Cancer Inst* 99, 1384-94 (2007).

72. Chu, K.C., Miller, B.A. & Springfield, S.A. Measures of racial/ethnic health disparities in cancer mortality rates and the influence of socioeconomic status. *J Natl Med Assoc* 99, 1092-100, 1102-4 (2007).

73. Kinsey, T., Jemal, A., Liff, J., Ward, E. & Thun, M. Secular trends in mortality from common cancers in the United States by educational attainment, 1993-2001. *J Natl Cancer Inst* 100, 1003-12 (2008).

74. Pollock, A.M. & Vickers, N. Breast, lung and colorectal cancer incidence and survival in South Thames Region, 1987-1992: the effect of social deprivation. *J Public Health Med* 19, 288-94 (1997).

75. Rosengren, A. & Wilhelmsen, L. Cancer incidence, mortality from cancer and survival in men of different occupational classes. *Eur J Epidemiol* 19, 533-40 (2004).

76. Shaw, C., Blakely, T., Sarfati, D., Fawcett, J. & Peace, J. Trends in colorectal cancer mortality by ethnicity and socio-economic position in New Zealand, 1981-99: one country, many stories. *Aust N Z J Public Health* 30, 64-70 (2006).

77. Ezendam, N.P., Stirbu, I., Leinsalu, M., Lundberg, O., Kalediene, R., Wojtyniak, B., Martikainen, P., Mackenbach, J. & Kunst, A. Educational inequalities in cancer mortality differ greatly between countries around the Baltic Sea. *Eur J Cancer* 44, 454-64 (2008).

78. Nishi, N., Sugiyama, H., Hsu, W.L., Soda, M., Kasagi, F., Mabuchi, K. & Kodama, K. Differences in mortality and incidence for major sites of cancer by education level in a Japanese population. *Ann Epidemiol* 18, 584-91 (2008).

2

79. West, N.J., Boustiere, C., Fischbach, W., Parente, F. & Leicester, R.J. Colorectal cancer screening in Europe: differences in approach; similar barriers to overcome. *Int J Colorectal Dis* 24, 731-40 (2009).

80. Centers for Disease Control and Prevention. Increased use of colorectal cancer tests - United States, 2002 and 2004. *MMWR* 55, 308-311 (2006).

81. Woods, L.M., Rachet, B. & Coleman, M.P. Origins of socio-economic inequalities in cancer survival: a review. *Ann Oncol* 17, 5-19 (2006).

82. Palmer, R.C. & Schneider, E.C. Social disparities across the continuum of colorectal cancer: a systematic review. *Cancer Causes Control* 16, 55-61 (2005).

83. Ciccone, G., Prastaro, C., Ivaldi, C., Giacometti, R. & Vineis, P. Access to hospital care, clinical stage and survival from colorectal cancer according to socio-economic status. *Ann Oncol* 11, 1201-4 (2000).

84. Munro, A.J. & Bentley, A.H. Deprivation, comorbidity and survival in a cohort of patients with colorectal cancer. *Eur J Cancer Care (Engl)* 13, 254-62 (2004).

85. Boyd, C., Zhang-Salomons, J.Y., Groome, P.A. & Mackillop, W.J. Associations between community income and cancer survival in Ontario, Canada, and the United States. *J Clin Oncol* 17, 2244-55 (1999).

86. Lyratzopoulos, G., Sheridan, G.F., Michie, H.R., McElduff, P. & Hobbiss, J.H. Absence of socioeconomic variation in survival from colorectal cancer in patients receiving surgical treatment in one health district: cohort study. *Colorectal Dis* 6, 512-7 (2004).

87. Parikh-Patel, A., Bates, J.H. & Campleman, S. Colorectal cancer stage at diagnosis by socioeconomic and urban/rural status in California, 1988-2000. *Cancer* 107, 1189-95 (2006).

88. Schwartz, K.L., Crossley-May, H., Vigneau, F.D., Brown, K. & Banerjee, M. Race, socioeconomic status and stage at diagnosis for five common malignancies. *Cancer Causes Control* 14, 761-6 (2003).

89. Ionescu, M.V., Carey, F., Tait, I.S. & Steele, R.J. Socioeconomic status and stage at presentation of colorectal cancer. *Lancet* 352, 1439 (1998).

90. Kogevinas, M. & Porta, M. Socioeconomic differences in cancer survival: a review of the evidence. *IARC Sci Publ*, 177-206 (1997).

91. Schrijvers, C.T., Mackenbach, J.P., Lutz, J.M., Quinn, M.J. & Coleman, M.P. Deprivation, stage at diagnosis and cancer survival. *Int J Cancer* 63, 324-9 (1995).

92. De Marco, M.F., Janssen-Heijnen, M.L., van der Heijden, L.H. & Coebergh, J.W. Comorbidity and colorectal cancer according to subsite and stage: a population-based study. *Eur J Cancer* 36, 95-9 (2000).

93. Hewitson, P., Glasziou, P., Watson, E., Towler, B. & Irwig, L. Cochrane systematic review of colorectal cancer screening using the fecal occult blood test (hemoccult): an update. *Am J Gastroenterol* 103, 1541-9 (2008).

94. Costantini, A.S., Martini, A., Puliti, D., Ciatto, S., Castiglione, G., Grazzini, G. & Zappa, M. Colorectal cancer mortality in two areas of Tuscany with different screening exposures. *J Natl Cancer Inst* 100, 1818-21 (2008).

95. Pornet, C., Dejardin, O., Morlais, F., Bouvier, V. & Launoy, G. Socioeconomic Determinants for Compliance to Colorectal Cancer Screening. A Multilevel Analysis. *J Epidemiol Community Health* 64, 318-24 (2010).

96. Lasser, K.E., Ayanian, J.Z., Fletcher, R.H. & Good, M.J. Barriers to colorectal cancer screening in community health centers: a qualitative study. *BMC Fam Pract* 9, 15 (2008).

Chapter 3

Cancer risk and detection

DECISION
ROLE
CURATIVE
SINCE 1990
data
RECOGNISING
OUTCOME
BRACHYTHERAPY
DETERMINANTS
CATEGORY
HOUSING
health seeking behaviour
METASTASIS
COVERAGE
INTERVAL CANCER
CHARLSON
CONTRIBUTION
RADIOTHERAPY
GP
estimated
staging
axillary
EAPC
material resources
DISCUSS
socioeconomic position
annual
percent
change
SMOKING
statistical
STUDIES
Comprehensive Cancer Centre South
HOSPITAL
staging
lifestyle
central nervous system
intelligence
education
hazard
ratio
Eindhoven Cancer Registry
dementia
stage
HORMONAL THERAPY
VISITS
ATTENDANCE
EXPLANATION
RISK FACTORS
diagnostics
distribution
DIAGNOSIS
SEP
SOCIAL SUPPORT
HYPERTENSION
mastectomy
CARDIOVASCULAR DISEASE
ADVANCED
FEAR
colorectal
therapy
HIGH
MENTAL
MAMMOGRAPHY
UPBRINGING
ENVIRONMENT
incidence
prostatectomy
p-value
QUESTIONNAIRE
HEALTH BEHAVIOUR
SF-36
GLOBE
PHYSICAL
SOCIOEC
NEIGHBOURHOOD
LOW
socioeconomic status
occupation
EXPOSURE
value of housing
physical activity
comorbidities
INVITATION
ALCOHOL CONSUMPTION
INTERMEDIATE
REVIEW
colorectal
cancer
CHEMORADIATION
TUBERCULOSIS
concomitant disease
screening
VARIATION
logistic
ACCESS TO CARE
INVASIVE
CONTACTS
gap
LOCALISED
regression
CONSULTATION
ASSETS
numbers
PSA
WORK
SCREEN-DETECTED TUMOUR
income
percentages
THE NETHERLANDS
HEALTH INSURANCE
health awareness
HOUSEHOLD
search
DETECTIO

Chapter 3.1

Reduction of socioeconomic inequality in cancer incidence in the South of the Netherlands during 1996-2008

M.J. Aarts, M.A. van der Aa, J.W.W. Coebergh, W.J. Louwman

ABSTRACT

Background

Cancer incidence varies according to socioeconomic status (SES) and time trends. SES category may thus point to differential effects of lifestyle changes but early detection may also affect this.

Patients and Methods

We studied patients diagnosed in 1996-2008 and registered in the South Netherlands Cancer registry. Incidence rates and estimated annual percent changes were calculated according to SES category, age group (25-44, 45-64 and ≥65) and sex.

Results

People with a low SES exhibited elevated incidence rates of cancer of the head and neck, upper airways (both sexes), gastro-intestinal tract, squamous cell skin cancer, breast (≥65) and all female genital, bladder, kidney and mature B-cells (all in females only), whereas prostate cancer, basal cell skin cancer (BCC) and melanoma (both except in older females) were most common among those with a high SES. Due to the greater increase in prostate cancer and melanoma in high SES males and the larger reduction of lung cancer in low SES males, incidence of all cancers combined became more elevated among males of ≥45 years with a high and intermediate SES, and approached rates for low SES men aged 45-64. In spite of more marked increases in the incidence of colon, rectal and lung cancer in high SES women, the incidence of all cancers combined remained highest for low SES women of ≥45 years. However, at age 25-44 years, the highest incidence of cancer of the breast and melanoma was observed among high SES females. During 1996-2008 inequalities increased unfavourably among higher SES people for prostate cancer, BCC (except in older women) and melanoma (at middle age), while decreasing favourably among low SES people for cancers of the oesophagus, stomach, pancreas and kidney (both in females only), breast (≥65 years), corpus uteri and ovary.

Conclusions

Although those with a low SES exhibited the highest incidence rates of the most common cancers, higher risks were observed among those with high SES for melanoma and BCC (both except older females), and for prostate and breast (young females) cancer. Altogether this might also have contributed to the recent higher cancer awareness in Dutch society which is usually promoted more by patients of high SES and those who know or surround them.

3.1

INTRODUCTION

More or less consistent excess risks for tobacco-related and other lifestyle-related cancers (i.e. respiratory cancers, cancers of the head and neck and upper gastro-intestinal (GI) tract, liver and cervix uteri) have been reported for people from the lower social strata, while their risks for cancers of the colon, breast and ovary and malignant melanoma are generally reduced.[1-12]

Studies of time trends in cancer incidence according to socioeconomic class in Finland from 1971 to 1995 showed decreases in relative differences among socioeconomic status (SES) categories, (albeit not quantified) for cancers of the colon, female breast, vulva, vagina, and testis, while such inequalities remained for cancers of the upper GI tract and rectum, liver, gallbladder and pancreas, female genital organs, prostate and penis.[13-15] Socioeconomic inequalities in oral cancer have perhaps been declining over recent decades in a few countries.[16] In contrast, older data from England and Wales suggested such inequalities to be increasing among males for all cancers combined and for cancers of the lung, larynx and stomach, and among females for all cancers combined and for cervical cancer.[1] More recently, increased inequalities from 1995 to 2004 were reported for melanoma, prostate and female breast and kidney cancers.[12]

Although health care in the Netherlands is accessible for everyone, also through obligatory health insurance since 2006 (and social insurance for the 70% with a lower income before then) and through broad availability of well trained general practitioners (one per 2000 people on average), social inequalities in cancer incidence have been reported for cancers of the cervix, lung, stomach, oropharynx, oesophagus and breast, being more common in people with a low SES,[17-20] contrasting breast[20] and colon cancer, albeit inconsistently.[21]

None of the Dutch studies was population-based and took information into account on SES of the complete population, which is typically known in Denmark, Sweden and Finland. Without this information, incidence rates of a specific SES group could not be calculated, and reporting proportions of patients with a specific SES group does not necessarily reflect true incidence. The SES of the population according to postal code has recently been made available by Statistics Netherlands and thus enable correct analyses of incidence according to SES. In addition, these previous studies were conducted on a selected sample and were thus not representative of a geographical area. No studies have yet been done of time trends in the association of incidence and SES in the Netherlands, which are likely to be affected by the various mass screening campaigns.[22] This information is also useful to understand potential changes in awareness of cancer, usually elevated in people of higher SES, and to assess the need for specific preventive interventions. Therefore we aimed to detect patterns in time trends in the incidence of the major cancers according to SES in the South of the Netherlands.

PATIENTS AND METHODS
Study population
The South Netherlands or Eindhoven Cancer Registry records data on all patients newly diagnosed with invasive cancer in the south-eastern part of the Netherlands, an area with 2.4 million inhabitants (about 15% of the Dutch population) and served by about 10 general

hospitals and 2 large radiotherapy institutes. Trained registry personnel actively collect data on diagnosis, staging, treatment and survival from the medical records after notification by pathologists and medical registration offices. We included all patients newly diagnosed between 1996 and 2008 with invasive cancers including those amenable to lifestyle,[23-25] i.e. cancers of the oesophagus (including cardia of the stomach); larynx; oropharynx; urinary bladder; lung; corpus uteri; kidney; stomach (non-cardia); colon; rectum; pancreas; breast; cervix uteri; acute and precursor leukaemia and lymphomas; melanoma; basal cell carcinomas (BCC) (for which there is a unique registration at the Eindhoven cancer registry[26]) and squamous cell cancers of the skin (including lip, SCC); as well as prostate; ovary; mature B-cell (including Hodgkin's lymphoma). In addition, we conducted analyses of *all* cancers combined, i.e. including those above plus all other cancers diagnosed, but excluding BCC.

Socioeconomic status

An indicator for SES developed by Statistics Netherlands was used.[27] SES of the patient was defined at the neighbourhood level (based on six-digit postal code of residence area) combining mean household income (in 1998) and mean economic value of the house/apartment (in 2000), derived from individual fiscal data provided at an aggregated level. On average each postal code area contains 17 households, thus covering a very small geographic area. The use of routinely collected income fiscal data assures the reliability of the estimates of household incomes. Postal codes were assigned to three SES categories: low (1st–3rd deciles), intermediate (4th–7th deciles) and high (8th–10th deciles). This SES measure is assumed to be valid for 10 years before and after the base year (2000).[27] A separate SES category was made for postal codes of care-providing institutions but these were excluded from the analyses because assigning SES to those living in a nursing home or other care-providing institution is very difficult.

For the year 2004, population data at the level of a six-digit postal code, i.e. according to SES, age and sex, were available from Statistics Netherlands, enabling calculation of specific incidence rates for each SES category. Since these source population data were not available for the other years, we corrected the SES-specific population for the changes in the general population (age distribution, sexes). This method appears to be valid because during 1996-2008 the sum of the specific SES populations never deviated more than 10% from the general population. Absolute inequalities, not relative inequalities, were investigated. Absolute inequalities were assessed through incidence rates.

Statistics

Incidence rates were calculated for the period 1996–2008; age-adjustment was performed by direct standardization according to the European Standard Population [European Standardised Rates (ESR), per 100,000 person-years]. SES-specific tumour incidence rates were calculated according to sex for each age category separately (25-44, 45-64, ≥65 years) in order to trace specific trends. The complete population according to SES was only provided for these age groups. Results are shown per age category only for the tumours with varying patterns. For the other tumours results are only presented for all ages together as 3-year moving averages (for 1996 and 2008 as 2-year moving averages). Incidence rates of >10 were rounded off to integer numbers, rates of 1-10 were rounded off to 1 decimal place

3.1

and rates <1.0 to 2 decimal places. Evaluation of the trend in incidence was performed by calculating the estimated annual percentage changes (EAPC). Incidence and EAPC analyses were performed using SAS 9.1 (SAS Institute, Cary, NC, USA). *P*-values were two-sided and values <0.05 were considered significant.

RESULTS

Localisation at diagnosis of the 133,690 tumours included in this study according to sex and SES is shown in Table 1. Cancers of the lung were most common in low SES, in contrast to cancers of the breast and prostate as well as BCCs.

All cancers

Associations of SES and *all* cancer incidence, i.e. all cancers diagnosed, have reversed over time for males, from highest incidence in low SES groups towards highest incidence in high SES groups (Figure 1A). Incidence for males with low SES has decreased slightly (EAPC -1.0%), while the incidence increased among those with intermediate (1.2%) and high (2.1%) SES (Table 2). In older males a similar shift was observed (EAPCs -1.0%, 1.6% and 2.7% for low, intermediate and high SES) (Figure 1D). For males aged 45-64 similar trends were observed for those with an intermediate and high SES (1.8% and 2.3%), but the trends for low SES people remained stable (-0.2%) and no shift occurred (Figure 1C). Although disparities seemed to be reduced for those of 25-44 years, no clear socioeconomic gradient was present (Figure 1B). For females we observed decreasing disparities due to an unchanged incidence among low SES over time (EAPC -0.1%) and a rising incidence for intermediate (EAPC 1.4%) and high (2.3%) SES (Figure 1E). These patterns were similar for those aged 45-64 and 65 and older (Figures 1G and 1H), but the association was inverse for females of 25-44 years (Figure 1F).

Tumour specific, males
High incidence in low SES
The association of SES and cancer incidence differed per tumour site (Table 2). Cancers of the head and neck, upper GI tract and airways were generally most common in people of a low SES. But incidence rates for stomach and lung cancer decreased markedly and differentially, the EAPCs for stomach cancer being -5.1% in low SES and -2.8% in high SES. EAPCs for lung were -3.2% for low and -2.2% for high SES (Figure 2A).

High incidence in high SES
Prostate cancer, melanoma and BCC remained generally more common among those with a high SES because of the increasing incidence for people with a high SES, while incidence for people with a low SES remained more or less unchanged, or only slightly increased in case of BCC (Table 2, Figures 3A-3C, 4A, 5A). In 1996, the incidence of prostate cancer was similar for each of the SES groups, but disparities increased due to strong increases in intermediate (3.9%) and high (5.1%) SES males, but only 0.5% in low SES males and even a decrease from 2005 onwards (Figure 3A). Incidence increased in all SES groups of those aged 45 and older, except low SES males of 65 and older, being most marked for those with a high SES, especially at middle age (Figure 3B, 3C). In the oldest males a plateau seemed to be reached around 2004 for intermediate and high SES (Figure 3C). Incidence of melanoma increased especially for people with an intermediate and high SES, in those aged 45 and older, but mostly in the

Table 1. *Localization of first tumours according to socioeconomic status diagnosed between January 1996 and December 31st, 2008, in the Eindhoven Cancer Registry, The Netherlands (N=133,690).*

| Tumour site | Males Socioeconomic status | | | | | | Females Socioeconomic status | | | | | |
| | low | | intermediate | | high | | low | | intermediate | | high | |
	N	%	N	%	N	%	N	%	N	%	N	%
Oropharyngeal	397	2	484	2	269	1	221	1	271	1	142	1
Larynx	338	2	386	1	263	1	87	0	77	0	34	0
Oesophagus (incl. cardia stomach)	542	3	853	3	600	2	237	1	268	1	178	1
Stomach, non-cardia	498	2	609	2	445	2	382	2	396	1	246	1
Colon	1379	7	2122	7	1725	7	1708	8	1951	7	1447	7
Rectum	842	4	1495	5	1173	5	720	3	947	3	668	3
Pancreas	325	2	496	2	364	1	364	2	406	1	274	1
Lung (incl. bronchus and trachea)	3818	19	4943	16	2903	12	1788	9	1927	7	971	5
Skin, melanoma	350	2	792	2	741	3	496	2	1053	4	921	4
Skin, squamous cell carcinoma incl. lip	910	4	1283	4	1078	4	625	3	713	2	506	2
Skin, basal cell carcinoma	3428	17	6072	19	5757	23	4165	20	6103	21	5429	25
Breast							4638	23	7849	27	5971	28
Cervix uteri							329	2	410	1	176	1
Corpus uteri							788	4	1065	4	782	4
Ovary							545	3	794	3	568	3
Prostate	3033	15	5096	16	4577	18						
Kidney	385	2	710	2	553	2	344	2	416	1	290	1
Urinary bladder	811	4	1216	4	822	3	302	1	323	1	190	1
Mature B-cell incl. Hodgkin	833	4	1478	5	1142	5	792	4	968	3	774	4
Acute/precursor leukemia/lymphoma	178	1	304	1	231	1	162	1	256	1	188	1
Subtotal	**18,067**	**89**	**28,339**	**89**	**22,643**	**91**	**18,693**	**91**	**26,193**	**91**	**19,755**	**93**
Total (=*all* cancers, incl. the cancers above but excl. basal cell carcinoma)	**16,798**		**25,639**		**19,254**		**16,421**		**22,557**		**15,882**	

3.1

3.1

A. Males, all ages

B. Males, 25-44 years

C. Males, 45-64 years

D. Males, ≥65 years

E. Females, all ages

F. Females, 25-44 years

G. Females, 45-64 years

H. Females, ≥65 years

◼ low
✳ intermediate
● high
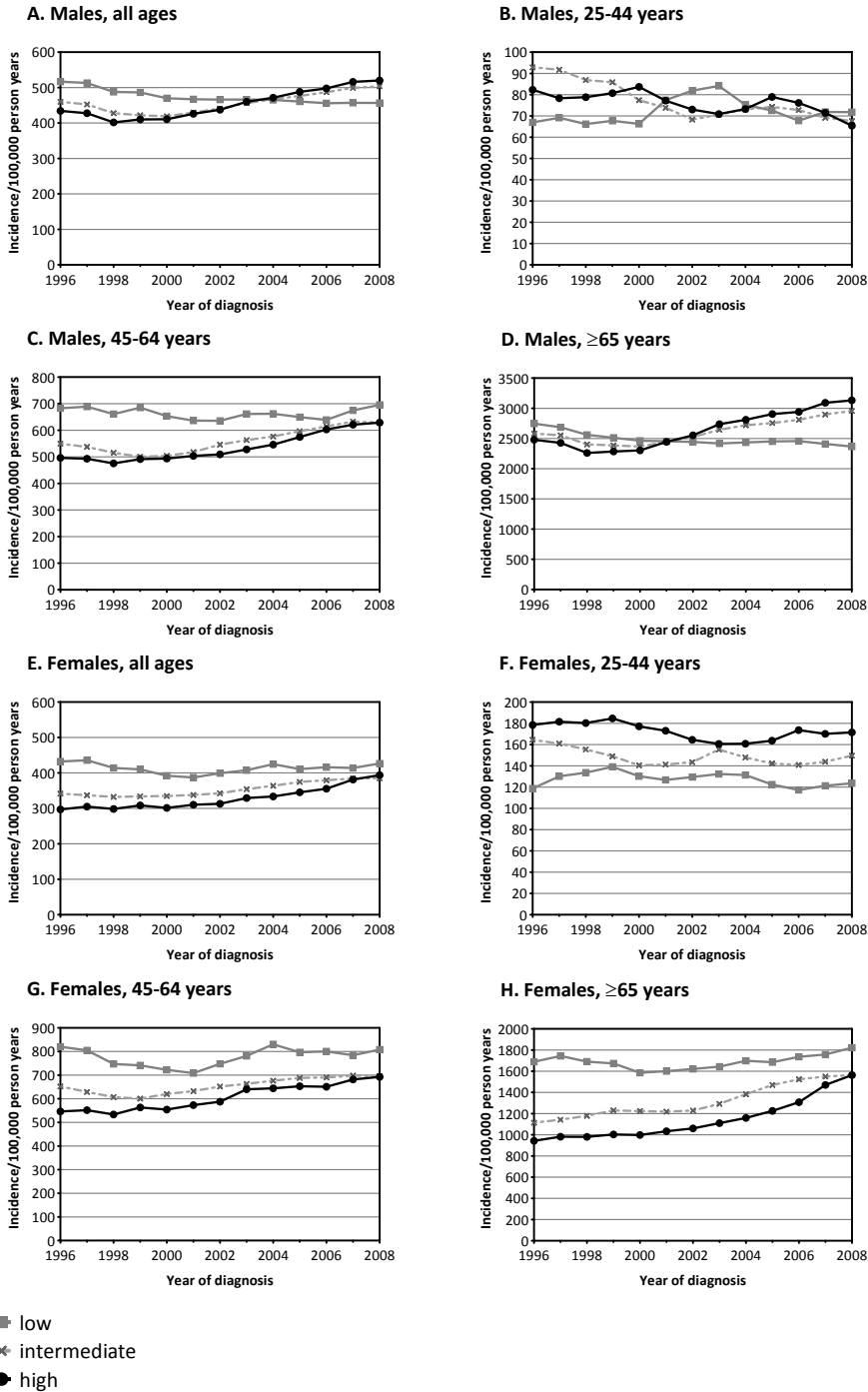
Figure 1. *Incidence of all cancers, excluding basal cell carcinoma, according to socioeconomic status.*

A. Males

B. Females

◾ low
✳ intermediate
● high
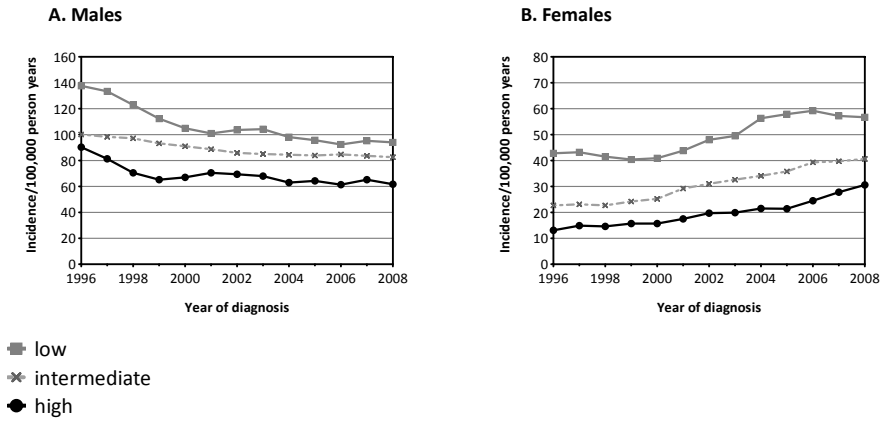
Figure 2. Incidence of lung cancer according to socioeconomic status.

A. Males, all ages

B. Males, 45-64 years

C. Males, ≥65 years

◾ low
✳ intermediate
● high

Figure 3. Incidence of prostate cancer according to socioeconomic status.

3.1

high SES groups (Figures 4A, 4C, 4D), except for males of 25-44 years (Figure 4B). People with a high SES generally exhibited the highest incidence of BCC of the skin and disparities increased mainly after 2001 (EAPC 6.0% for high compared to 1.7% for low SES males) (Figure 5A). Similar patterns were seen for males of 45 and older as well as of 25-44 years, but with larger variations (Figures 5B-5D).

SHIFTING OR INCONSISTENT ASSOCIATIONS

Incidence of colon cancer became slightly higher for people with a high SES after 2000 (Figure 6A). Similar associations were observed for squamous cell cancer (SCC) of the skin and kidney cancer (Table 2). There were no such associations for cancers of mature B cells and acute and precursor leukaemia and lymphomas (Table 2). No increase in low SES compared to intermediate and high SES was observed for rectal cancer (Figure 7A). The shift from highest towards lowest incidence of cancer of the pancreas in people of low SES was of borderline significance (Table 2).

Tumour specific, females

HIGH INCIDENCE IN LOW SES

Generally, the females of low SES retained the highest incidence for cancers of oropharynx, larynx, lung, SCC of the skin, cervix uteri and urinary bladder. Disparities among SES groups were reduced for cancers of the oesophagus, stomach, pancreas, colon, rectum, corpus uteri, ovary, kidney and mature B cells (Table 2). Lung cancer incidence increased more for women with a high SES, the EAPC for low SES women being 3.7%, intermediate 5.9% and high SES 7.1% (Figure 2B). Furthermore, colon and rectal cancer incidence remained highest in women with a low SES, but disparities diminished due to marked increases in those with a high and intermediate SES since 1996 (EAPC colon low 0.7%, intermediate 2.0% and high SES 3.3%, for rectal 0.9%, 1.0% and 2.9%, respectively) (Figure 6B, 7B).

HIGH INCIDENCE IN HIGH SES

Melanoma remained and BCC became more common in persons with intermediate and high SES (EAPCs 1.9% and 5.1% and 3.1% and 6.1%, respectively) (Figure 4E, 5E). Remarkably, incidence rates for people with a high SES were highest only at age 25-64 years, in contrast to the highest incidence rates among older women with a low SES until 2005 (Figure 4E-4H, 5E-5H).

AGE-DEPENDENT AND INCONSISTENT ASSOCIATIONS

Incidence of breast cancer according to SES remained fairly similar for all SES groups at middle age (Figure 8C), but among younger women the highest incidence was observed in women with a high SES (Figure 8B). In 1996 rates were highest in older women of low SES, but the pattern changed due to more markedly increased rates for intermediate and high SES women and in 2008 incidence did not differ by SES anymore (Figure 8A, 8D). No association was observed for acute and precursor leukaemia and lymphomas (Table 2).

A. Males, all ages

B. Males, 25-44 years

3.1

C. Males, 45-64 years

D. Males, ≥65 years

E. Females, all ages

F. Females, 25-44 years

G. Females, 45-64 years

H. Females, ≥65 years
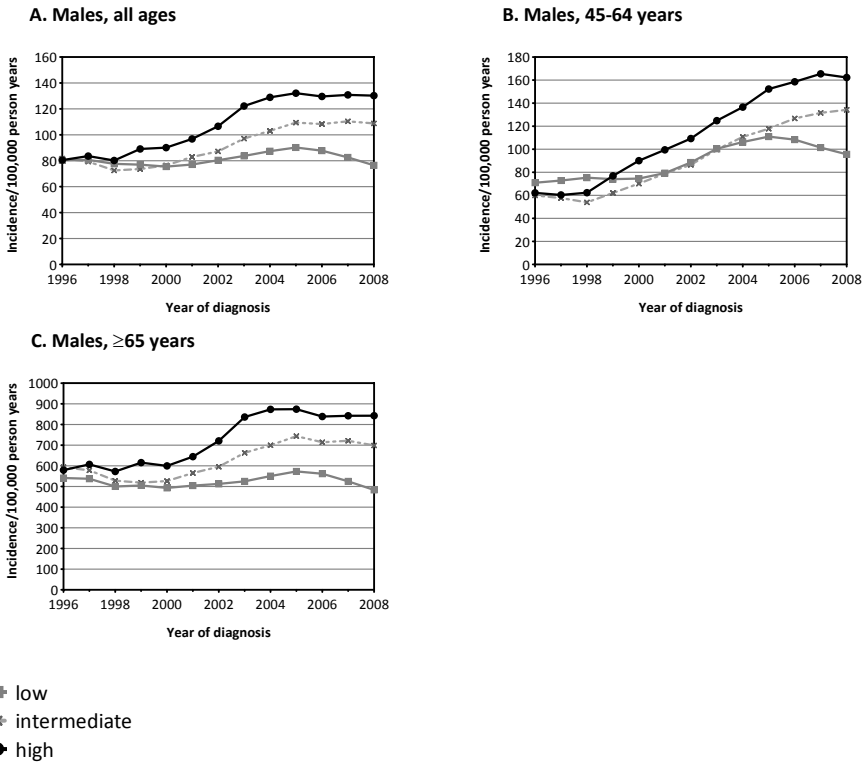
■ low

� intermediate

● high
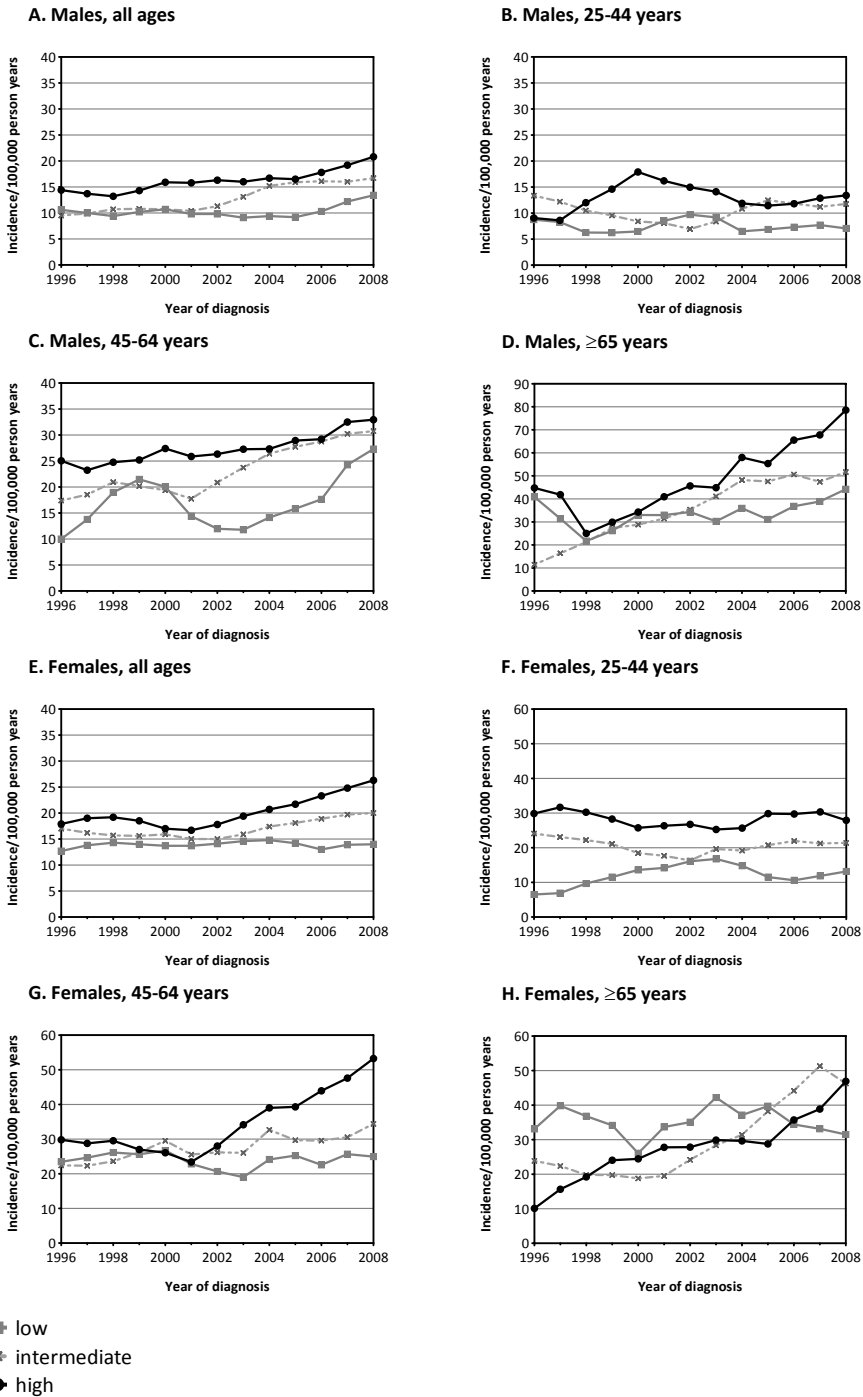
Figure 4. *Incidence of melanoma according to socioeconomic status.*

3.1
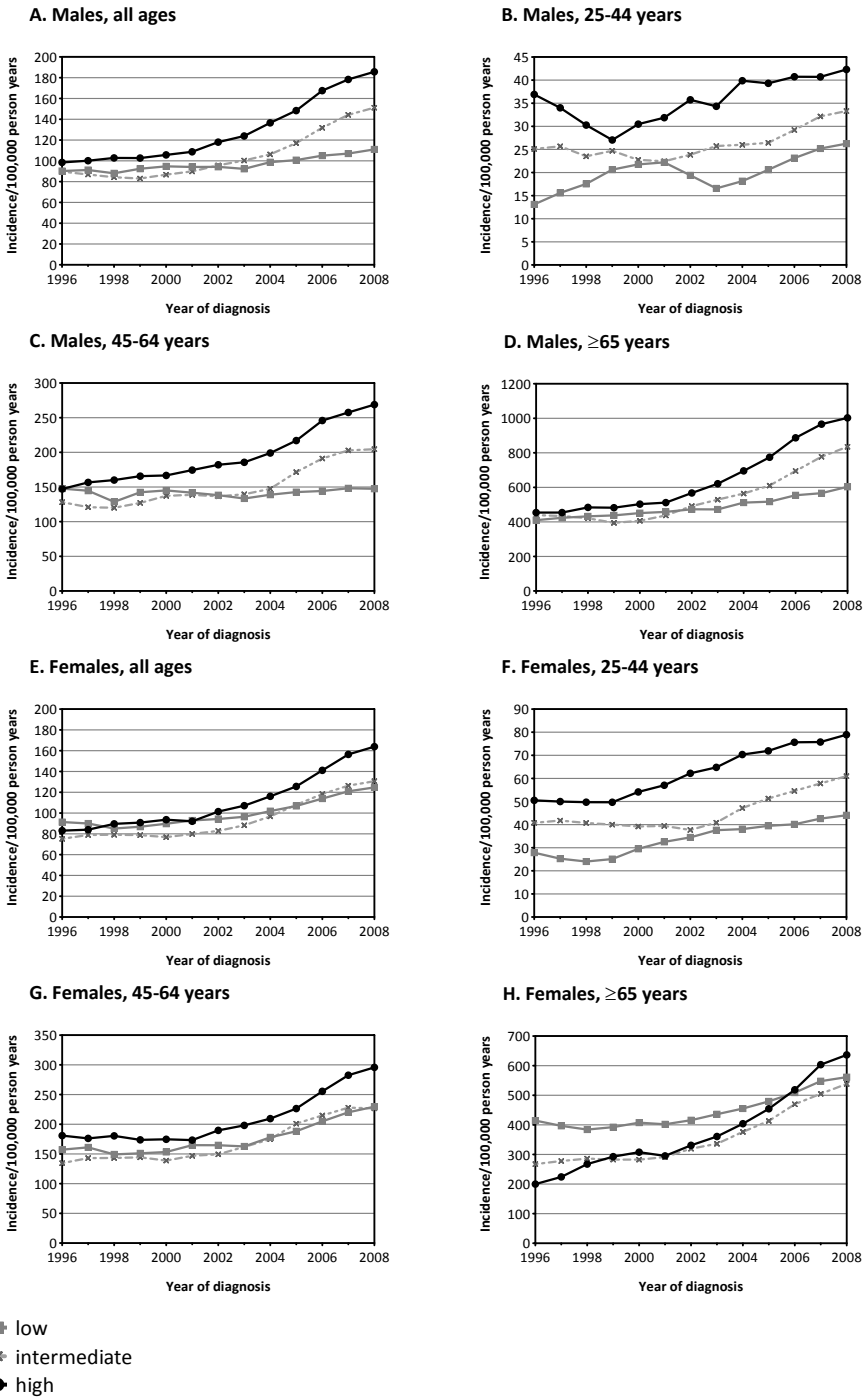
Figure 5. *Incidence of basal cell carcinoma according to socioeconomic status.*

A. Males

B. Females

■ low
✳ intermediate
◆ high
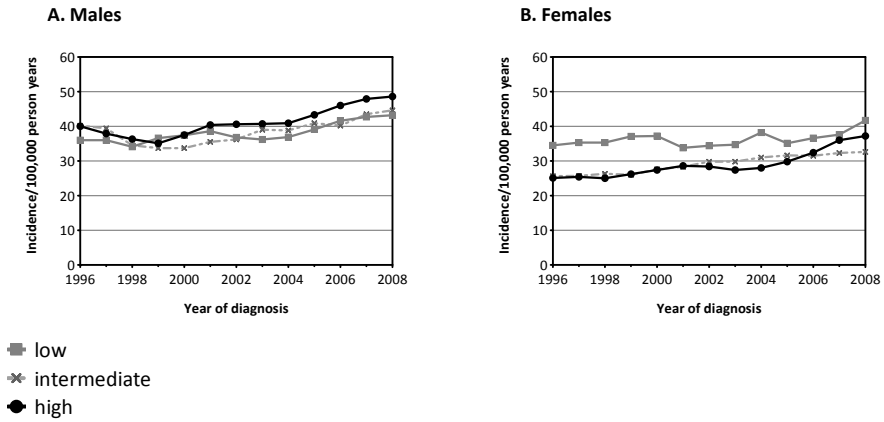
Figure 6. Incidence of colon cancer according to socioeconomic status.

A. Males

B. Females

■ low
✳ intermediate
◆ high
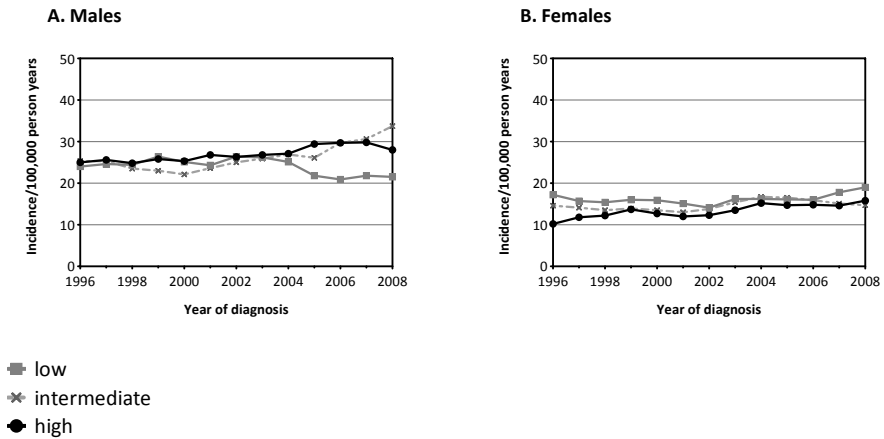
Figure 7. Incidence of rectal cancer according to socioeconomic status.

3.1

3.1

A. Females, all ages

B. Females, 25-44 years

C. Females, 45-64 years

D. Females, ≥65 years

low
intermediate
high
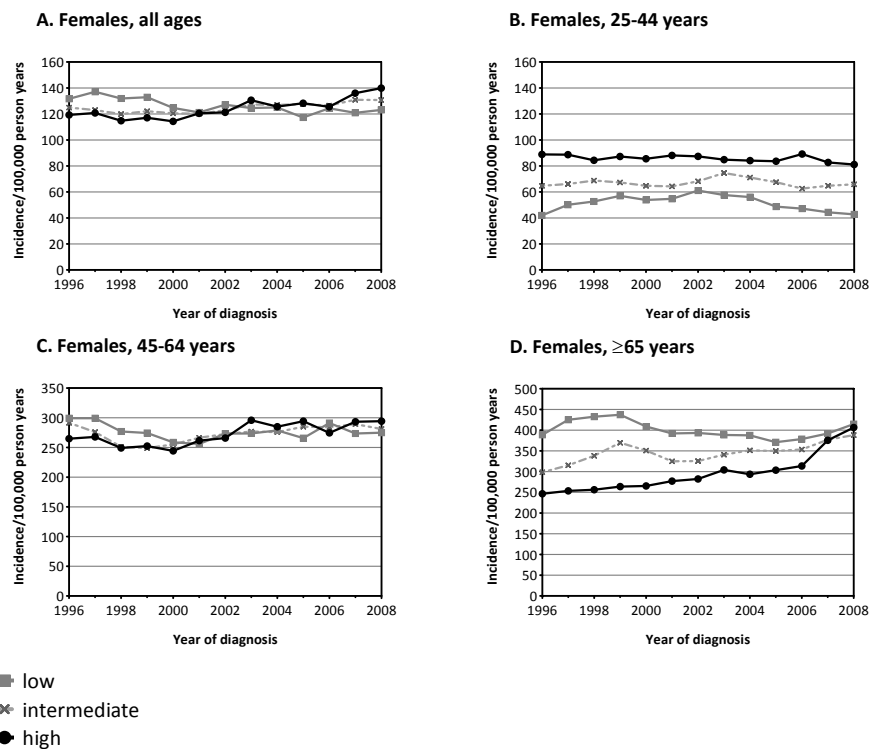
Figure 8. *Incidence of breast cancer according to socioeconomic status.*

Table 2. Cancer incidence according to sex and socioeconomic status, 3-year moving averages for 1996, 2002 and 2008.

	Socioeconomic status	Males						Females					
		Incidence (ESR)						Incidence (ESR)					
		1996	2002	2008	EAPC	95%CI		1996	2002	2008	EAPC	95%CI	
Total (excl BCC)													
All ages	1. low	517	466	457	**-1.0**	-1.7	-0.4	432	399	427	-0.1	-1.1	0.8
	2. intermediate	460	441	504	**1.2**	0.3	2.1	341	343	385	**1.4**	0.8	1.9
	3. high	434	437	520	**2.1**	1.0	3.1	297	313	394	**2.3**	1.4	3.2
25-44 years	1. low	67	82	72	0.8	-1.3	2.8	119	130	124	-0.5	-1.9	1.0
	2. intermediate	93	68	68	**-2.6**	-4.0	-1.2	164	143	150	-1.0	-2.3	0.4
	3. high	82	73	65	-1.4	-3.2	0.3	178	165	171	-0.9	-1.9	0.1
45-64 years	1. low	683	636	696	-0.2	-1.4	1.1	820	748	808	0.2	-1.1	1.6
	2. intermediate	549	546	629	**1.8**	0.8	2.7	652	652	695	**1.1**	0.4	1.8
	3. high	496	509	629	**2.3**	1.4	3.2	546	588	693	**2.3**	1.2	3.3
≥65 years	1. low	2747	2444	2367	**-1.0**	-1.6	-0.4	1689	1621	1822	0.4	-0.5	1.4
	2. intermediate	2581	2524	2956	**1.6**	0.6	2.5	1114	1228	1563	**3.1**	2.3	3.9
	3. high	2478	2553	3131	**2.7**	1.6	3.9	943	1060	1564	**4.2**	3.0	5.4
Oropharyngeal	1. low	12	11	14	-0.4	-3.1	2.3	6.8	6.4	7.9	1.6	-1.9	5.0
	2. intermediate	8.1	8.9	7.3	0.9	-2.6	4.4	3.6	4.2	4.9	2.0	-1.5	5.5
	3. high	5.5	5.1	7.0	0.7	-2.4	3.7	3.2	2.3	3.7	2.7	-1.3	6.6
Larynx	1. low	8.6	10	9.1	-0.4	-3.7	3.0	1.9	2.8	2.9	3.2	-2.5	8.8
	2. intermediate	7.5	8.0	5.6	-1.7	-5.3	1.9	1.3	1.0	1.4	2.8	-1.2	6.9
	3. high	7.1	5.6	6.2	-0.1	-3.0	2.8	0.40	0.80	0.85	1.7	-9.2	12.7
Oesophagus (incl cardia stomach)	1. low	12	15	17	2.9	-2.0	7.8	6.1	5.1	4.2	-3.1	-6.4	0.3
	2. intermediate	13	15	20	**4.0**	1.9	6.1	3.1	4.3	3.9	2.7	-2.4	7.7
	3. high	11	13	17	**3.4**	0.4	6.4	2.9	3.2	4.8	**2.8**	0.1	5.6
Stomach (non-cardia)	1. low	19	14	11	**-5.1**	-8.5	-1.6	11	8.3	6.2	-2.8	-6.1	0.5
	2. intermediate	17	11	9.2	**-4.2**	-7.0	-1.4	5.9	5.1	6.5	-1.2	-4.8	2.4
	3. high	13	10	9.3	**-2.8**	-5.1	-0.6	4.6	4.8	5.7	2.6	-2.1	7.4

Table 2 continues on next page

3.1

Continuation of table 2.

	Socioeconomic status	Males					Females				
		Incidence (ESR)					Incidence (ESR)				
		1996	2002	2008	EAPC	95%CI	1996	2002	2008	EAPC	95%CI
Colon	1. low	36	37	43	**1.5**	0.3 2.7	35	34	42	0.7	-1.4 2.8
	2. intermediate	40	36	45	1.4	-0.7 3.5	26	30	33	**2.5**	1.7 3.3
	3. high	40	41	49	**2.4**	1.1 3.7	25	28	37	**3.3**	1.9 4.6
Rectum	1. low	24	26	22	-1.4	-3.7 1.0	17	14	19	0.9	-1.5 3.3
	2. intermediate	25	25	34	**2.3**	0.4 4.2	15	14	15	1.0	-0.8 2.8
	3. high	25	26	28	**1.5**	0.4 2.7	10	12	16	**2.9**	0.3 5.4
Pancreas	1. low	10	8.4	8	-3.3	-7.3 0.7	9.9	6.4	7.1	-2.5	-5.8 0.9
	2. intermediate	8.8	8.0	11	**2.3**	0.2 4.3	5.4	6.0	6.4	2.5	-0.1 5.1
	3. high	6.8	7.1	12	3.7	-0.1 7.5	5.2	4.6	7.3	**4.1**	0.6 7.5
Lung, Bronchus and Trachea	1. low	138	104	94	**-3.2**	-4.6 -1.9	43	48	57	**3.7**	2.1 5.3
	2. intermediate	100	86	83	**-1.7**	-2.5 -0.8	23	31	41	**5.9**	4.6 7.1
	3. high	90	69	62	**-2.2**	-4.3 -0.2	13	20	31	**7.1**	5.0 9.1
Skin, melanoma *All ages*	1. low	11	10	13	1.2	-1.8 4.2	13	14	14	0.7	-1.4 2.8
	2. intermediate	9.5	11	17	**5.5**	3.7 7.3	17	15	20	1.9	-0.1 3.9
	3. high	14	16	21	**3.1**	1.3 4.9	18	18	26	**3.1**	1.2 5.0
25-44 years	1. low	8.8	9.7	7.1	-0.5	-6.3 5.4	6.5	16	13	4.8	-0.6 10.1
	2. intermediate	13	6.9	12	0.1	-5.3 5.6	24	16	21	-1.1	-4.4 2.1
	3. high	9.1	15	13	1.2	-4.1 6.6	30	27	28	-0.3	-3.2 2.6
45-64 years	1. low	10	12	27	4.9	-2.5 12.4	23	21	25	0.8	-5.7 7.4
	2. intermediate	17	21	31	**5.3**	3.2 7.5	22	26	34	3.2	-0.7 7.1
	3. high	25	26	33	**2.7**	0.9 4.5	30	28	53	**5.5**	2.2 8.9
≥65 years	1. low	41	34	44	2.8	-3.7 9.4	33	35	32	0.0	-4.3 4.3
	2. intermediate	11	35	52	**12.5**	8.3 16.7	24	24	46	**8.7**	2.6 14.7
	3. high	45	46	79	**7.6**	0.8 14.4	10	28	47	**10.2**	5.3 15.0
Skin, Basal cell carcinoma (BCC) *All ages*	1. low	90	94	111	**1.7**	0.5 2.9	91	94	125	**3.1**	1.9 4.3
	2. intermediate	90	96	151	**5.1**	3.4 6.8	75	83	131	**5.1**	3.6 6.6
	3. high	99	118	186	**6.0**	4.8 7.2	83	101	164	**6.1**	4.7 7.5

3.1

25-44 years	1. low	13	19	26	**4.5**	1.1	7.9	28	34	44	**5.4**	3.4	7.4
	2. intermediate	25	24	33	2.2	-0.2	4.6	41	38	61	**3.9**	1.4	6.5
	3. high	37	36	42	**2.8**	0.1	5.4	51	62	79	**4.6**	3.5	5.7
45-64 years	1. low	148	138	147	0.2	-2.0	2.3	157	165	230	**3.7**	1.5	5.8
	2. intermediate	128	137	205	**4.7**	2.6	6.7	134	149	227	**5.1**	3.5	6.6
	3. high	147	182	269	**5.1**	3.9	6.4	181	190	296	**4.6**	2.7	6.5
≥65 years	1. low	410	473	603	**3.2**	2.2	4.1	415	416	561	**3.0**	1.7	4.4
	2. intermediate	439	491	835	**6.3**	4.3	8.3	267	319	538	**6.4**	4.4	8.3
	3. high	454	568	1003	**7.8**	6.3	9.3	200	331	636	**9.9**	8.1	11.7
Skin, squamous cell, including lip	1. low	25	26	29	1.4	-1.6	4.4	9.2	11	19	**7.5**	3.8	11.1
	2. intermediate	21	23	34	**4.7**	2.8	6.5	8.4	9.2	16	**6.1**	3.5	8.7
	3. high	20	24	43	**6.5**	4.3	8.7	8.4	8.7	16	**7.9**	4.1	11.7
Breast													
All ages	1. low							132	127	123	-1.2	-2.6	0.2
	2. intermediate							125	123	131	0.6	-0.3	1.4
	3. high							119	121	140	**1.3**	0.1	2.6
24-44 years	1. low							42	61	43	-0.7	-3.6	2.3
	2. intermediate							65	68	66	0.0	-1.4	1.4
	3. high							89	87	81	-0.8	-2.2	0.6
45-64 years	1. low							299	273	275	-0.9	-2.7	1.1
	2. intermediate							291	273	281	0.6	-0.7	1.8
	3. high							265	266	294	1.3	-0.3	2.9
≥65 years	1. low							389	393	415	-0.7	-2.1	0.8
	2. intermediate							298	325	388	1.5	-0.3	3.3
	3. high							247	282	406	**3.8**	2.1	5.4
Cervix uteri	1. low							8.2	8.0	9.2	-0.7	-5.1	3.7
	2. intermediate							8.4	5.5	6.5	-2.6	-7.2	2.1
	3. high							5.5	2.8	3.4	-3.1	-8.4	2.1

Table 2 continues on next page

3.1

Continuation of table 2.

Socioeconomic status	Males Incidence (ESR) 1996	2002	2008	EAPC	95%CI	Females Incidence (ESR) 1996	2002	2008	EAPC	95%CI
Corpus uteri										
1. low						25	19	20	-1.2	-3.2 0.9
2. intermediate						19	14	17	0.3	-2.7 3.3
3. high						12	17	19	**3.4**	1.1 5.8
Ovary										
1. low						16	16	13	-3.4	-7.5 0.7
2. intermediate						17	13	10	**-4.1**	-5.9 -2.3
3. high						13	12	12	**-1.8**	-3.2 -0.3
Prostate										
All ages										
1. low	80	80	77	0.5	-0.7 1.8					
2. intermediate	82	87	109	**3.9**	2.2 5.6					
3. high	81	107	130	**5.1**	3.2 7.0					
45-64 years										
1. low	71	89	96	**3.9**	2.0 5.8					
2. intermediate	60	86	134	**8.9**	6.7 11.2					
3. high	62	109	162	**10.3**	8.1 12.5					
≥65 years										
1. low	541	512	483	0.0	-1.4 1.4					
2. intermediate	593	595	698	**2.9**	1.2 4.6					
3. high	579	721	843	**4.1**	2.1 6.2					
Kidney										
1. low	11	10	11	0.4	-1.7 2.5	11	7.3	7.4	-2.0	-5.3 1.3
2. intermediate	13	10	16	1.7	-1.5 4.8	6.9	6.5	7.8	1.0	-1.5 3.5
3. high	12	10	16	**3.2**	0.5 6.0	5.6	6.3	6.5	1.9	-2.1 5.9
Urinary bladder										
1. low	26	22	19	-2.6	-4.7 -0.6	7.8	5.2	8.5	0.8	-4.0 5.6
2. intermediate	21	23	22	0.6	-1.1 2.3	4.0	5.0	5.5	**4.1**	1.8 6.4
3. high	22	19	23	1.1	-0.9 3.1	4.1	4.1	3.5	3.0	-3.6 9.6
Mature B cell including										
1. low	28	24	25	-0.5	-3.4 2.4	22	22	17	-0.4	-3.1 2.3
Hodgkin 2. intermediate	28	25	28	0.7	-0.8 2.3	15	14	15	1.6	-0.5 3.7
3. high	27	26	28	1.2	-0.4 2.7	15	14	19	**2.4**	0.5 4.3
Acute/precursor										
1. low	8.1	5.8	4.1	**-5.4**	-10.1 -0.8	6.2	2.7	5.8	1.7	-4.8 8.2
leukemia/lymphoma 2. intermediate	6.1	5.1	5.4	-0.8	-3.9 2.3	3.6	3.3	4.8	0.6	-4.3 5.5
3. high	5.4	6.9	5.6	-1.8	-7.4 3.7	4.5	3.2	5.7	1.8	-2.7 6.4

95% CI: 95% confidence interval of EAPC; ESR: European Standardised Rate (3-year moving averages); and EAPC: Estimated Annual Percent Change.

DISCUSSION

In this study in the South of the Netherlands, people with a low SES retained the highest incidence rates for most (including smoking-related) cancers. However, prostate cancer became more common among those with a high SES and these patterns became more pronounced for BCC and melanoma (both except older females). These trends contributed to decreasing disparities in incidence of all cancers combined in those of 45 and older and even to a shift towards higher risks among older males with a high SES. People with a high SES retained the highest incidence of all cancers combined in females of 25-44 years, largely breast cancer, while a decrease in the inequalities was observed for males of this age without a clear gradient being present.

Incidence of all cancers combined

In this study higher incidence rates of all cancers combined were reported for males with a low SES in line with those reported in literature,[1, 11, 12, 28-30] except for the shift towards highest rates for men with a high SES. However, such results could not easily be compared because age- and SES-specific incidence rates have never been reported[1, 11, 12, 28-30] and for another period.[1, 29] Could we be signalling a new trend and might this have implications for implementation of prevention?

Incidence of all cancers combined increased most markedly in males with a high SES, followed by intermediate SES, while it remained stable or was even reduced in the low SES group. These patterns are probably explained by cancers of the lung and prostate and melanoma.

In contrast to males, increased risk[12, 28] as well as (non-significant) decreased risks[29, 31] of all cancers were reported for low SES females, which in Italy seemed to depend on the SES indicator.[11] Incidence remained highest for females of 25-44 years with a high SES, which was largely determined by breast cancer and possibly melanoma. For females of 45 and older, the low SES group had more or less the highest incidence of all cancers combined but inequalities decreased over time due to strongly increasing incidence in the high SES group, probably largely influenced by breast, colon, rectal and lung cancer.

Males – incidence of cancer at specific subsites

Increasing inequalities in prostate cancer incidence were observed due to increases in the high SES groups, similar to England.[12] Most other European studies did not report such changes albeit high SES males indeed exhibited high incidence before 1998[14, 29, 31] and 2004.[32] Prostate cancer incidence in the Netherlands remained constant from 1995-2000, but rose from 2000 to 2006,[33] most likely caused by PSA testing which is more common among high SES males.[34, 35] It seems likely to explain the differential trends since 2000, i.e. small increases in low SES groups, moderate increases in intermediate and marked increases in high SES groups. Remarkable decreases in prostate cancer incidence among low SES have been observed after 2005, which we could not explain. Possibly the 'prevalent' pool of prostate cancer may become exhausted similar to the United States (US) situation,[36] but this probably applies to all SES groups. Although PSA testing continued to increase for all males of 40 and older,[37] it may have hardly increased or even decreased in low SES groups. Since 2003/2004 remarkable plateaus were observed among intermediate and high SES males of

65 and older, possibly related to awareness of overdiagnosis in this age group as experience with prostate cancer screening in the Netherlands was having effects. The following years we will observe whether these trends will persist or perhaps even decrease.

Incidence of melanoma and BCC increased markedly, especially in high SES males. Previously, incidence of melanoma was lowest among the lower SES groups[1, 12, 29, 32, 38] and an increasing incidence of BCC was found especially among the high SES group.[39] Health awareness and sun tanning behaviour (especially at young age) on sunny holidays may have been responsible for this trend.[39] During the last two decades the availability has also increased for those with a lower SES and we therefore expect the incidence to increase in this group.

Females – incidence of cancer at specific subsites

For females of 25-44 years breast cancer incidence remained highest for those with a high SES, probably due to better health awareness and older age at first birth.[40] In contrast, no inequalities were observed for women aged 45-64. This probably relates to the free breast cancer mass screening programme that started in 1991 and was fully implemented in 1996 for all women of 50-69 years, although we found higher participation in high SES females (87% versus 79% of low SES, Aarts 2010). In 1998 the upper age limit of the screening programme was extended to 75. This likely had more effect on attendance of females with a high SES and thus may have reduced socioeconomic disparities in breast cancer incidence rates which were no longer highest in low SES groups in 2008.

For females, remarkable trends in melanoma, BCC, colon and rectal cancers were observed, as reported for melanoma and BCC (without distinction according to age).[1, 8, 12, 29, 38] Up to 65, increases in melanoma and BCC were largest in high SES females (as observed for males), while older women with a low SES had the highest incidence until around 2004 but patterns became inconsistent during the last years. In a previous study we observed that elderly women with a low SES mainly had BCCs at extremities, head and neck, i.e. related to chronic exposure, while high SES males had the highest incidence rates for all subsites and all age groups.[39] This points to more chronic exposure of elderly women and sun tanning exposure of males; the shift around the mid-2000s may result from differences in sun tanning behaviour or from better awareness of skin cancers a few decades ago.[41]

Females with a high SES had the highest risks of colon and rectal cancer, while only a slightly higher incidence rate of colon cancer was observed for high SES males, in agreement with other European studies.[42] Poor diet and low physical activity levels have become more common in low SES working men in the past few decades. However, in association with greater health awareness, opportunistic screening may be more common in high SES groups in the Netherlands which is reflected in the largest increases in high SES males, although only small differences in stage distribution were present (data not shown). In view of the upcoming screening programme it is important to provide equal access to achieve early detection.[42]

European context

Despite different levels and types of SES indicators, other European studies performed in the same period have shown results fairly similar to ours in the overlapping period (1996-2004). For all cancers combined males exhibited similar inequalities (i.e. 0-20% increased for low SES) to England, Italy, Iceland and Denmark, while inequalities for females from these countries and Norway were smaller (varying from 20% reduced to 20% increased in low SES) than we observed (20-50% increased risk in low SES).[11, 12, 29, 32, 43, 44] This seems to be associated with large inequalities in risks of tobacco-related and alcohol-related cancers in the Netherlands compared to Italy, Iceland, Denmark and (inconsistently) England.[2-4, 11, 12, 32, 45] In addition, inequalities in breast cancer risk were absent in our study (for all ages combined), while decreased risks for low SES were reported in Norway, Sweden, Denmark, Iceland, England and Italy.[9, 12, 29, 43, 45, 46] Furthermore, although we observed a strong socioeconomic gradient in melanoma risk, inequalities were larger in England, Italy and Iceland (the latter only in males),[12, 29, 45] while inequalities were similar to Denmark and Iceland (females), and slightly smaller than in Norway.[8, 32, 43]

Lifestyle and early detection

The higher risks and generally more marked increases among the high SES groups seem largely to result from early detection, i.e. for BCC, melanoma (both except females of 65 and older) and prostate cancer. Detection rates probably rose more markedly in high SES groups due to their greater awareness and knowledge of cancers and willingness to seek medical advice.[47-50] In other studies, this was reflected by earlier stages of disease,[51-54] as we also observed for breast (low versus high SES: 38% versus 42% pathological stage 1), cervix uteri (47% versus 55%) and prostate (66% versus 72% clinically localised disease). In addition, relative survival rates for cancer patients with a low SES are usually worse.[1, 42, 55] Prognosis of early detected cancers is generally good, largely because of this early stage at diagnosis. However, the improvement of survival due to early detection could partly be attributed to bias, e.g. lead time bias (an artifactual increase in time from diagnosis to death) and length bias (an artifactual decrease in hazard rates because some early detected cancers progress too slowly to kill). The proportion of early detected cancers will increase more in people of high SES and thus contributing to their already high life expectancy, while no or only little improvement will be present in the low SES group. As a consequence inequalities in survival will increase, although early detection mainly applies to tumours with good prognosis and thus these increasing inequalities will be relatively small. Due to increasing disparities in cancer incidence resulting from e.g. screening, survival inequalities are likely to increase to the disadvantage of the low SES groups.[56]

On the other hand, incidence rates of lifestyle-related cancers were generally highest in low SES, e.g. lung cancer. In males, smoking prevalence has been decreasing since 1960s[57] and prevalence shifted around that time from highest towards lowest prevalence in high social classes.[58] In females this shift occurred approximately 10 years later, and prevalence has been increasing until early 1970s,[57] in line with the increasing incidence rates we observed (due to the latency time). Smoking explains 40-50% of inequalities in lung cancer incidence, compared to 23% for physical exercise while diet plays only a small role.[18, 59] Although low SES had also increased risks of other tobacco-related cancers (i.e. oropharynx,

oesophagus, bladder), incidence rates were not necessarily reducing due to decreasing smoking prevalence. Besides, risk of obesity-related cancers like corpus uteri were indeed more common (but inconsistently) in low SES, while associations for breast were inconsistent due to the screening programme.

Inequalities in cancer risk and prognosis can be addressed by changing lifestyle behaviours, e.g. by addressing smoking. For Denmark several differences in smoking prevalence have been modelled, and all models will reduce the absolute differences in incidence rates of lung cancer between the SES groups, but none will reduce relative inequalities.[60] As it is difficult to change lifestyle behaviours, extra attention should be paid to increase cancer awareness and to ensure early detection, especially in the low SES groups. Thereby prognosis of the low SES individuals will approach those of high SES and socioeconomic disparities will diminish on the long term. However equal access to early detection should then be realised, e.g. by introducing cancer screening programmes. For breast cancer we indeed observed an improved stage distribution (mainly observed for in situ cancers, which were excluded in this study) and survival of all SES groups, but low SES clearly benefited less from the introduction of the screening programme. Thus, socioeconomic inequalities in survival rates even increased,[61] possibly resulting from inequalities in screening participation.[62] In view of the upcoming colorectal cancer screening programme, a high participation rate needs to be realised of low SES individuals.

The following limitations of this study should be mentioned. Firstly, we used an indicator of SES based on the postal code of a residential area and not on individual data on income, education, etc. Since this aggregate covers a relatively small geographical area (on average 17 households), it is likely to represent a reliable approximation of individual SES. Furthermore, routinely collected income tax data have been found to provide reliable estimates of household income.[63] Previous studies in the Netherlands have proven that socioeconomic differences based on neighbourhood data tend to reflect socioeconomic differences accurately at the individual level.[63-65] Secondly, we assumed that the SES indicator did not change during the 10 years before and after 2000. Similar results for survival were obtained with another SES indicator during the period 1983-2002.[61] Thirdly, there were no data on early cancer detection (for example, screening) nor on lifestyle changes, such that causal inferences to explain the observed trends could not be directly evaluated. However, uptake in both breast cancer screening and PSA testing was highest in high SES in the Netherlands.[35] Fourthly, higher life expectancy may explain part of the higher risk in high SES,[66] but we could not address this issue because the exact age distribution of the population was unknown. However, 16% of the male population with low SES was in the oldest group compared to 10% in high SES; for females these percentages were 21% and 13%, respectively.

Nevertheless, calculation of SES-specific incidence rates would better reflect the socioeconomic inequalities than the proportional distribution of the SES categories among the patients which is used in most studies, with the exception of Denmark, Finland and Sweden, which have SES data at the individual level. Furthermore, selection is unlikely to have influenced the results of this population-based study.

Thus, people with a low SES ultimately exhibited the highest incidence of the most common cancers, but over time higher risks were observed among high SES people for frequent cancers like BCC, melanoma (both except females ≥65), breast (females 25-44 years) and prostate cancer. Whether cause or consequence, this may to some extent explain the higher cancer awareness in high SES groups which further increases due to high detection rates. Paradoxically, socioeconomic inequalities in cancer risk may reduce by improving cancer awareness.

ACKNOWLEDGEMENTS

3.1

REFERENCES

1. Faggiano, F., Partanen, T., Kogevinas, M. & Boffetta, P. Socioeconomic differences in cancer incidence and mortality. *IARC Sci Publ*, 65-176 (1997).

2. Dalton, S.O., Steding-Jessen, M., Engholm, G., Schuz, J. & Olsen, J.H. Social inequality and incidence of and survival from lung cancer in a population-based study in Denmark, 1994-2003. *Eur J Cancer* 44, 1989-95 (2008).

3. Baastrup, R., Sorensen, M., Hansen, J., Hansen, R.D., Wurtzen, H. & Winther, J.F. Social inequality and incidence of and survival from cancers of the oesophagus, stomach and pancreas in a population-based study in Denmark, 1994-2003. *Eur J Cancer* 44, 1962-77 (2008).

4. Andersen, Z.J., Lassen, C.F. & Clemmensen, I.H. Social inequality and incidence of and survival from cancers of the mouth, pharynx and larynx in a population-based study in Denmark, 1994-2003. *Eur J Cancer* 44, 1950-61 (2008).

5. Egeberg, R., Halkjaer, J., Rottmann, N., Hansen, L. & Holten, I. Social inequality and incidence of and survival from cancers of the colon and rectum in a population-based study in Denmark, 1994-2003. *Eur J Cancer* 44, 1978-88 (2008).

6. Eriksen, K.T., Petersen, A., Poulsen, A.H., Deltour, I. & Raaschou-Nielsen, O. Social inequality and incidence of and survival from cancers of the kidney and urinary bladder in a population-based study in Denmark, 1994-2003. *Eur J Cancer* 44, 2030-42 (2008).

7. Jensen, K.E., Hannibal, C.G., Nielsen, A., Jensen, A., Nohr, B., Munk, C. & Kjaer, S.K. Social inequality and incidence of and survival from cancer of the female genital organs in a population-based study in Denmark, 1994-2003. *Eur J Cancer* 44, 2003-17 (2008).

8. Birch-Johansen, F., Hvilsom, G., Kjaer, T. & Storm, H. Social inequality and incidence of and survival from malignant melanoma in a population-based study in Denmark, 1994-2003. *Eur J Cancer* 44, 2043-9 (2008).

9. Carlsen, K., Hoybye, M.T., Dalton, S.O. & Tjonneland, A. Social inequality and incidence of and survival from breast cancer in a population-based study in Denmark, 1994-2003. *Eur J Cancer* 44, 1996-2002 (2008).

10. Marsa, K., Johnsen, N.F., Bidstrup, P.E., Johannesen-Henry, C.T. & Friis, S. Social inequality and incidence of and survival from male genital cancer in a population-based study in Denmark, 1994-2003. *Eur J Cancer* 44, 2018-29 (2008).

11. Spadea, T., Zengarini, N., Kunst, A., Zanetti, R., Rosso, S. & Costa, G. Cancer risk in relationship to different indicators of adult socioeconomic position in Turin, Italy. *Cancer Causes Control* 21, 1117-30 (2010).

12. National Cancer Intelligence Network. in Cancer incidence by deprivation. England, 1995-2004 (London, 2009).

13. Pukkala, E. & Weiderpass, E. Time trends in socio-economic differences in incidence rates of cancers of the breast and female genital organs (Finland, 1971-1995). *Int J Cancer* 81, 56-61 (1999).

14. Pukkala, E. & Weiderpass, E. Socio-economic differences in incidence rates of cancers of the male genital organs in Finland, 1971-95. *Int J Cancer* 102, 643-8 (2002).

15. Weiderpass, E. & Pukkala, E. Time trends in socioeconomic differences in incidence rates of cancers of gastro-intestinal tract in Finland. *BMC Gastroenterol* 6, 41 (2006).

16. Conway, D.I., Petticrew, M., Marlborough, H., Berthiller, J., Hashibe, M. & Macpherson, L.M. Socioeconomic inequalities and oral cancer risk: a systematic review and meta-analysis of case-control studies. *Int J Cancer* 122, 2811-9 (2008).

17. van der Aa, M.A., Siesling, S., Louwman, M.W., Visser, O., Pukkala, E. & Coebergh, J.W. Geographical relationships between sociodemographic factors and incidence of cervical cancer in the Netherlands 1989-2003. *Eur J Cancer Prev* 17, 453-9 (2008).

18. Louwman, W.J., van Lenthe, F.J., Coebergh, J.W. & Mackenbach, J.P. Behaviour partly explains educational differences in cancer incidence in the south-eastern Netherlands: the longitudinal GLOBE study. *Eur J Cancer Prev* 13, 119-25 (2004).

3.1

19. de Kok, I.M., van Lenthe, F.J., Avendano, M., Louwman, M., Coebergh, J.W. & Mackenbach, J.P. Childhood social class and cancer incidence: results of the globe study. *Soc Sci Med* 66, 1131-9 (2008).

20. van Loon, A.J., Brug, J., Goldbohm, R.A., van den Brandt, P.A. & Burg, J. Differences in cancer incidence and mortality among socio-economic groups. *Scand J Soc Med* 23, 110-20 (1995).

21. van Loon, A.J., van den Brandt, P.A. & Golbohm, R.A. Socioeconomic status and colon cancer incidence: a prospective cohort study. *Br J Cancer* 71, 882-7 (1995).

22. Smith, R.A., Cokkinides, V., Brooks, D., Saslow, D. & Brawley, O.W. Cancer screening in the United States, 2010: a review of current American Cancer Society guidelines and issues in cancer screening. *CA Cancer J Clin* 60, 99-119 (2010).

23. Soerjomataram, I., de Vries, E., Pukkala, E. & Coebergh, J.W. Excess of cancers in Europe: a study of eleven major cancers amenable to lifestyle change. *Int J Cancer* 120, 1336-43 (2007).

24. Martin-Moreno, J.M., Soerjomataram, I. & Magnusson, G. Cancer causes and prevention: a condensed appraisal in Europe in 2008. *Eur J Cancer* 44, 1390-403 (2008).

25. Soerjomataram, I., Pukkala, E., Brenner, H. & Coebergh, J.W. On the avoidability of breast cancer in industrialized societies: older mean age at first birth as an indicator of excess breast cancer risk. *Breast Cancer Res Treat* 111, 297-302 (2008).

26. de Vries, E., Louwman, M., Bastiaens, M., de Gruijl, F. & Coebergh, J.W. Rapid and continuous increases in incidence rates of basal cell carcinoma in the southeast Netherlands since 1973. *J Invest Dermatol* 123, 634-8 (2004).

27. Duin van, C. & Keij, I. Sociaal-economische status indicator op postcodeniveau. *Maandstatistiek van de bevolking* 50, 32-35 (2002).

28. Nishi, N., Sugiyama, H., Hsu, W.L., Soda, M., Kasagi, F., Mabuchi, K. & Kodama, K. Differences in mortality and incidence for major sites of cancer by education level in a Japanese population. *Ann Epidemiol* 18, 584-91 (2008).

29. Spadea, T., D'Errico, A., Demaria, M., Faggiano, F., Pasian, S., Zanetti, R., Rosso, S., Vicari, P. & Costa, G. Educational inequalities in cancer incidence in Turin, Italy. *Eur J Cancer Prev* 18, 169-78 (2009).

30. Karim-Kos, H.E., de Vries, E., Soerjomataram, I., Lemmens, V., Siesling, S. & Coebergh, J.W. Recent trends of cancer in Europe: A combined approach of incidence, survival and mortality for 17 cancer sites since the 1990s. *Eur J Cancer* 44, 1345-89 (2008).

31. Hemminki, K., Zhang, H. & Czene, K. Socioeconomic factors in cancer in Sweden. *Int J Cancer* 105, 692-700 (2003).

32. Vidarsdottir, H., Gunnarsdottir, H.K., Olafsdottir, E.J., Olafsdottir, G.H., Pukkala, E. & Tryggvadottir, L. Cancer risk by education in Iceland; a census-based cohort study. *Acta Oncol* 47, 385-90 (2008).

33. Cremers, R.G.H.M., Karim-Kos, H.E., Houterman, S., Verhoeven, R.H.A., Schroder, F.H., Van der Kwast, T.H., Kil, P.J.M., Coebergh, J.W.W. & Kiemeney, L.A.L.M. Prostate cancer: trends in incidence, survival and mortality in the Netherlands, 1989-2006. *Eur J Cancer* 46, 2077-2087 (2010).

34. Scales, C.D., Jr., Antonelli, J., Curtis, L.H., Schulman, K.A. & Moul, J.W. Prostate-specific antigen screening among young men in the United States. *Cancer* 113, 1315-23 (2008).

35. Nijs, H.G., Essink-Bot, M.L., DeKoning, H.J., Kirkels, W.J. & Schroder, F.H. Why do men refuse or attend population-based screening for prostate cancer? *J Public Health Med* 22, 312-6 (2000).

36. Horner MJ, R.L., Krapcho M, et al. . in SEER cancer statistics review (1975-2006).

37. Central Bureau of Statistics. in Permanent research into the living situation - Health inquiry (POLS) (Dutch). (2009).

38. Doherty, V.R., Brewster, D.H., Jensen, S. & Gorman, D. Trends in skin cancer incidence by socioeconomic position in Scotland, 1978-2004. *Br J Cancer* 102, 1661-4 (2010).

39. van Hattem, S., Aarts, M.J., Louwman, W.J., Neumann, H.A., Coebergh, J.W., Looman, C.W., Nijsten, T. & de Vries, E. Increase in basal cell carcinoma incidence steepest in individuals with high socioeconomic status: results of a cancer registry study in the Netherlands. *Br J Dermatol* 161, 840-5 (2009).

40. Kelsey, J.L., Gammon, M.D. & John, E.M. Reproductive factors and breast cancer. *Epidemiol Rev* 15, 36-47 (1993).

3.1

41. Rhodes, A.R. Public education and cancer of the skin. What do people need to know about melanoma and nonmelanoma skin cancer? *Cancer* 75, 613-36 (1995).

42. Aarts, M.J., Lemmens, V.E.P.P., Louwman, W.J., Kunst, A.E. & Coebergh, J.W.W. Socioeconomic status and changing inequalities in colorectal cancer? A review of the associations with risk, treatment and outcome. *Eur J Cancer* 46, 2681-95 (2010).

43. Braaten, T., Weiderpass, E., Kumle, M. & Lund, E. Explaining the socioeconomic variation in cancer risk in the Norwegian Women and Cancer Study. *Cancer Epidemiol Biomarkers Prev* 14, 2591-7 (2005).

44. Dalton, S.O., Schuz, J., Engholm, G., Johansen, C., Kjaer, S.K., Steding-Jessen, M., Storm, H.H. & Olsen, J.H. Social inequality in incidence of and survival from cancer in a population-based study in Denmark, 1994-2003: Summary of findings. *Eur J Cancer* 44, 2074-85 (2008).

45. Shack, L., Jordan, C., Thomson, C.S., Mak, V. & Moller, H. Variation in incidence of breast, lung and cervical cancer and malignant melanoma of skin by socioeconomic group in England. *BMC Cancer* 8, 271 (2008).

46. Hussain, S.K., Altieri, A., Sundquist, J. & Hemminki, K. Influence of education level on breast cancer risk and survival in Sweden between 1990 and 2004. *Int J Cancer* 122, 165-9 (2008).

47. Adlard, J.W. & Hume, M.J. Cancer knowledge of the general public in the United Kingdom: survey in a primary care setting and review of the literature. *Clin Oncol (R Coll Radiol)* 15, 174-80 (2003).

48. Fitzpatrick, P., Corcoran, N. & Fitzpatrick, J.M. Prostate cancer: how aware is the public? *Br J Urol* 82, 43-8 (1998).

49. Robb, K., Stubbings, S., Ramirez, A., Macleod, U., Austoker, J., Waller, J., Hiom, S. & Wardle, J. Public awareness of cancer in Britain: a population-based survey of adults. *Br J Cancer* 101 Suppl 2, S18-23 (2009).

50. Schernhammer, E., Haidinger, G., Waldhor, T., Vargas, R. & Vutuc, C. A study of trends in beliefs and attitudes toward cancer. *J Cancer Educ* 25, 211-6 (2010).

51. Parikh-Patel, A., Bates, J.H. & Campleman, S. Colorectal cancer stage at diagnosis by socioeconomic and urban/rural status in California, 1988-2000. *Cancer* 107, 1189-95 (2006).

52. Adams, J., White, M. & Forman, D. Are there socioeconomic gradients in stage and grade of breast cancer at diagnosis? Cross sectional analysis of UK cancer registry data. *Bmj* 329, 142 (2004).

53. Dalton, S.O., During, M., Ross, L., Carlsen, K., Mortensen, P.B., Lynch, J. & Johansen, C. The relation between socioeconomic and demographic factors and tumour stage in women diagnosed with breast cancer in Denmark, 1983-1999. *Br J Cancer* 95, 653-9 (2006).

54. Macleod, U., Mitchell, E.D., Burgess, C., Macdonald, S. & Ramirez, A.J. Risk factors for delayed presentation and referral of symptomatic cancer: evidence for common cancers. *Br J Cancer* 101 Suppl 2, S92-S101 (2009).

55. Kunst, A.E., Groenhof, F., Mackenbach, J.P. & Health, E.W. Occupational class and cause specific mortality in middle aged men in 11 European countries: comparison of population based studies. EU Working Group on Socioeconomic Inequalities in Health. *Bmj* 316, 1636-42 (1998).

56. National Cancer Intelligence Network. in Evidence to March 2010 on cancer inequalities in England (2010).

57. STIVORO. in Trendpublicatie percentage rokers (STIVORO, The Hague, 2010).

58. Graham, H. Smoking prevalence among women in the European community 1950-1990. *Soc Sci Med* 43, 243-54 (1996).

59. Menvielle, G., Boshuizen, H., Kunst, A.E., Dalton, S.O., Vineis, P., Bergmann, M.M., Hermann, S., Ferrari, P., Raaschou-Nielsen, O., Tjonneland, A., Kaaks, R., Linseisen, J., Kosti, M., Trichopoulou, A., Dilis, V., Palli, D., Krogh, V., Panico, S., Tumino, R., Buchner, F.L., van Gils, C.H., Peeters, P.H., Braaten, T., Gram, I.T., Lund, E., Rodriguez, L., Agudo, A., Sanchez, M.J., Tormo, M.J., Ardanaz, E., Manjer, J., Wirfalt, E., Hallmans, G., Rasmuson, T., Bingham, S., Khaw, K.T., Allen, N., Key, T., Boffetta, P., Duell, E.J., Slimani, N., Gallo, V., Riboli, E. & Bueno-de-Mesquita, H.B. The role of smoking and diet in explaining educational inequalities in lung cancer incidence. *J Natl Cancer Inst* 101, 321-30 (2009).

60. Menvielle, G., Soerjomataram, I., de Vries, E., Engholm, G., Barendregt, J.J., Coebergh, J.W. & Kunst, A.E. Scenarios of future lung cancer incidence by educational level: modelling study in Denmark. *European Journal of Cancer* 46, 2625-32 (2010).

61. Louwman, W.J., van de Poll-Franse, L.V., Fracheboud, J., Roukema, J.A. & Coebergh, J.W. Impact of a programme of mass mammography screening for breast cancer on socio-economic variation in survival: a population-based study. *Breast Cancer Res Treat* 105, 369-75 (2007).

62. Aarts, M.J., Voogd, A.C., Duijm, L.E.M., Coebergh, J.W. & Louwman, M. Socioeconomic inequalities in attending the mass screening for breast cancer in the south of the Netherlands - associations with stage at diagnosis and survival. *Breast Cancer Res Treat* 128, 517-25 (2011).

63. Bos, V., Kunst, A.E. & Mackenbach, J. in Verslag aan de Programmacommissie Sociaal-economische gezondheidsverschillen II (Instituut Maatschappelijke Gezondheidszorg, Erasmus Universiteit, Rotterdam, 2000).

64. Smits, J., Keij, I. & Westert, G.P. Effecten van sociaal-economische status van kleine, middelgrote en grote geografische eenheden op de sterfte [in Dutch]. *Maandstatistiek van de bevolking* 11, 4-10 (2001).

65. Bos, V., Kunst, A.E. & Mackenbach, J.P. in Sociaal-economische gezondheidsverschillen: Van verklaren naar verkleinen (ed. Stronks, K.) 8-20 (Zon/MW, Den Haag, 2001).

66. Kardal, M., Lodder, B.J. & Garssen, J. [Life expectancy increasing, but gap between people of higher and lower educational level remains]. *Ned Tijdschr Geneeskd* 153, A689 (2009).

3.1

DECISION
CURATIVE
ROLE
SINCE 1990
data
RECOGNISING
OUTCOME
BRACHYTHERAPY
DETERMINANTS
CATEGORY
HOUSING
health seeking behaviour
METASTASIS
CONTRIBUTION
RADIOTHERAPY
COVERAGE
INTERVAL CANCER
CHARLSON
socioeconomic position
GP
estimated
annual
percent
change
axillary
staging
material resources
EAPC
DISCUSS
statistical
STUDIES
SMOKING
central nervous system
HOSPITAL
staging
socioeconomic status
lifestyle
Eindhoven Cancer Registry
dementia
Comprehensive Cancer Centre South
intelligence
education
hazard
ratio
HYPERTENSION
RISK FACTORS
mastectomy
diagnostics
DIAGNOSIS
distribution
CARDIOVASCULAR DISEASE
SEP
stage
HORMONAL THERAPY
VISITS
ATTENDANCE
EXPLANATION
SOCIAL SUPPORT
FEAR
colorectal
therapy
HIGH
MENTAL
ADVANCED
UPBRINGING
ENVIRONMENT
MAMMOGRAPHY
PHYSICAL
prostatectomy
p-value
QUESTIONNAIRE
incidence
HEALTH BEHAVIOUR
SF-36
GLOBE
NEIGHBOURHOOD
EXPOSURE
LOW
value of housing
socioeconomic
SOCIOEC
occupation
ALCOHOL CONSUMPTION
INTERMEDIATE
TUBERCULOSIS
physical activity
REVIEW
colorectal
cancer
screening
comorbidities
CHEMORADIATION
INVITATION
INVASIVE
CONTACTS
gap
concomitant disease
VARIATION
logistic
regression
ACCESS TO CARE
CONSULTATION
ASSETS
numbers
PSA
LOCALISED
WORK
SCREEN-DETECTED TUMOUR
income
percentages
THE NETHERLANDS
HEALTH INSURANCE
health awareness
HOUSEHOLD
search
DETECTIO

Chapter 3.2

Increase in basal cell carcinoma incidence steepest in individuals with high socioeconomic status: results of a cancer registry study in the Netherlands

S. van Hattem, M.J. Aarts, W.J. Louwman, H.A.M. Neumann, J.W.W. Coebergh, C.W.N. Looman, T. Nijsten, E. de Vries

ABSTRACT

Background

Basal Cell Carcinoma (BCC) and Malignant Cutaneous Melanoma (MM) development are both associated with acute and intermittent sun exposure. In contrast to MM, the association between socioeconomic status (SES) and BCC is not well documented.

Objectives

To investigate the incidence of BCC according to SES, stratifying by age and tumour localization in a large population-based cohort. To assess changes over time in the distribution of the BCC patients across the SES categories.

Methods

All patients with a histologically confirmed first primary BCC (N=27,027) diagnosed between 1988 and 2005 in the Southeast of the Netherlands were stratified by sex, age (25-44, 45-64 and ≥65 years), period of diagnosis, SES category (based on income and value of housing) and localization of the BCC. Age-standardized BCC incidence rates were calculated for the year 2004 by SES category and localization. Ordinal regression was used to assess changes over time in the proportion of BCC patients, by sex, age and SES.

Results

For men in all age groups higher BCC incidence in the highest SES category was observed, which remained significant after stratification for tumour localization. For females a consistent relationship was only found in younger females (<65 years) for truncal BCCs, occurring more frequently in high SES groups. Between 1990 and 2004, the proportion of BCC patients with high SES increased (+6%) and the proportion with low SES decreased (-7%).

Conclusion

High SES is associated with increased incidence of BCC among men. Our data suggest that BCC is changing from a disease of the poor to a disease of the rich.

3.2

INTRODUCTION

Basal Cell Carcinoma (BCC) is the most common malignancy in Caucasians and incidence rates are still increasing.[1] BCC associated mortality is extremely rare, but BCCs often cause considerable functional and cosmetic morbidity and costs because of their high prevalence.[2-5] Malignant melanoma (MM), another type of skin cancer, and BCC share several interesting features such as the risk factor of acute and intermittent UV exposure at young age. MM is more common among those with high socioeconomic status (SES).[6-8] The distribution of BCC by SES groups is scarcely documented: higher incidence of BCC among high SES has been described in a cohort in the U.K.[9], in Finland (non-significant gradient)[10] and in a small cohort in the Southeast of the Netherlands.[11] None of these reports focused on trends over time in the distribution of patients across the SES categories. Since the 1980s the exposure to UV radiation among Dutch inhabitants has probably changed due to (SES-related) changes in sun tanning behaviour, increased affordability of holidays to the sun and outdoor activities.[11]

No reports are available on the sublocalization of BCCs in association with SES. It appears that BCCs are shifting from head and neck in elderly males to truncal BCCs in young and middle aged females.[2, 12] This is most likely related to increased intermittent exposure to UV radiation[2, 12] that may be socioeconomically determined.

To address these issues, the primary objective of this study was to describe the distribution of BCC patients by SES group in a large population-based study, stratifying by sex, age and anatomical localization. The secondary objective was to assess changes in SES distribution over time by determining the proportion of BCC patients in different SES groups by period of diagnosis.

METHODS
Study population
Data on patients diagnosed with BCC between 1988 and 2005 were retrieved from the Eindhoven Cancer Registry (ECR), which is recognised traditionally as the monitoring registry for BCC within the Netherlands Cancer Registry. The ECR records data on all patients newly diagnosed with cancer in the south-eastern part of the Netherlands and covers an area with 2.4 million inhabitants (about 15% of the Dutch population) and has been described in detail previously.[2] All persons with a histological proven first primary BCC diagnosed between 1988 and 2005 were included. Data were presented following the STROBE guidelines.[13]

Socioeconomic Status
An indicator for SES developed by Statistics Netherlands was used.[14] SES of the patient was defined at the neighbourhood level (based on 6-digit postal code of residence area) combining mean household income (in 1998) and mean economic value of the house/apartment (in 2000), derived from individual fiscal data made available at an aggregated level. On average each postal code area contains 17 households, thus a very small geographic area.[14, 15] The use of routinely collected income fiscal data assures the reliability of the estimates of household incomes. Postal codes were assigned to three SES categories: low (1st-3rd deciles), intermediate (4th-7th deciles) and high (8th-10th deciles). A separate SES category was made with postal codes of care providing institutions, because assigning SES for those

3.2

living in a nursing home or other care providing institution is very difficult (if not impossible). This SES measure is assumed to be valid for 10 years before and after the base year (2000) and is therefore available from 1990 to 2004.[14, 15]

For the year 2004, population data according to SES, age and sex were available, enabling calculation of specific incidence rates for each SES category. Such source population data were not available for the other years. Therefore, trends in SES distribution over time (1990-2004) were calculated using proportions of BCC patients by SES category.

Analysis

Incidence rates were calculated for the period 1988-2005, age-adjustment was performed by direct standardization according to the European Standard Population (European Standardized Rates (ESR), per 100,000 person-years). SES-specific BCC incidence rates in the year 2004 were calculated by sex and tumour localization for each age category separately (25-44, 45-64, 65+ years) and were age-standardized (ESR). Tests for trends were calculated using Poisson regression.

To assess changes in SES distribution over time, ordinal logistic regression analysis was performed. The model used for calculating the distribution of BCC patients across SES categories at a certain point in time (t_x) is given in Appendix 1.

Incidence analyses were performed using SAS 9.1, other analyses were performed using SPSS 15 software. *P*-values were two-sided and values <0.05 were considered significant.

RESULTS

Overall incidence data

BCC incidence was higher among men than among women. Between 1988 and 2005, age-adjusted incidence rates (ESR) increased from 54.0 to 113.6/100,000 person-years in women and from 79.3 to 127.4/100,000 person-years in men (Figure 1).
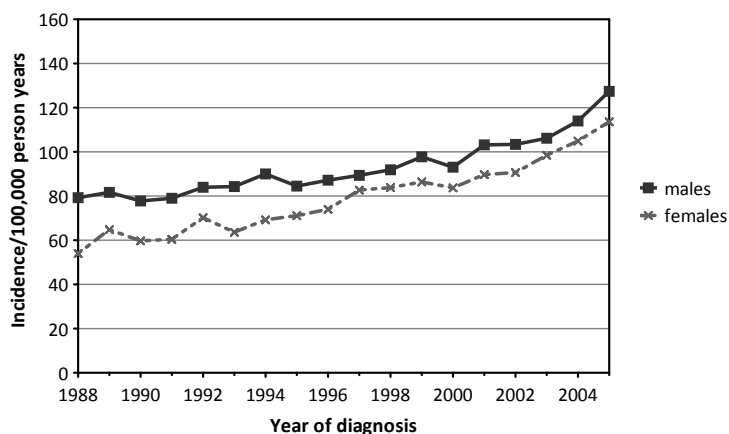

Figure 1. Age-adjusted incidence rates (European Standardized Rates) for basal cell carcinoma from 1988 to 2005.

Basal cell carcinoma incidence by socioeconomic status

Detailed data by SES were available for 27,027 persons diagnosed with a first primary BCC (missing SES data n= 493 [1.8%]). BCC incidence was calculated for the year 2004, stratified by SES, age and sex (Figure 2). A significant relationship between BCC incidence and SES was found for men only: a higher BCC incidence rate in the high SES category in all age groups (men: $P<0.001$ and women: $P=0.7$). Elderly (≥65 years) male patients were significantly more likely to develop a first BCC than females in all SES categories ($P <0.001$), while the incidence among women of 25 to 44 years was twice the incidence among men ($P <0.0001$).

In both sexes and age groups, the proportion of BCC patients increased significantly with 6% in the high SES category and decreased with 7% in the lowest SES group between 1990 and 2004 (P -value for trend for α and β <0.05, Figure 3). The proportion of BCC patients in the high SES category increased more markedly in people <65 years than in those ≥65 years. The proportion of patients with missing SES data was small (<3% per year) but fluctuated significantly over time ($P=0.001$, data not shown).
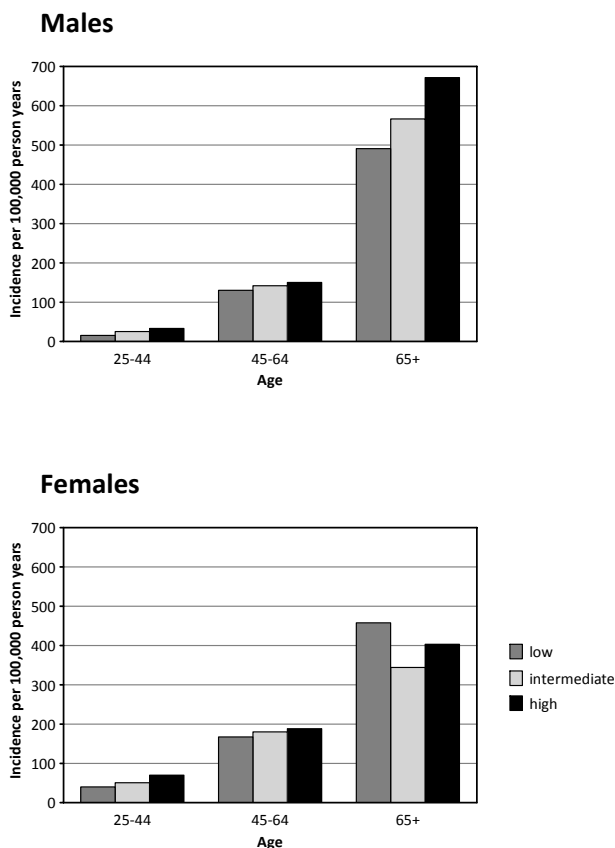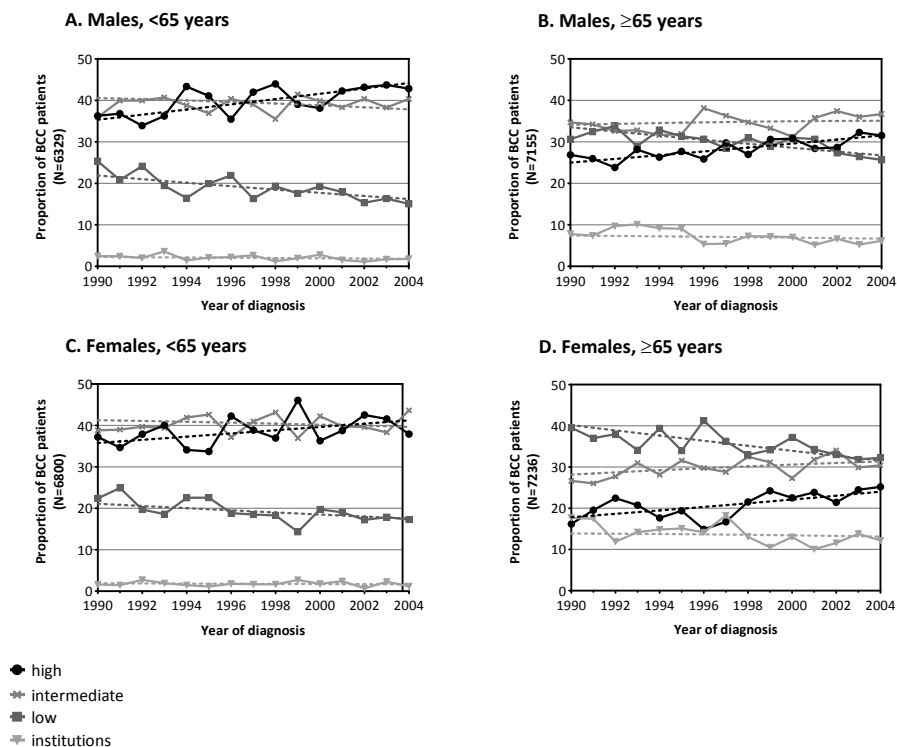
3.2

Figure 2. *Age-specific incidence rates for basal cell carcinoma by socioeconomic status and sex, 2004.*

A. Males, <65 years

B. Males, ≥65 years

C. Females, <65 years

D. Females, ≥65 years

3.2

● high
＊ intermediate
■ low
┬ institutions

Males <65 years:
αSES_{low} = -1.272 P = 0.000
$\alpha SES_{institutions}$ = -1.145 P = 0.000
$\alpha SES_{intermediate}$ = 0.605 P = 0.000
β = 0.02648 P = 0.000

Males ≥ 65 years:
αSES_{low} = -0.685 P = 0.000
$\alpha SES_{institutions}$ = -0.367 P = 0.001
$\alpha SES_{intermediate}$ = 1.099 P = 0.000
β = 0.02311 P = 0.000

Females <65 years:
αSES_{low} = -1.319 P = 0.000
$\alpha SES_{institutions}$ = -1.209 P = 0.000
$\alpha SES_{intermediate}$ = 0.586 P = 0.000
β = 0.01646 P = 0.002

Females ≥ 65 years:
αSES_{low} = -0.399 P = 0.000
$\alpha SES_{institutions}$ = 0.161 P = 0.001
$\alpha SES_{intermediate}$ = 1.528 P = 0.000
β = 0.02678 P = 0.000

For females <65 years, subdivision of different SES categories in 1990 (=0) is calculated using the model:

$$propSES_{low,1990} = \frac{\exp(-1.319 - 0.01646 * (1990 - 1990))}{1 + \exp(-1.319 - 0.01646 * (1990 - 1990))}$$

$$propSES_{institutions,1990} = \frac{\exp(-1.209 - 0.01646 * (1990 - 1990))}{1 + \exp(-1.209 - 0.01646 * (1990 - 1990))} - prop(SES_{low,1990})$$

$$propSES_{intermediate,1990} = \frac{\exp(0.586 - 0.01646 * (1990 - 1990))}{1 + \exp(0.586 - 0.01646 * (1990 - 1990))} - \sum prop(SES_{low} + SES_{institutions})$$

$$propSES_{high,1990} = 1 - \sum prop(SES_{low} + SES_{institutions} + SES_{intermediate})$$

Figure 3. *Proportion of patients with basal cell carcinoma (BCC) according to socioeconomic status (SES) and time.*

Basal cell carcinoma incidence rates by socioeconomic status category, sex and localization

Among men, highest BCC incidence rates were observed in the high SES categories across all age groups (Table 1). Among women this association was less consistent. The majority of all BCCs (73%) occurred in the head and neck region. After stratification by localization of BCC, incidence was still significantly highest among high SES in males in all localizations. Among females this association was only noted for truncal BCC (Table 1). For young (<45 years) and middle aged women (45-64 years) rates for BCC on intermittently exposed body sites (trunk, arms and legs) were significantly higher across all SES categories than for males in the same age category.

3.2

Table 1. Age-specific incidence rates (per 100,000 person-years) for basal cell carcinoma by socioeconomic status, localization, sex and age category, 2004. P-values are for trends, independent of age.

Age (years)	Head and neck			Trunk			Extremities		
	Socioeconomic status			Socioeconomic status			Socioeconomic status		
	Low	Inter-mediate	High	Low	Inter-mediate	High	Low	Inter-mediate	High
Men									
25-44	9.0	14.6	21.4	5.2	6.3	7.5	1.3	4.4	4.3
45-64	102.7	94.9	118.6	22.0	30.9	41.6	5.5	16.2	28.1
65+	370.8	412.4	457.6	73.1	68.7	114.4	47.0	85.4	99.7
P-value trend	0.009			0.004			0.000		
Women									
25-44	21.4	27.6	24.4	16.0	20.4	32.2	2.7	2.6	13.3
45-64	120.7	113.8	105.7	33.1	39.3	43.2	13.6	27.0	39.4
65+	322.7	228.5	281.0	40.3	54.7	52.1	94.8	61.1	70.2
P-value trend	0.2			0.027			0.2		

DISCUSSION

In this large Dutch population-based study we investigated whether incidence of BCC was higher among high SES groups and how the distribution of BCC patients across SES categories changed over time. During the study period (1988-2005), we observed rising incidence of BCC, with highest incidence among males and diminishing sex differences.

Among males, incidence of BCC was consistently higher among high SES in 2004, confirming results of previous studies.[9-11] The association of BCC and SES was less consistent in females, probably resulting from more homogenous UV exposure.[16] Previous studies postulated that the increased risk of BCC in high SES was due to more frequent travel overseas,[9] i.e. intermittent sun exposure.[17-19] Furthermore, better health-awareness and more health-seeking behaviour were reported among high SES,[9] although the latter should only have minor influence in the Netherlands since access to Dutch care is equal due to universal health insurance.

To our knowledge, this is the first study about anatomical localization of BCC and SES. In males incidence was highest among high SES for all subsites; in females this trend was only significant for truncal BCCs. For MM, increased risk of non-facial parts in high SES males has been reported, while for facial MM and in women no clear associations were noted.[16] Different aetiological pathways of BCC development between anatomical sites may be involved in the subsite inequalities observed between males and females.[8, 16] Furthermore, recreational sun exposure, clothing habits and tanning behaviour[2, 16, 20] may differ across sexes, resulting in different UV exposure patterns. Nodular BCCs mainly occur on chronically sun-exposed skin, such as the face, whereas superficial BCC occur more frequently on intermittently exposed skin, such as the trunk.[8, 21] If the exposure pattern differs between sex, then the occurrence of BCCs on the chronically and intermittently exposed body sites is likely to be influenced more by this sex difference in exposure then by SES gradients.

From 1990 to 2004 the proportion of BCC patients with high SES was increasing at approximately the same rate as the rate of decrease of the proportion with low SES. This suggests that BCC is changing from a poor to a rich people's disease. Indeed, as discussed previously, UV exposure patterns have changed in The Netherlands since the 1980s and these are likely related to SES.[11] Furthermore, better awareness of BCCs among high social classes may also result in increased reporting.

The SES indicator is an aggregate measure at one point in time (2000) and we assumed that it did not change 10 years before and after the base year. This assumption seems to be valid, since an older indicator gave similar results during the period 1983-2002.[22] Therefore, we assumed the SES indicator is valid from 1990 to 2002, and will also be valid from 2003 to 2005.

In more than 27,000 BCC patients from the Dutch population, the association between BCC incidence and SES was studied, also stratified for localization. A major limitation of this study is the absence of data on skin type and UV exposure patterns, which are not included in the cancer registry and about which no articles have been published. UV exposure differences

3.2

are most likely limited due to the small geographic area covered by the Eindhoven Cancer Registry, although behaviour patterns may still result in different exposures. The perhaps higher percentage of immigrants among low SES groups could potentially affect our results since immigrants probably have a lower risk of SES due to a darker skin. However, only few immigrants live in the study region, therefore, this influence will be of minor importance.[23] Better health-awareness and health-seeking behaviour among high SES could induce selection bias. On the other hand, better health awareness may be associated with safer UV exposure patterns and increased reporting of BCCs, thereby reducing the effect of selection bias.

In conclusion, this study shows that incidence of BCC was consistently higher among high SES in men for all subsites, while in females less consistent results were found. During the 15-year study period the proportion of BCC patients in the high SES categories increased at the same rate as the proportion with low SES was decreasing. This observation needs to be confirmed in additional studies that include histopathology, skin type and UV exposure data, but suggests that BCC is changing from a disease of the poor to a disease of the rich.

ACKNOWLEDGEMENTS

3.2

REFERENCES

1. Marks, R. An overview of skin cancers. Incidence and causation. *Cancer* 75, 607-12 (1995).

2. de Vries, E., Louwman, M., Bastiaens, M., de Gruijl, F. & Coebergh, J.W. Rapid and continuous increases in incidence rates of basal cell carcinoma in the southeast Netherlands since 1973. *J Invest Dermatol* 123, 634-8 (2004).

3. Marcil, I. & Stern, R.S. Risk of developing a subsequent nonmelanoma skin cancer in patients with a history of nonmelanoma skin cancer: a critical review of the literature and meta-analysis. *Arch Dermatol* 136, 1524-30 (2000).

4. Preston, D.S. & Stern, R.S. Nonmelanoma cancers of the skin. *N Engl J Med* 327, 1649-62 (1992).

5. Roenigk, R.K., Ratz, J.L., Bailin, P.L. & Wheeland, R.G. Trends in the presentation and treatment of basal cell carcinomas. *J Dermatol Surg Oncol* 12, 860-5 (1986).

6. Aase, A. & Bentham, G. Gender, geography and socio-economic status in the diffusion of malignant melanoma risk. *Soc Sci Med* 42, 1621-37 (1996).

7. Braaten, T., Weiderpass, E., Kumle, M. & Lund, E. Explaining the socioeconomic variation in cancer risk in the Norwegian Women and Cancer Study. *Cancer Epidemiol Biomarkers Prev* 14, 2591-7 (2005).

8. Lee, J.A. & Strickland, D. Malignant melanoma: social status and outdoor work. *Br J Cancer* 41, 757-63 (1980).

9. Lear, J.T., Tan, B.B., Smith, A.G., Bowers, W., Jones, P.W., Heagerty, A.H., Strange, R.C. & Fryer, A.A. Risk factors for basal cell carcinoma in the UK: case-control study in 806 patients. *J R Soc Med* 90, 371-4 (1997).

10. Milan, T., Verkasalo, P.K., Kaprio, J. & Koskenvuo, M. Lifestyle differences in twin pairs discordant for basal cell carcinoma of the skin. *Br J Dermatol* 149, 115-23 (2003).

11. de Kok, I.M., van Lenthe, F.J., Avendano, M., Louwman, M., Coebergh, J.W. & Mackenbach, J.P. Childhood social class and cancer incidence: results of the globe study. *Soc Sci Med* 66, 1131-9 (2008).

12. Coebergh, J.W., Neumann, H.A., Vrints, L.W., van der Heijden, L., Meijer, W.J. & Verhagen-Teulings, M.T. Trends in the incidence of non-melanoma skin cancer in the SE Netherlands 1975-1988: a registry-based study. *Br J Dermatol* 125, 353-9 (1991).

13. von Elm, E., Altman, D.G., Egger, M., Pocock, S.J., Gotzsche, P.C. & Vandenbroucke, J.P. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Bmj* 335, 806-8 (2007).

14. Duin van, C. & Keij, I. Sociaal-economische status indicator op postcodeniveau. *Maandstatistiek van de bevolking* 50, 32-35 (2002).

15. Louwman, W.J., van de Poll-Franse, L.V., Fracheboud, J., Roukema, J.A. & Coebergh, J.W. Impact of a programme of mass mammography screening for breast cancer on socio-economic variation in survival: a population-based study. *Breast Cancer Res Treat* 105, 369-75 (2007).

16. Perez-Gomez, B., Aragones, N., Gustavsson, P., Lope, V., Lopez-Abente, G. & Pollan, M. Socio-economic class, rurality and risk of cutaneous melanoma by site and gender in Sweden. *BMC Public Health* 8, 33 (2008).

17. Armstrong, B.K. & Kricker, A. The epidemiology of UV induced skin cancer. *J Photochem Photobiol B* 63, 8-18 (2001).

18. Kricker, A., Armstrong, B.K., English, D.R. & Heenan, P.J. Does intermittent sun exposure cause basal cell carcinoma? a case-control study in Western Australia. *Int J Cancer* 60, 489-94 (1995).

19. Rosso, S., Zanetti, R., Pippione, M. & Sancho-Garnier, H. Parallel risk assessment of melanoma and basal cell carcinoma: skin characteristics and sun exposure. *Melanoma Res* 8, 573-83 (1998).

20. Boyd, A.S., Shyr, Y. & King, L.E., Jr. Basal cell carcinoma in young women: an evaluation of the association of tanning bed use and smoking. *J Am Acad Dermatol* 46, 706-9 (2002).

21. McCormack, C.J., Kelly, J.W. & Dorevitch, A.P. Differences in age and body site distribution of the histological subtypes of basal cell carcinoma. A possible indicator of differing causes. *Arch Dermatol* 133, 593-6 (1997).

3.2

22. Schrijvers, C.T., Coebergh, J.W., van der Heijden, L.H. & Mackenbach, J.P. Socioeconomic variation in cancer survival in the southeastern Netherlands, 1980-1989. *Cancer* 75, 2946-53 (1995).

23. Tas, R. & De Jong, A. in Regionale vestingspatronen van immigranten, 1988-2002 [WWW document]. URL http:// www.cbs.nl/nl-NL/menu/themas/dossiers/allochtonen/publicaties/artikelen/ archief/2003/2003-k4-b-15-p038-art.htm (Central Bureau of Statistics, 2003).

Appendix 1.

Model to calculate the distribution of BCC patients across SES categories at a certain point in time t_x. For values α and β see Figure 3A-D.

$$\text{propSES}_{low,1990} = \frac{\exp(-1.319 - 0.01646 * (1990 - 1990))}{1 + \exp(-1.319 - 0.01646 * (1990 - 1990))}$$

$$\text{propSES}_{institutions,1990} = \frac{\exp(-1.209 - 0.01646 * (1990 - 1990))}{1 + \exp(-1.209 - 0.01646 * (1990 - 1990))} - \text{prop}(\text{SES}_{low,1990})$$

$$\text{propSES}_{intermediate,1990} = \frac{\exp(0.586 - 0.01646 * (1990 - 1990))}{1 + \exp(0.586 - 0.01646 * (1990 - 1990))} - \sum \text{prop}(\text{SES}_{low} + \text{SES}_{institutions})$$

$$\text{propSES}_{high,1990} = 1 - \sum \text{prop}(\text{SES}_{low} + \text{SES}_{institutions} + \text{SES}_{intermediate})$$

1990= the year 1990 (reference point).
α: intercept; the mean value of SES (low, intermediate, institutions or high) at t=0 (=1990).
β represents the slope and indicates the average change in proportion of SES with increasing year of diagnosis.

Chapter 3.3

Socioeconomic inequalities in attending the mass screening for breast cancer in the south of the Netherlands - associations with stage at diagnosis and survival

M.J. Aarts, A.C. Voogd, L.E.M. Duijm, J.W.W. Coebergh, W.J. Louwman

ABSTRACT

Purpose
The associations of socioeconomic status (SES) and participation in the breast cancer screening program, as well as consequences for stage of disease and prognosis were studied in the Netherlands, where no financial barriers for participating or health care use exist.

Methods
From 1998 to 2005 1,067,952 invitations for biennial mammography were sent to women aged 50-75 in the region covered by the Eindhoven Cancer Registry. Screening attendance rates according to SES were calculated. Tumor stage and survival were studied according to SES group for patients diagnosed with breast cancer between 1998 and 2006, whether screen-detected, interval carcinoma or not attended screening at all.

Results
Attendance rates were rather high: 79%, 85% and 87% in women with low, intermediate and high SES (p<0.001). Compared to the low SES group, odds ratios for attendance were 1.5 (95%CI:1.5-1.6) for the intermediate SES group and 1.8 (95%CI:1.7-1.8) for the high SES group. Moreover, women with low SES had an unfavorable TNM stage compared to those with high SES. This was seen in non-attendees, among women with interval cancers and with screen-detected cancers. Among non-attendees and interval cancers the socioeconomic survival disparities were largely explained by stage distribution (48% and 35%) and to a lesser degree by therapy (16% and 16%). Comorbidity explained most survival inequalities among screen-detected patients (23%).

Conclusions
Despite the absence of financial barriers for participation in the Dutch mass screening program, socioeconomic inequalities in attendance rates exist, and women with low SES had a significantly worse tumor stage and lower survival rate.

3.3

INTRODUCTION

Breast cancer screening programs aim to reduce breast cancer mortality rates through early cancer detection. To optimize the effectiveness of the current screening programs it is especially important to reach women at high risk of advanced stage disease at diagnosis and concomitant lower survival rates.

In many countries, the proportion of women having a screening mammogram has been highest among those with high socioeconomic status (SES), independent of the presence of organized breast screening programs.[1-4] For example, between 2000 and 2005, in the U.S. 65% of women aged 40 years or older with a low income had a screening mammogram within the previous two years compared to 83% of women with a high income.[1]

Patients with low SES have a more advanced stage distribution than those with high SES,[5-7] which may be due to their lower screening attendance. Furthermore, breast cancer survival rates are highest among patients with high SES.[8-11] Conflicting reports exist as to whether socioeconomic differences in breast cancer survival are due to socioeconomic differences in stage distribution.[12-14] The presence of concomitant diseases may also partly explain a SES gradient in breast cancer survival.[15]

Socioeconomic inequalities in adherence to mammography screening have been found in several countries.[1-4] For the Netherlands, a country with equal access to screening and care for all women, these data are lacking. We hypothesized that Dutch women with low SES also show lower screening attendance rates, more advanced stage breast cancers and worse survival. Therefore, we conducted a regional study on SES and screening attendance and we explored the consequences of socioeconomic differences in attendance rate for the stage distribution at diagnosis and survival.

MATERIALS AND METHODS

The population-based screening program for breast cancer in southern Netherlands (Bevolkings Onderzoek Borstkanker Zuid, BoBZ) was started in 1991 and fully implemented in 1996. The program initially offered biennial screening mammography to women aged 50-69 years; in 1998 the upper age limit was extended to 75. The attendance rate was more than 84%.[16] The BoBZ database was used to select all women invited for screening from 1998 to 2005. These women received an invitation letter approximately 2 weeks before the screening. Reminder letters with a new appointment were sent to women who did not appear.

The Eindhoven Cancer Registry (ECR) records data on all patients newly diagnosed with cancer in the southern part of the Netherlands, an area with currently 2.4 million inhabitants (about 15% of the Dutch population) and only non-university hospitals. Trained registry personnel actively collects data on diagnosis, staging (Tumor-Node-Metastasis–TNM [17]), treatment and comorbidity (slightly adapted from Charlson [18]) from the medical records after notification by pathologists and medical registration offices. Previous admissions, letters from and to general practitioners and other specialists, medical history and preoperative

screening were used as sources. Pathological and clinical TNM were combined into one variable, primarily referring to the pathological stage unless missing.

The regions of the BoBZ and ECR cover an area of approximately 2.2 million inhabitants. Linkage of the databases of BoBZ and the ECR enabled us to compare stage at diagnosis of patients who attended with those who did not attend screening in the two years preceding diagnosis. Only invasive breast cancers and ductal carcinoma *in situ* (DCIS) were included. Screen-detected breast cancers were defined as registry-ascertained cancers if breast cancer had been diagnosed within 1 year following positive screening mammography (i.e., a woman had been referred for evaluation of a screening abnormality). Interval cancers were registry-ascertained cancers if 1) breast cancer had been diagnosed within 24 months following a negative screen (i.e., a woman had not been referred after screening mammography); or 2) breast cancer had been diagnosed 12-24 months after a positive screen. Patients with breast cancer diagnosed more than 2 years after screening mammography were considered to have not attended the screening program.

Statistics Netherlands developed an indicator of SES, using individual fiscal data based on the economic value of the home and household income. This SES indicator is provided at an aggregated level for each postal code (covering an average of 17 households). SES was categorized as low (deciles 1-3), medium (deciles 4-7), or high (deciles 8-10). A separate class was used for postal codes in areas comprising a long-term care providing institution (such as a nursing home).[19]

Statistics

Statistical analyses were performed using SAS version 9.1 (SAS Institute Inc., Cary, NC, U.S.A.). All tests were two-sided and considered significant if $p \leq 0.05$. The distribution of sociodemographic and clinical characteristics were studied across the SES strata. Significance was tested with non-parametric tests (continuous variables) and χ^2-tests (categorical variables). Attendance rates according to SES were computed according to year of invitation and age category. Stage comparisons were based on invasive and non-invasive tumors. Survival analyses were based on invasive cancers only. Survival time was defined as the time from diagnosis to death or January 1st, 2009 for the patients who were still alive. Survival analyses were stratified into 1) screen-detected cancers, 2) interval cancers 3) patients who did not attend the screening program.

Univariate SES differences in survival were evaluated with the log rank test. The crude survival was calculated with the life test method and the independent prognostic effect of SES was estimated using Cox regression analyses. The hazard rates for death were adjusted for age (51≤60 versus ≤50, 61≤70, 71≤75 or ≥76). Subsequently we added the mediators stage (stages I versus II, III, IV or unknown) and therapy (surgery+radiotherapy versus surgery+radiotherapy+systemic therapy, surgery alone, surgery+systemic therapy or systemic therapy alone/other therapy/unknown), and the confounder comorbidity (no versus yes or unknown), and the combination of these to investigate whether the effect of SES on prognosis could be explained by differences in stage, treatment or comorbidity. Hazard ratios (HR) with 95% confidence intervals were reported. The relative contributions of comorbidity,

3.3

treatment or stage were calculated with the formula: (((HR model adjusted for age) - (HR model adjusted for age +comorbidity or stage or treatment))/(HR model adjusted for age − 1))*100.

RESULTS
Attendance rates

From 1998 to 2005, the BoBZ sent 1,112,263 invitations for breast examination to women living in the area covered by the ECR. Those with unknown SES (11,166) and those living at a postal code that includes an institution, such as nursing homes or rehabilitation centers, (33,145) were excluded, leaving data of 1,067,952 invitations to be analyzed (Figure 1, Table 1).

Attendance rates showed a positive correlation with increasing SES and were respectively 79%, 85% and 87% for women with low, intermediate or high SES ($p<0.001$). Among screening attendees, the first screening mammography was made for 12%, 14% and 15% of low, intermediate and high SES. During the study period, attendance increased slightly from 77%, 84% and 86% to 80%, 87% and 88% for low, intermediate and high SES (Figure 2). The socioeconomic inequalities in screening attendance was significant in all years and in all age categories ($p<0.001$). Among non-attendees, women with high SES more often informed

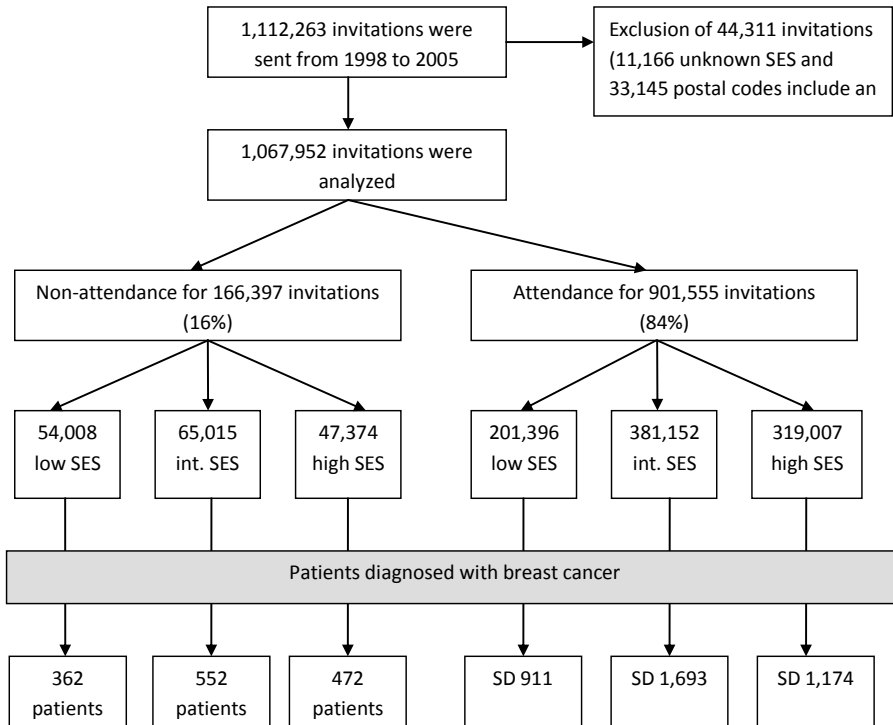
Figure 1. *Flow-chart of the invitations and attendance of breast cancer screening according to socioeconomic status. Int.: intermediate, interv: interval cancer, SD: screen-detected cancer, SES: socioeconomic status.*

Table 1. *Characteristics of women invited for mass breast cancer screening and multivariable analyses of the odds of attending the mass breast cancer screening in southern Netherlands.*

	Characteristics				Multivariable analyses	
	Not attended		Attended		Odds of attending	
	N	%	N	%	OR	(95%CI)
Age						
<50	12586	8%	67768	8%	**0.96**	(0.9-1.0)
50-54	34097	20%	190490	21%	1.00	
55-59	34533	21%	207443	23%	**1.08**	(1.1-1.1)
60-64	27779	17%	169409	19%	**1.13**	(1.1-1.1)
65-69	25886	16%	147179	16%	**1.08**	(1.1-1.1)
70-75	27247	16%	108970	12%	**0.73**	(0.7-0.7)
>75	4269	3%	10296	1%	**0.31**	(0.2-0.4)
Year of invitation						
1998	19329	12%	95121	11%	1.00	
1999	20007	12%	100765	11%	**1.09**	(1.1-1.1)
2000	21490	13%	113472	13%	**1.11**	(1.1-1.1)
2001	20487	12%	103502	11%	**1.09**	(1.1-1.1)
2002	22396	13%	123958	14%	**1.15**	(1.1-1.2)
2003	19427	12%	114023	13%	**1.26**	(1.2-1.3)
2004	23397	14%	132171	15%	**1.16**	(1.1-1.2)
2005	19864	12%	118543	13%	**1.27**	(1.2-1.3)
Socioeconomic status						
Low	54008	32%	201396	22%	1.00	
Intermediate	65015	39%	381152	42%	**1.54**	(1.5-1.6)
High	47374	28%	319007	35%	**1.75**	(1.7-1.8)

All values are adjusted for age, year of invitation and socioeconomic status. OR: odds ratio, 95% CI: 95% confidence interval. Values in bold are significant.
Women <50 were included as they are first invited in the year of their 50th birthday. Some women aged >75 were included as they received their last invitation just before their 76th birthday.

the screening organization about their refusal (54%) than women with low SES (38%). The most common reason for not attending the screening was "having a self-reported medical condition related to the breast."

After adjustment for age and year of invitation, an odds ratio (OR) for attending breast screening of 1.75 (95% confidence interval: 1.7-1.8) was found if comparing women with high SES to women with low SES, whereas women with intermediate SES had an OR of 1.54 (95% CI: 1.5-1.6, Table 1). The odds of attending the screening increased from the age of 50 until 70 and with each year of invitation.
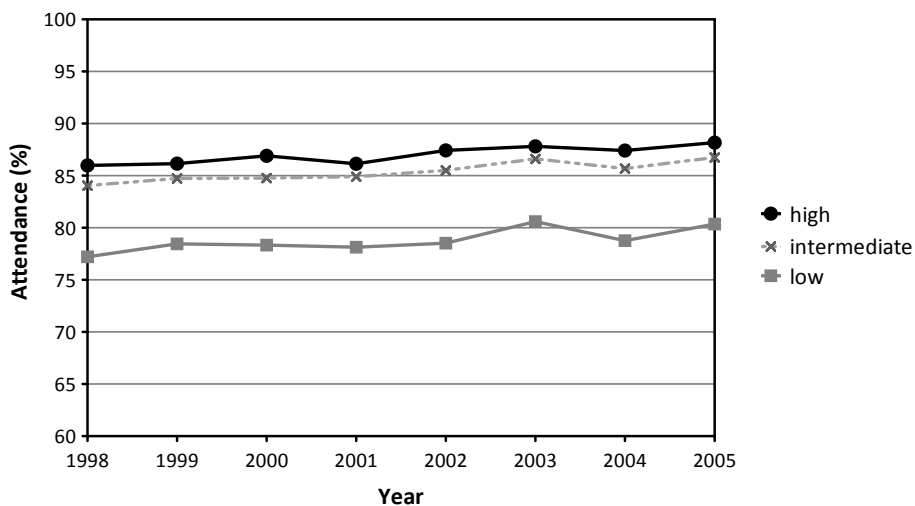
3.3

Figure 2. *Attendance of breast cancer screening according to socioeconomic status in southern Netherlands 1998-2005.*

3.3

Stage at diagnosis

From 1998 to 2006 6,086 women eligible for screening were diagnosed with invasive breast cancer or DCIS in the overlapping regions of the BoBZ and IKZ. After exclusion of patients with non-carcinoma (N=22: 3 benign neoplasms NOS; 1 leiomyosarcoma NOS; 2 carcinosarcomas NOS; 2 malignant myoepitheliomas; 12 phyllodes tumours; 2 hemangiosarcomas), data on 6,064 patients could be analyzed (Figure 1).

Among patients with screen-detected cancer, those with high SES had slightly more *in situ* tumors and less stage 1 tumors (17% versus 12% *in situ* and 56% versus 52% stage 1, $p<0.01$, Figure 3). For patients with interval cancer, stage 4 disease was significantly less common in the high SES group compared to the low SES group (2% versus 8%, $p<0.05$). Within the SES groups of both screen-detected and interval cancers, no differences were observed in stage distribution between tumors detected by the initial screening mammogram versus those detected by subsequent mammograms (data not shown). Among non-attendees, stage 4 cancers were found in respectively 10% and 5% of women with low SES or high SES ($p<0.01$). No significant differences in stage distribution were found for low versus intermediate and intermediate versus high SES in non-attenders.

In low stages of disease treatment differences were present. In stage 1, high SES patients more often received radiotherapy in addition to surgery for screen-detected cancers, and less often received surgery alone or the combination of surgery, radiotherapy and systemic therapy for interval cancer. In stage 2, surgery plus radiotherapy was less common in high SES patients with interval cancer, while high SES patients who did not attend the screening program more often received surgery alone.
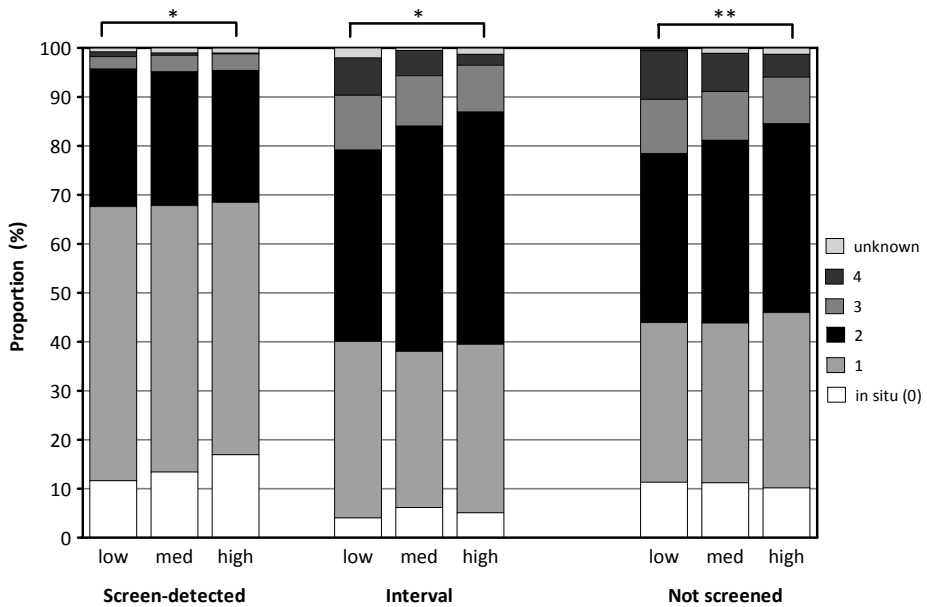
Figure 3. *Stage distribution (pathological) among patients according to attendance of screening within two years before diagnosis and socioeconomic status.*
* p<0.05, ** p<0.01, med=intermediate.

Survival

Complete follow up had been obtained of all but 18 (0.3%) patients with invasive cancer. Crude five-year survival was 89% among screening attendees (N=4,098), more specifically 83% in interval cancers (N=852), 91% in screen-detected cancers (N=3,246), and 77% among non-attendees (N=1,233, log-rank test *p*<0.001). A socioeconomic gradient in survival was observed, with worst survival for women with low SES and best survival for women with high SES (Figure 4). Patients with low SES and screen-detected cancer had worse survival (89%) compared to patients with intermediate SES (91%, log rank-test p<0.01) and high SES (91%, *p*<0.01). Patients with low SES and interval cancer had a worse survival (81%) compared to those with high SES (89%, p<0.01), and those with intermediate SES and interval cancer had worse survival rates than those with high SES as well (81%, *p*=0.02). Within the groups of screen-detected and interval cancer, no significant differences were observed for survival of initial versus subsequent screening rounds, although survival rates were generally slightly higher for cancers detected at subsequent screening mammography (data not shown). Patients with low SES and who had not attended screening showed significantly worse survival compared to women with intermediate SES (crude 5-year survival 74 versus 77%, log rank test: *p*<0.01) and high SES (81%, *p*<0.001).

3.3

The socioeconomic inequalities in survival remained after age adjustment, with a hazard ratio (HR) of 1.4 (1.1-1.9) for low SES if compared to high SES in non-attendees, and 1.3 (1.0-1.7) and 1.7 (1.1-2.6) for screen-detected cancers and interval cancers (Table 2). As comorbidity was inversely associated with SES (46%, 39% and 32% in low, intermediate and high SES), we additionally adjusted for comorbidity in the age-adjusted model. Socioeconomic inequalities in breast cancer survival seemed to be related to socioeconomic inequalities in presence of comorbidities in screen-detected cancers (23%), but had less impact in interval cancers or in non-attenders. In these latter two groups, survival disparities seemed to be largely related to stage, which explained respectively 35% and 48% of the survival disparities, while treatment had a minor role (16% and 16%, respectively).

3.3
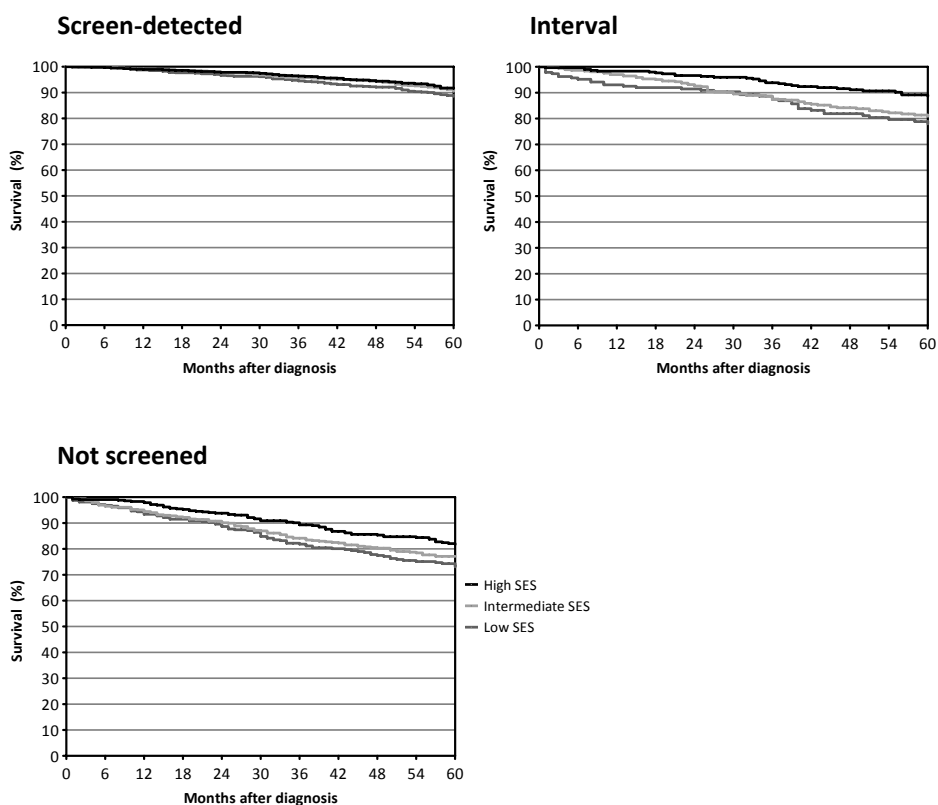
Figure 4. *5-year survival according to (non) attendance to breast cancer screening and socioeconomic status.*

Table 2. Hazard ratios of death from breast cancer according to screening attendance and the contribution of comorbidity and stage to socioeconomic differences.

	Model adjusted for age	Model adjusted for age + comorbidity		Model adjusted for age + stage		Model adjusted for age + therapy		Model adjusted for age + comorbidity + stage + therapy	
	HR§ (95%CI)	HR (95%CI)	Relative contribution comorbidity#	HR (95%CI)	Relative contribution stage$	HR (95%CI)	Relative contribution therapy+	HR (95%CI)	Relative contribution stage, comorbidity and therapy*
Screening attendees									
Screen-detected	**1.30** (1.0-1.7)	1.23 (1.0-1.6)	23%	**1.32** (1.0-1.7)	-7%	1.26 (1.0-1.6)	13%	1.23 (0.9-1.6)	24%
Interval	**1.72** (1.1-2.6)	**1.67** (1.1-2.6)	7%	1.47 (1.0-2.3)	35%	**1.60** (1.0-2.4)	16%	1.45 (0.9-2.2)	37%
Non-attendees									
Not screened	**1.42** (1.1-1.9)	**1.37** (1.0-1.8)	12%	1.22 (0.9-1.6)	48%	**1.35** (1.0-1.8)	16%	1.17 (0.9-1.6)	60%

§ HR = Hazard Ratio, low versus high socioeconomic status. Values in bold are significant.
# ((HR model adjusted for age - (HR model adjusted for age+comorbidity))/(HR model adjusted for age − 1))*100%
$ ((HR model adjusted for age - (HR model adjusted for age+stage))/(HR model adjusted for age − 1))*100%
+ ((HR model adjusted for age - (HR model adjusted for age+therapy))/(HR model adjusted for age − 1))**100%
* ((HR model adjusted for age - (HR model adjusted for age+comorbidity +stage))/(HR model adjusted for age − 1))*100.

3.3

DISCUSSION

The current study shows that women with high SES show higher attendance rates for breast cancer screening in the south of the Netherlands. Socioeconomic inequalities persist resulting in significantly worse stage and lower survival for women with low SES.

Compared to other European countries, Dutch screening attendance rates are rather high: 84% compared to 65% in Sweden (1990-2003, clinical trial),[20] 73% in England (3-year screening, 2007-2008)[21] and 63% (1999-2001) in Copenhagen.[22] Comparable attendance rates were reported in another Danish region (around 84% from 1991-2001)[23] and in a Spanish screening program (82%, 1995-1998).[24] The socioeconomic inequalities in attendance rates in this study (OR 1.75 for high compared to low SES) are somewhat smaller than the results presented by others, although the magnitude seems to depend on the SES indicator used.[2, 20, 25] Studies on the association with education however have given mixed results, with some showing higher educational levels had a tendency toward lower non-attendance rates[2, 25] and one study shown higher[20] non-attendance rates. A U-shaped association has also been reported.[26]

In contrast to many European countries, breast cancer screening in the U.S. is done opportunistically. This may contribute to the larger socioeconomic inequalities in attendance rates in the U.S., where around 60% of women with low and 75-80% with high income (or education) (self)reported to have had a mammogram or clinical breast examination in the past 2 years.[1, 3, 27, 28] In line with the trend we observed, U.S. participation rates increased over time from 77% (1988-1990) to even 92% (1998-2000) in the health-aware nurses in the Nurses Health Study.[29]

Not attending screening may be related to inadequate knowledge of cancer, attitudes, health consciousness, cultural differences, language problems and illiteracy.[3, 30] These are all more often seen in people with low SES[31, 32] and could thus have contributed to the socioeconomic gradient in attendance rate. In the Netherlands, immigrants were found to have lower attendance rates,[33] which might be attributed to a lack of proficiency of the Dutch language.[30] Nowadays, the Dutch screening organization has invitations and accompanying information leaflets in the Dutch, English, Turkish and Arabic language. Presence of financial and health system barriers also have been suggested as reasons for not attending the screening.[3] However, the Dutch government offers mammographies free of charge, thus this is unlikely to play a role in the Netherlands. Because non-attendees are not inclined to seek mammography elsewhere,[34] it is very important to reach all women for screening.

In previous studies having a low SES has also been associated with more advanced stage at diagnosis[5-7, 11, 35] but to our knowledge this has not been studied in association with attendance to screening. It is likely that at least part of this association can be attributed to socioeconomic inequalities in attendance rates of screening programs. For example, 36-47% of the breast tumors in Switzerland is stage 2 or higher in regions with screening programs, compared to 50-64% in regions without a screening program.[36] Studies from Italy and Sweden found comparable results.[20, 37] Not surprisingly, patients who attended screening had a more favorable stage distribution than those who did not attend, and patients with high SES had

less advanced tumors than low SES. Remarkable socioeconomic stage differences were observed in screen-detected cancer, suggesting other tumor biology.[38] In screen-detected cancers, we observed small differences in morphology (65% had infiltrating duct carcinoma versus 71% in low SES), estrogen receptor status (88% ER+ versus 85%) and progesterone receptor status (10% PR+ versus 12%) but not in tumor size or grade. For cervical cancer higher proliferation rates have been suggested in low SES,[39] which could hold for breast cancer as well.

The presence of a socioeconomic gradient in breast cancer survival has been reported in previous studies[8, 11, 12, 40] and our results show that this is, at least partly, related to screening attendance. The crude 5-year survival rates we observed (respectively 89% and 76% for those who did and did not attend screening, i.e. RR 1.2) were fairly comparable to results reported in Sweden, where the age and stage adjusted relative risk of death was 1.4 for non-attenders.[20] Moreover, the crude 5-year survival rates observed in our study (77% for patients with cancers not detected by screening versus 91% for those with screen-detected cancers) are comparable to the rates of 84% and 94% observed in a study performed in Northern Italy.[37] Unfortunately, no SES-specific life tables were available to estimate breast cancer specific survival according to SES. Similar patterns to overall survival were observed when using general life tables, although this may lead to underestimation of the relative survival rates in low SES and overestimation in high SES.

In this study, Cox regression has been applied to assess causality in socioeconomic inequalities in survival from breast cancer. This method requires several stringent assumptions to be satisfied and does not allow for interactions between exposure (SES) and mediators (stage and treatment).[41] Furthermore, for hazard ratios the decomposition into effects was stated not to be valid.[41] To the best of our knowledge, there is no accessible better way to analyze mediation than via Cox' regression. Although interpretation of effects from regression models should be guarded, these results suggest an effect of stage on survival differences for interval cancers and in non-attenders, while comorbidities affected survival in screen-detected patients.

The socioeconomic differences in stage at diagnosis explained some of the socioeconomic inequalities in breast cancer survival. Stage distribution was only slightly different between the SES categories in screen-detected cancers, while differences were larger in patients who did not attend the screening and especially in interval cancers. In these latter two groups, stage indeed explained (part of) the socioeconomic differences. In three other studies in the U.K. and France socioeconomic inequalities in breast cancer survival were ascribed to stage.[6, 11, 13] However, in an older study from the U.K., including patients diagnosed between 1980 and 1987, tumor stage or biology did not contribute to the socioeconomic gradient in breast cancer survival.[14] More recently, a study in the Netherlands on breast cancer patients diagnosed from 1995 to 2005 observed that 10-year relative survival rates were 79% in high SES compared to 74% in low SES, and the accompanying relative excess risk of dying from breast cancer was 1.19. This was after adjustment for (among others) grade, stage, nodal status, treatment.[12] Only one of the foreign studies took into account the role of breast cancer

3.3

screening and compared the survival of cancers detected clinically with those detected in the screening program. Survival inequalities were only present for stage 3.[11]

Interventions to increase screening participation have been reviewed and distinguished into factors related to invitees, health-care providers, health-care context, and media and financial factors.[42] Most important to increase participation in the Netherlands will be the factors related to invitees, e.g. by timing of invitation, personal factors (perceived risk of cancer, perceived self-efficacy), customizing invitation to the individual needs (for example by telephone counseling), and address psychological mediators of cancer screening behavior.[42]

A limitation of this study is the fact that we do not know the reasons of non-participation in 54% of the cases. To increase attendance rates, this should be studied. Comorbidity could explain (part of) the non-participation, as it was present at diagnosis in 42% of the women who did not compared to 37% in women who did attend.

As stated earlier, we used an indicator of SES based on the postal code of a residential area and not on individual data on income, education, etc. Since this aggregate covers a relatively small geographical area (on average 17 households), it is likely to represent a reliable approximation of individual SES.

Furthermore, routinely collected income tax data have been found to provide reliable estimates of household income.[43] Previous studies in the Netherlands have proven that socioeconomic differences based on neighborhood data tend to reflect socioeconomic differences accurately at the individual level.[43-45] In addition, we defined non-participation in patients as women who did not attend the screening program within the last 2 years before diagnosis. In fact, 64% of these women indeed never attended, but 32% had attended more than 3 but less than 4 years before diagnosis, and 4% had attended the program more than 3 years before diagnosis.

Despite these limitations, the results of this study form an important contribution to the limited information available on socioeconomic inequalities in screening attendance and the consequences in terms of stage at diagnosis and survival in the Netherlands. Moreover, in this large population-based study we included all women being eligible for breast cancer screening and all breast cancer patients.

In conclusion, despite the absence of financial barriers for participation in the Dutch mass screening program, socioeconomic inequalities in attendance rates remain present, resulting in a significantly worse tumor stage and lower survival rate for women with low SES. Therefore, these results underline the importance of increasing participation among women of all SES groups, with special attention to those with low SES.

ACKNOWLEDGEMENT

REFERENCES

1. Kim, J. & Jang, S.N. Socioeconomic disparities in breast cancer screening among US women: trends from 2000 to 2005. *J Prev Med Public Health* 41, 186-94 (2008).

2. Moser, K., Patnick, J. & Beral, V. Inequalities in reported use of breast and cervical screening in Great Britain: analysis of cross sectional survey data. *Bmj* 338, b2025 (2009).

3. Peek, M.E. & Han, J.H. Disparities in screening mammography. Current status, interventions and implications. *J Gen Intern Med* 19, 184-94 (2004).

4. Zackrisson, S., Lindstrom, M., Moghaddassi, M., Andersson, I. & Janzon, L. Social predictors of non-attendance in an urban mammographic screening programme: a multilevel analysis. *Scand J Public Health* 35, 548-54 (2007).

5. Dalton, S.O., During, M., Ross, L., Carlsen, K., Mortensen, P.B., Lynch, J. & Johansen, C. The relation between socioeconomic and demographic factors and tumour stage in women diagnosed with breast cancer in Denmark, 1983-1999. *Br J Cancer* 95, 653-9 (2006).

6. Macleod, U., Ross, S., Gillis, C., McConnachie, A., Twelves, C. & Watt, G.C. Socio-economic deprivation and stage of disease at presentation in women with breast cancer. *Ann Oncol* 11, 105-7 (2000).

7. Schrijvers, C.T., Mackenbach, J.P., Lutz, J.M., Quinn, M.J. & Coleman, M.P. Deprivation, stage at diagnosis and cancer survival. *Int J Cancer* 63, 324-9 (1995).

8. Schrijvers, C.T., Coebergh, J.W., van der Heijden, L.H. & Mackenbach, J.P. Socioeconomic variation in cancer survival in the southeastern Netherlands, 1980-1989. *Cancer* 75, 2946-53 (1995).

9. Dalton, S.O., Ross, L., During, M., Carlsen, K., Mortensen, P.B., Lynch, J. & Johansen, C. Influence of socioeconomic factors on survival after breast cancer--a nationwide cohort study of women diagnosed with breast cancer in Denmark 1983-1999. *Int J Cancer* 121, 2524-31 (2007).

10. Louwman, W.J., van de Poll-Franse, L.V., Fracheboud, J., Roukema, J.A. & Coebergh, J.W. Impact of a programme of mass mammography screening for breast cancer on socio-economic variation in survival: a population-based study. *Breast Cancer Res Treat* 105, 369-75 (2007).

11. Gentil-Brevet, J., Colonna, M., Danzon, A., Grosclaude, P., Chaplain, G., Velten, M., Bonnetain, F. & Arveux, P. The influence of socio-economic and surveillance characteristics on breast cancer survival: a French population-based study. *Br J Cancer* 98, 217-24 (2008).

12. Bastiaannet, E., de Craen, A.J., Kuppen, P.J., Aarts, M.J., van der Geest, L.G., van de Velde, C.J., Westendorp, R.G. & Liefers, G.J. Socioeconomic differences in survival among breast cancer patients in the Netherlands not explained by tumor size. *Breast Cancer Res Treat* (2010).

13. Kaffashian, F., Godward, S., Davies, T., Solomon, L., McCann, J. & Duffy, S.W. Socioeconomic effects on breast cancer survival: proportion attributable to stage and morphology. *Br J Cancer* 89, 1693-6 (2003).

14. Carnon, A.G., Ssemwogerere, A., Lamont, D.W., Hole, D.J., Mallon, E.A., George, W.D. & Gillis, G.R. Relation between socioeconomic deprivation and pathological prognostic factors in women with breast cancer. *Bmj* 309, 1054-7 (1994).

15. Louwman, W.J., Aarts, M.J., Houterman, S., van Lenthe, F.J., Coebergh, J.W. & Janssen-Heijnen, M.L. A 50% higher prevalence of life-shortening chronic conditions among cancer patients with low socioeconomic status. *Br J Cancer* 103, 1742-1748 (2010).

16. BoBZ. in Jaarverslag 2007 [in Dutch] (2007).

17. Sobin, L. & Wittekind, C. UICC International Union against Cancer. TNM Classification of malignant tumours, ed 5th Geneva, Switzerland: Wiley-Liss. (1997).

18. Charlson, M.E., Pompei, P., Ales, K.L. & MacKenzie, C.R. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 40, 373-83 (1987).

19. Van Duin, C. & Keij, I. Sociaal-economische status indicator op postcodeniveau [in Dutch]. *Maandstatistiek van de bevolking* 50, 32-35 (2002).

20. Zackrisson, S., Andersson, I., Manjer, J. & Janzon, L. Non-attendance in breast cancer screening is associated with unfavourable socio-economic circumstances and advanced carcinoma. *Int J Cancer* 108, 754-60 (2004).

3.3

21. The Health and Social Care Information Centre. in Breast screening programme, England (NHS, 2009).

22. Vejborg, I., Olsen, A.H., Jensen, M.B., Rank, F., Tange, U.B. & Lynge, E. Early outcome of mammography screening in Copenhagen 1991-99. *J Med Screen* 9, 115-9 (2002).

23. von Euler-Chelpin, M., Olsen, A.H., Njor, S., Vejborg, I., Schwartz, W. & Lynge, E. Women's patterns of participation in mammography screening in Denmark. *Eur J Epidemiol* 21, 203-9 (2006).

24. Bare, M.L., Montes, J., Florensa, R., Sentis, M. & Donoso, L. Factors related to non-participation in a population-based breast cancer screening programme. *Eur J Cancer Prev* 12, 487-94 (2003).

25. Duport, N. & Ancelle-Park, R. Do socio-demographic factors influence mammography use of French women? Analysis of a French cross-sectional survey. *Eur J Cancer Prev* 15, 219-24 (2006).

26. von Euler-Chelpin, M., Olsen, A.H., Njor, S., Jensen, A., Vejborg, I., Schwartz, W. & Lynge, E. Does educational level determine screening participation? *Eur J Cancer Prev* 17, 273-8 (2008).

27. American Cancer Society. in Cancer Prevention & Early Detection Facts & Figures 2009 (Atlanta, GA, 2009).

28. Coughlin, S.S., Uhler, R.J., Bobo, J.K. & Caplan, L. Breast cancer screening practices among women in the United States, 2000. *Cancer Causes Control* 15, 159-70 (2004).

29. Cook, N.R., Rosner, B.A., Hankinson, S.E. & Colditz, G.A. Mammographic Screening and Risk Factors for Breast Cancer. *Am J Epidemiol* 170, 1422-32 (2009).

30. Lale, N., Öry, F. & Detmar, S. Factors associated with non-participation of Turkish women to cervical cancer screening in the Netherlands. *Tijdschrift Sociale Geneeskunde* 81, 184-188 (2003).

31. Stein, K., Zhao, L., Crammer, C. & Gansler, T. Prevalence and sociodemographic correlates of beliefs regarding cancer risks. *Cancer* 110, 1139-48 (2007).

32. Wardle, J. & Steptoe, A. Socioeconomic differences in attitudes and beliefs about healthy lifestyles. *J Epidemiol Community Health* 57, 440-3 (2003).

33. Visser, O., van Peppen, A.M., Ory, F.G. & van Leeuwen, F.E. Results of breast cancer screening in first generation migrants in Northwest Netherlands. *Eur J Cancer Prev* 14, 251-5 (2005).

34. Jensen, A., Olsen, A.H., von Euler-Chelpin, M., Helle Njor, S., Vejborg, I. & Lynge, E. Do nonattenders in mammography screening programmes seek mammography elsewhere? *Int J Cancer* 113, 464-70 (2005).

35. Adams, J., White, M. & Forman, D. Are there socioeconomic gradients in stage and grade of breast cancer at diagnosis? Cross sectional analysis of UK cancer registry data. *Bmj* 329, 142 (2004).

36. Bulliard, J.L., Ducros, C., Jemelin, C., Arzel, B., Fioretta, G. & Levi, F. Effectiveness of organised versus opportunistic mammography screening. *Ann Oncol* 20, 1199-202 (2009).

37. Cortesi, L., Chiuri, V.E., Ruscelli, S., Bellelli, V., Negri, R., Rashid, I., Cirilli, C., Fracca, A., Gallo, E. & Federico, M. Prognosis of screen-detected breast cancers: results of a population based study. *BMC Cancer* 6, 17 (2006).

38. Taylor, A. & Cheng, K.K. Social deprivation and breast cancer. *J Public Health Med* 25, 228-33 (2003).

39. Symonds, P., Bolger, B., Hole, D., Mao, J.H. & Cooke, T. Advanced-stage cervix cancer: rapid tumour growth rather than late diagnosis. *Br J Cancer* 83, 566-8 (2000).

40. Schrijvers, C.T. & Mackenbach, J.P. Cancer patient survival by socioeconomic status in seven countries: a review for six common cancer sites [corrected]. *J Epidemiol Community Health* 48, 441-6 (1994).

41. Kaufman, J.S., Maclehose, R.F. & Kaufman, S. A further critique of the analytic strategy of adjusting for covariates to identify biologic mediation. *Epidemiol Perspect Innov* 1, 4 (2004).

42. Weller, D.P., Patnick, J., McIntosh, H.M. & Dietrich, A.J. Uptake in cancer screening programmes. *Lancet Oncol* 10, 693-9 (2009).

43. Bos, V., Kunst, A.E. & Mackenbach, J. in Verslag aan de Programmacommissie Sociaal-economische gezondheidsverschillen II (Instituut Maatschappelijke Gezondheidszorg, Erasmus Universiteit, Rotterdam, 2000).

44. Bos, V., Kunst, A.E. & Mackenbach, J.P. in Sociaal-economische gezondheidsverschillen: Van verklaren naar verkleinen (ed. Stronks, K.) 8-20 (Zon/MW, Den Haag, 2001).

3.3

45. Smits, J., Keij, I. & Westert, G.P. Effecten van sociaal-economische status van kleine, middelgrote en grote geografische eenheden op de sterfte [in Dutch]. *Maandstatistiek van de bevolking* 11, 4-10 (2001).

3.3

Chapter 4

Cancer outcome

DECISION
CURATIVE
ROLE
SINCE 1990
data
BRACHYTHERAPY
DETERMINANTS
CATEGORY
material resources
HOUSING
RECOGNISING
OUTCOME
INTERVAL CANCER
health seeking behaviour
METASTASIS
CHARLSON
CONTRIBUTION
RADIOTHERAPY
COVERAGE
estimated
annual
percent
change
axillary
staging
EAPC
socioeconomic position
statistical
GP
SMOKING
STUDIES
HOSPITAL
staging
lifestyle
central nervous system
Comprehensive Cancer Centre South
intelligence
education
Eindhoven Cancer Registry
dementia
DISCUSS
socioeconomic status
stage
VISITS
ATTENDANCE
hazard
ratio
EXPLANATION
RISK FACTORS
DIAGNOSIS
SEP
SOCIAL SUPPORT
diagnostics
distribution
CARDIOVASCULAR DISEASE
HORMONAL THERAPY
ADVANCED
FEAR
mastectomy
therapy
HIGH
MAMMOGRAPHY
HYPERTENSION
colorectal
UPBRINGING
ENVIRONMENT
MENTAL
incidence
prostatectomy
p-value
QUESTIONNAIRE
HEALTH BEHAVIOUR
SF-36
GLOBE
PHYSICAL
SOCIOEC
NEIGHBOURHOOD
LOW
occupation
EXPOSURE
value of housing
physical activity
comorbidities
INVITATION
INTERMEDIATE
REVIEW
colorectal
cancer
screening
CHEMORADIATION
TUBERCULOSIS
concomitant disease
VARIATION
logistic
regression
ACCESS TO CARE
ALCOHOL CONSUMPTION
INVASIVE
numbers
CONTACTS
gap
LOCALISED
CONSULTATION
ASSETS
PSA
WORK
SCREEN-DETECTED TUMOUR
income
percentages
THE NETHERLANDS
HEALTH INSURANCE
health awareness
HOUSEHOLD
search
DETECTIO

Chapter 4.1

A 50% higher prevalence of life-shortening chronic conditions among cancer patients with low socioeconomic status

W.J. Louwman, M.J. Aarts, S. Houterman, F.J. van Lenthe, J.W.W. Coebergh, M.L.G. Janssen-Heijnen

ABSTRACT

Background

Comorbidity and socioeconomic status (SES) may be related among cancer patients.

Method

Population-based cancer registry study among 72,153 patients diagnosed during 1997-2006.

Results

Low SES patients had 50% higher risk of serious comorbidity than those with high SES. Prevalence was increased for each cancer site. Low SES cancer patients had significantly higher risk of also having cardiovascular disease, chronic obstructive pulmonary diseases, diabetes mellitus, cerebrovascular disease, tuberculosis, dementia, and gastrointestinal disease. One-year survival was significantly worse in lowest vs highest SES, partly explained by comorbidity.

Conclusion

This illustrates the enormous heterogeneity of cancer patients and stresses the need for optimal treatment of cancer patients with a variety of concomitant chronic conditions.

4.1

INTRODUCTION

People of a lower socioeconomic status (SES) generally have poorer health status and higher mortality than people from higher socioeconomic groups,[1, 2] also with respect to cancer, with in general higher incidence rate of all cancers combined among people from lower socioeconomic groups.[3] A differential distribution of known risk factors for specific neoplasms between SES groups seems a likely explanation for the above inequalities. For example, the prevalence of smokers has become higher among lower classes,[4, 5] probably resulting in higher rates of cancer of the lung, larynx, mouth, pharynx, oesophagus, and bladder.[6-8] However, smoking is not only related to cancer, but also to chronic obstructive pulmonary diseases (COPD) and cardiovascular diseases.[9] Hence, the high prevalence of comorbidity among lung cancer patients.[10] Socioeconomic status may thus be associated with comorbidity among cancer patients. Thus, medical doctors are presented with a very heterogeneous group of cancer patients, for whom appropriate individual treatment must be chosen, taking concomitant conditions into account.[11-16]

We studied in a large population-based group of cancer patients the prevalence of comorbidity according to SES, not only by number of concomitant diseases, but also for specific diseases that affect patients with the various tumour sites.

METHODS

4.1

The Eindhoven Cancer Registry records data on all patients newly diagnosed with cancer in the south of the Netherlands (2.4 million inhabitants, 15% of the Dutch population); it also records serious comorbidity according to an adaptation of the list.[17] Chronic obstructive pulmonary diseases, cardio- and cerebrovascular diseases, peripheral arterial disease, other malignancies, and diabetes mellitus, connective tissue diseases, rheumatoid arthritis, kidney, bowel, and liver diseases, dementia, tuberculosis and other chronic infections were also recorded. For most analyses peripheral arterial disease was included in the cardiovascular diseases, although gastrointestinal diseases were grouped (gastric diseases, Crohn's disease, ulcerative colitis, liver cirrhosis, and hepatitis). Comorbidity was defined as life-shortening disease that was present at the time of cancer diagnosis and/or received treatment or surveillance. Trained registry personnel actively collect data on diagnosis, staging, and treatment from the medical records after notification by pathologists and medical registration offices. Previous admissions, letters from and to general practitioners and other specialists, the medical history and preoperative screening were used as sources.

Patients with cancer of the oesophagus, stomach, colon or rectum, pancreas, lung, melanoma, breast, cervix uteri, corpus uteri, ovary, prostate, bladder, kidney, and non-Hodgkin's lymphoma (NHL), newly diagnosed between 1997 and 2006 (n=72,153), were included in this study; cancers diagnosed at autopsy (n=369) were excluded.

Statistics Netherlands developed an indicator of SES, using individual fiscal data on the economic value of the home and household income, and is provided at aggregated level for each postal code (covering an average of 17 households). Socioeconomic status was categorised as low (deciles 1-3), medium (deciles 4-7), or high social class (deciles 8-10), and a separate class for postal codes for a long-term care providing institution (such as a

nursing home).[18] We calculated the distribution of cancer patients across socioeconomic strata according to tumour localisation, also by gender and age. Patients for whom the SES was unknown (n=766, 1%) or for whom the postal code included a care providing institution (n=3,569, 5%), as well as those with unknown comorbidity (n=8,399, 12%) were excluded from the analyses of SES and comorbidity. Differences in distribution were tested with the Chi-square test. Logistic regression analyses of the odds of having a specific concomitant disease were performed age- and gender-adjusted for all tumour sites combined, and according to tumour site for four concomitant diseases separately; cardiovascular disease, COPD, diabetes mellitus, and gastro-intestinal disease. Statistical significance of an overall effect of SES on the prevalence of a specific condition was tested using the χ^2-likelihood ratio test. Crude 1-year survival rates were calculated for all studied tumours combined and for the most important tumour sites separately. Cox's regression models were used to compute multivariate rates (Hazard Ratio=HR) and 95% confidence intervals (95%CI). The relative contribution (%) of adding comorbidity to the model was calculated as follows: ((HR model A- HR model B)/(HR model A-1))*100, where model A is the basic model (age- and gender-adjusted) and in model B comorbidity is added to model A. All statistical analyses were performed using SAS V9.12 (SAS Institute Inc, Cary, NC, USA).

RESULTS

Male cancer patients were older than female patients (Table 1), the median age being 69 and 64 years, respectively (*P*<0.0001). At the time of the diagnosis of the cancer 71% of male and 58% of female cancer patients had at least one concomitant disease. The most frequent concomitant condition for males with cancer was cardiovascular disease (23%), for women hypertension (20%), among cancer patients older than 70 the prevalence of these diseases was 34% and 31%, respectively. In the subgroup of cancer patients with two or more concomitant diseases, the most frequent combination of diseases among males was cardiovascular disease with hypertension (14%) and in females diabetes with hypertension (21%).

The proportion of patients by SES varied for the different tumour sites (Table 2). Patients under age 70 with stomach, lung, bladder, or cervical cancer more often had low SES. High SES was more frequent among patients with melanoma or breast, colorectal, or prostate cancer in this age group.

Among patients aged 70+ with cancer of the oesophagus, stomach, or lung low SES was clearly over-represented. High SES was more frequent among patients with prostate cancer or NHL.

For all tumour localisations the proportion of patients without comorbidity was highest in the high SES group (Figure 1). A gradient towards more concomitant conditions appeared in lower SES groups (*P*<0.001), which had a significantly higher risk of cardiovascular disease (OR$_{low vs high SES}$=1.4, 95%CI:1.3-1.5), COPD (OR=1.8 (1.7-1.9)), diabetes mellitus (OR=1.5 (1.4-1.6)), cerebrovascular disease (OR=1.5 (1.4-1.7)), tuberculosis (OR=1.3 (1.1-1.6)), dementia (OR=1.3 (1.0-1.8)), gastrointestinal disease (OR=1.5 (1.4-1.6)), and two or more concomitant conditions (OR=1.8 (1.7-1.9)) in addition to their cancer (Table 3). The risk of having cancer and also at

4.1

Table 1. *Description of all cancer patients diagnosed with selected tumours between 1997-2006 in the Eindhoven Cancer Registry.*

	Males		Females		Total	
	n	**%**	**n**	**%**	**n**	**%**
Tumour localisation						
Oesophagus	1079	3	398	1	1477	2
Stomach	1723	5	1032	3	2755	4
Colorectal	6815	19	6014	17	12829	18
Pancreas	907	2	849	2	1756	2
Lung	9354	26	3591	10	12945	18
Melanoma	1405	4	1899	5	3304	5
Breast	-		14859	41	14859	20
Cervix uteri	-		725	2	725	1
Corpus uteri	-		2128	6	2128	3
Ovary	-		1540	4	1540	2
Prostate	9987	27	-		9987	14
Kidney	1201	3	806	2	2007	3
Urinary bladder	2306	6	679	2	2985	4
Non-Hodgkin's lymphoma	1846	5	1413	4	3259	4
Age						
< 45	1156	3	3884	11	5040	7
45-59	6624	18	10578	29	17202	24
60-74	18984	52	13142	37	32126	44
>75	9859	27	8329	23	18188	25
SES						
Low	9518	26	9953	28	19471	27
Intermediate	14309	39	13824	38	28133	39
High	10812	30	9741	27	20553	28
Institution	1569	4	2032	6	3601	5
Unknown	415	1	383	1	798	1
Comorbidity						
Number of concomitant diseases						
0	10688	29	14826	41	25514	35
1	10775	29	9353	26	20128	28
>2	10992	30	7050	20	18042	25
unknown	4168	11	4704	13	8872	12
Concomitant disease[a]						
Previous cancer	4460	12	3565	10	7977	11
Cardiovascular disease	8353	23	3854	11	12127	17
Peripheral arterial disease	3445	9	1358	4	4767	7
COPD	5347	15	2674	7	7994	11
Hypertension	6367	17	7184	20	13462	19

Table 1 continues on next page

Diabetes mellitus	3586	10	3482	10	7026	10
Cerebrovascular disease	1754	5	1044	3	2779	4
Tuberculosis	553	2	409	1	947	1
Central nervous system[b]	221	1	354	1	568	1
Gastro-intestinal disease	2629	7	1294	4	3900	5
Other diseases	925	3	1078	3	1987	3
Total	36623	50	35933	50	72556	100

Abbreviations: COPD = chronic obstructive pulmonary diseases; SES = socioeconomic status.
[a]Patients may suffer from more than one condition. [b]Dementia in 96% of these patients.

Table 2. *Distribution of cancer patients newly diagnosed in 1997-2006 according to gender, age and socioeconomic status (SES).*

	Males				Females			
	<70		70+		<70		70+	
Tumour localisation	**No. patients**	**% low SES**	**No. patients**	**% low SES**	**No. patients**	**% low SES**	**No. patients**	**% low SES**
Oesophagus	589	23	342	37	170	30	161	43
Stomach	767	26	719	37	386	31	465	44
Colorectal	3176	21	2662	32	2266	24	2630	40
Pancreas	433	24	339	36	325	28	374	44
Lung	4498	29	3827	38	2226	35	923	50
Melanoma	563	15	169	33	729	16	194	43
Breast	-	-	-	-	9070	21	3094	42
Cervix uteri	-	-	-	-	476	37	120	43
Corpus uteri	-	-	-	-	1189	25	576	42
Ovary	-	-	-	-	875	23	438	42
Prostate	3930	20	4149	30	-	-	-	-
Kidney	639	22	392	32	372	31	300	41
Urinary bladder	855	25	1027	33	216	32	308	40
Non-Hodgkin's Lymphoma	1060	21	575	31	703	25	514	42
Total of these sites	16510	23	14201	34	19003	24	10097	42

4.1

least one other serious concomitant disease was 50% higher in the low SES than in the high SES group (OR=1.5 (1.4-1.6)).

For four concomitant conditions we stratified by tumour localisation (Figure 2). The risk of cardiovascular disease among low compared with high SES patients was significantly higher (1.4 - 1.6 times) for patients with stomach, colorectal, lung, breast, prostate and bladder cancer. The risk of COPD was elevated among low SES patients with cancer of the stomach, colorectum, pancreas, lung, breast, corpus uteri, prostate, and kidney (OR's ranging from 1.4 to 2.2). The risk of diabetes mellitus was highest among people from low SES with breast

4.1
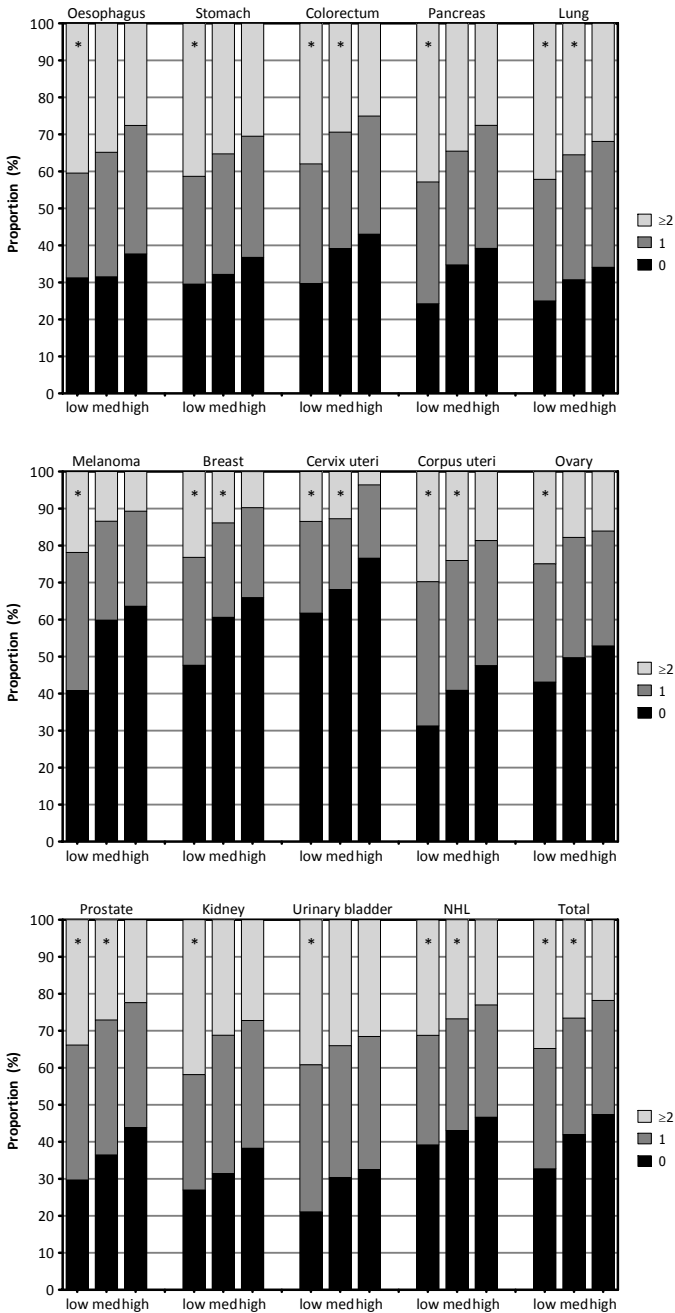
Figure 1. *Number of concomitant diseases among cancer patients diagnosed in 1997-2006 in the Southeastern Netherlands.*
*Med=medium. *Distribution of number of concomitant diseases significantly different from the highest socioeconomic status category.*

Table 3. *Risk of specific concomitant diseases according to socioeconomic status adjusted for age and gender among cancer patients diagnosed in 1997-2006.*

Concomitant disease	Socioeconomic status			
	Low	Intermediate	High	P^a
Previous cancer	1.01	0.99	1.00	0.7
Cardiovascular disease	1.42[b]	1.23[b]	1.00	0.0001
COPD	1.81[b]	1.37[b]	1.00	0.0001
Hypertension	0.98	1.03	1.00	0.2
Diabetes mellitus	1.52[b]	1.32[b]	1.00	0.0001
Cerebrovascular disease	1.53[b]	1.27[b]	1.00	0.0001
Tuberculosis	1.34[b]	1.17	1.00	0.01
Central nervous system	1.34[b]	1.05	1.00	0.05
Gastrointestinal	1.48[b]	1.27[b]	1.00	0.0001
Other	1.22[b]	1.10	1.00	0.01
1 or more concomitant disease	1.50[b]	1.24[b]	1.00	0.0001
2 or more concomitant diseases	1.80[b]	1.36[b]	1.00	0.0001

Abbreviations: COPD = chronic obstructive pulmonary diseases; SES = socioeconomic status.
[a]*P-value for overall effect of SES (X^2 likelihood ratio).* [b]*Confidence interval does not include 1.00.*

4.1
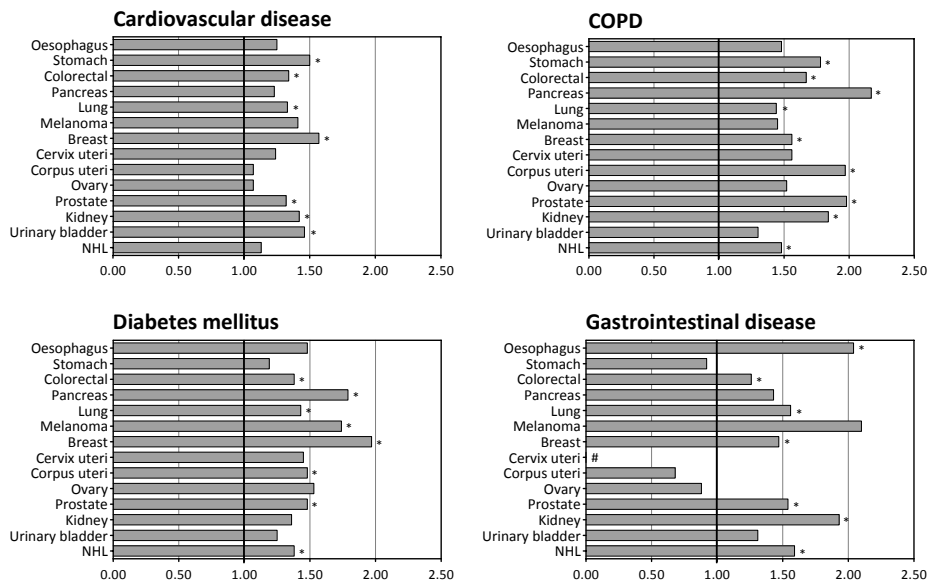
Figure 2. *Risk of four concomitant diseases among cancer patients with the lowest socioeconomic status (SES) compared with those with the highest SES (=reference, 1.00) according to tumour localisation with adjustment for age and gender.*
*95% confidence interval does not include 1.00. # No reliable estimate because less than 5 cases in reference category.

Table 4. *Crude survival, risk of death, and contribution of comorbidity to risk of death according to tumour site and SES among cancer patients diagnosed in 1997-2006.*

	1-yr survival rate (%)			model A[a]		model B[a]		relative contribution comorbidity[b]
	Low SES	Inter- mediate	High SES	HR[c]	(95%CI)	HR[c]	(95%CI)	
Males								
Colorectum	72	78	78	1.13	(1.0-1.3)	1.10	(1.0-1.3)	23%
Lung	36	39	41	1.11	(1.0-1.2)	1.11	(1.0-1.2)	0%
Prostate	90	94	95	1.47	(1.2-1.8)	1.36	(1.1-1.7)	22%
Total[d]	59	66	70	1.40	(1.3-1.5)	1.35	(1.3-1.4)	12%
Females								
Colorectum	74	78	79	1.09	(0.9-1.3)	1.06	(0.9-1.2)	33%
Lung	41	42	46	1.09	(1.0-1.2)	1.09	(1.0-1.2)	0%
Breast	94	97	98	1.68	(1.3-2.2)	1.56	(1.2-2.0)	18%
Total[d]	74	81	84	1.40	(1.3-1.5)	1.34	(1.3-1.4)	15%

[a]Model A: adjusted for age, Model B: adjusted for age and the presence of concomitant diseases (yes vs no). [b]((HR model A- (HR model A + comorbidity))/(1-HR model A))*100. [c]Hazard Ratio (HR) of lowest SES group compared with highest (=reference). [d]All studied sites combined (oesophagus, stomach, colorectum, pancreas, lung, melanoma, breast, cervix uteri, corpus uteri, ovary, prostate, kidney, urinary bladder, non-Hodgkin's lymphoma).

4.1

cancer (OR=2.0 (1.2-2.4)) and the risk of gastrointestinal diseases was highest among patients with oesophageal cancer (OR=2.0 (1.2-3.4)).

Crude 1-year survival of cancer patients from lower SES was worse compared with the highest SES for all tumour sites combined and for the major sites separately (Table 4). The age-adjusted risk of death was significantly elevated for both men (HR$_{low vs high SES}$ = 1.40, 95%CI: 1.3-1.4) and women (HR 1.40 (1.3-1.5)). Adding comorbidity to the model reduced HR to 1.35 for men and 1.34 for women. The relative contribution of comorbidity in explaining the inequality in 1-year survival varied from 0% for lung cancer patients to 33% among female colorectal cancer patients.

DISCUSSION

To our knowledge, this is the first large population-based study to demonstrate the impact of SES on the prevalence of concomitant diseases among cancer patients, with increased prevalence of comorbidity in lower socioeconomic strata for each type of cancer. Cancer patients with low SES had a 50% higher risk of suffering from at least one other serious disease compared to those with high SES. The prevalence of comorbidity was significantly higher with newly diagnosed cancer of lower compared with higher SES for all 14 cancer sites studied. The diseases significantly related to SES among cancer patients were cardiovascular disease, COPD, diabetes mellitus, cerebrovascular disease, tuberculosis, diseases of the central nervous system and gastrointestinal disease. Although both the prevalence of comorbidity and the proportional distribution of SES vary significantly among tumour types, the gradient of more comorbidity from high to low SES was apparent among all tumour types.

Smoking is probably responsible for the higher risk of cardiovascular disease, COPD, and cerebrovascular disease among low SES groups.[7, 9] This is confirmed by the higher prevalence of those diseases among patients with smoking-related tumours: cancers of the stomach, lung, bladder and kidney.[10, 19] Diabetes was more frequent among low SES for patients with cancers of the colorectum, pancreas, lung, breast, corpus uteri or prostate, or melanoma or NHL. Diabetes has been linked to pancreas cancer[20, 21] either as a risk factor or as the clinical manifestation of cancer itself.[22] Diabetes has also been associated with an increased risk for breast,[23] endometrial[24] and colorectal cancer[25] probably because of a relation with obesity.[26] Substantial evidence exists for the association of obesity with low SES.[27-29]

The prevalence of gastrointestinal diseases was highest for low SES patients with oesophageal, colorectal, lung, breast, prostate or kidney cancer, or NHL. Oesophageal cancer has also been associated with gastrointestinal diseases.[19] A lower consumption of vegetables, fruit and fibres, which may protect from oesophageal[30, 31] and colorectal cancer,[32-37] has been reported among lower SES.[38-40]

We used an indicator of SES based on the postal code of a residential area. This aggregate covers a very small geographical area, and thus represents a reliable approximation of individual SES. Furthermore, routinely collected income tax data (no questionnaires or interviews) have been found to provide reliable estimates of household income. Previous studies have proven that socioeconomic differences based on neighbourhood data tend to reflect socioeconomic differences well at the individual level.[41-43] Furthermore, this objective measure of SES is also applicable for older women (born before 1955), whose occupation or education does not always properly reflect their social class.[44]

Previously, we found that patients with comorbidity were often treated less aggressively, if alternative treatment strategies were available. Except for patients with a tumour with poor survival, comorbidity has an independent prognostic effect.[45] This negative impact of comorbidity on survival of cancer might have several mechanisms: the increased risk of death due to the co-morbid condition itself, more contra-indications for the cancer treatment, more indications for dose reduction and a higher rate of treatment-related complications such as infections and cardiovascular events. In several of our recent studies the adverse effects of comorbidity on survival appeared to be independent of treatment, so less aggressive treatment could not (fully) account for the observed differences in survival between patients with and without comorbidity.[13-15, 46, 47] As SES represents a combination of lifestyle, health and risk of suboptimal treatment, cancer patients with comorbidity could also (partly) explain the poorer prognosis. Although an in-depth study remains necessary to reveal whether stage at diagnosis and treatment contributed to the socioeconomic gradient in survival, also for longer survival periods, our preliminary analyses demonstrated a clear gradient in 1-year survival rates, which could partly be attributed to comorbidity.

Our study shows considerable variation in comorbidity by tumour type and a higher risk of concomitant disease among patients from lower SES. Given the aetiology of the type of tumours as well as the aetiology of the concomitant diseases that occur more frequently among patients from low SES background, a lot can probably be gained from preventive

4.1

measures related to lifestyle (such as smoking and obesity). Considering survival is worse for patients of low SES, our results stress the need for reduction of socioeconomic differences in health.

ACKNOWLEDGEMENTS

4.1

REFERENCES

1. Mackenbach, J.P., Stirbu, I., Roskam, A.J., Schaap, M.M., Menvielle, G., Leinsalu, M. & Kunst, A.E. Socioeconomic inequalities in health in 22 European countries. *N Engl J Med* 358, 2468-81 (2008).

2. Jemal, A., Thun, M.J., Ward, E.E., Henley, S.J., Cokkinides, V.E. & Murray, T.E. Mortality from leading causes by education and race in the United States, 2001. *Am J Prev Med* 34, 1-8 (2008).

3. Dalton, S.O., Schuz, J., Engholm, G., Johansen, C., Kjaer, S.K., Steding-Jessen, M., Storm, H.H. & Olsen, J.H. Social inequality in incidence of and survival from cancer in a population-based study in Denmark, 1994-2003: Summary of findings. *Eur J Cancer* (2008).

4. Stronks, K., van de Mheen, H.D., Looman, C.W. & Mackenbach, J.P. Cultural, material, and psychosocial correlates of the socioeconomic gradient in smoking behavior among adults. *Prev Med* 26, 754-66 (1997).

5. Lahelma, E., Rahkonen, O., Berg, M.A., Helakorp, S., Prattala, R., Puska, P. & Uutela, A. Changes in health status and health behavior among Finnish adults 1978-1993. *Scand J Work Environ Health* 23 Suppl 3, 85-90 (1997).

6. Siemiatycki, J., Krewski, D., Franco, E. & Kaiserman, M. Associations between cigarette smoking and each of 21 types of cancer: a multi-site case-control study. *Int J Epidemiol* 24, 504-14 (1995).

7. Stellman, S.D. & Resnicow, K. Tobacco smoking, cancer and social class. *IARC Sci Publ*, 229-50 (1997).

8. Tyczynski, J.E., Bray, F. & Parkin, D.M. Lung cancer in Europe in 2000: epidemiology, prevention, and early detection. *Lancet Oncol* 4, 45-55 (2003).

9. Doll, R., Peto, R., Wheatley, K., Gray, R. & Sutherland, I. Mortality in relation to smoking: 40 years' observations on male British doctors. *Bmj* 309, 901-11 (1994).

10. Janssen-Heijnen, M.L., Schipper, R.M., Razenberg, P.P., Crommelin, M.A. & Coebergh, J.W. Prevalence of co-morbidity in lung cancer patients and its relationship with treatment: a population-based study. *Lung Cancer* 21, 105-13 (1998).

11. Ayanian, J.Z., Zaslavsky, A.M., Fuchs, C.S., Guadagnoli, E., Creech, C.M., Cress, R.D., O'Connor, L.C., West, D.W., Allen, M.E., Wolf, R.E. & Wright, W.E. Use of adjuvant chemotherapy and radiation therapy for colorectal cancer in a population-based cohort. *J Clin Oncol* 21, 1293-300 (2003).

12. Lash, T.L., Thwin, S.S., Horton, N.J., Guadagnoli, E. & Silliman, R.A. Multiple informants: a new method to assess breast cancer patients' comorbidity. *Am J Epidemiol* 157, 249-57 (2003).

13. Lemmens, V.E., Janssen-Heijnen, M.L., Verheij, C.D., Houterman, S., Repelaer van Driel, O.J. & Coebergh, J.W. Co-morbidity leads to altered treatment and worse survival of elderly patients with colorectal cancer. *Br J Surg* 92, 615-23 (2005).

14. Louwman, W.J., Janssen-Heijnen, M.L., Houterman, S., Voogd, A.C., van der Sangen, M.J., Nieuwenhuijzen, G.A. & Coebergh, J.W. Less extensive treatment and inferior prognosis for breast cancer patient with comorbidity: A population-based study. *Eur J Cancer* 41, 779-85 (2005).

15. van Spronsen, D.J., Janssen-Heijnen, M.L., Lemmens, V.E., Peters, W.G. & Coebergh, J.W. Independent prognostic effect of co-morbidity in lymphoma patients: results of the population-based Eindhoven Cancer Registry. *Eur J Cancer* 41, 1051-7 (2005).

16. Janssen-Heijnen, M.L., Smulders, S., Lemmens, V.E., Smeenk, F.W., van Geffen, H.J. & Coebergh, J.W. Effect of comorbidity on the treatment and prognosis of elderly patients with non-small cell lung cancer. *Thorax* 59, 602-7 (2004).

17. Charlson, M.E., Pompei, P., Ales, K.L. & MacKenzie, C.R. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 40, 373-83 (1987).

18. van Duijn, C. & Keij, I. Sociaal-economische status indicator op postcode niveau. *Maandstatistiek van de bevolking* 50, 32-35 (2002).

19. Koppert, L.B., Janssen-Heijnen, M.L., Louwman, M.W., Lemmens, V.E., Wijnhoven, B.P., Tilanus, H.W. & Coebergh, J.W. Comparison of comorbidity prevalence in oesophageal and gastric carcinoma patients: a population-based study. *Eur J Gastroenterol Hepatol* 16, 681-8 (2004).

20. Jain, M., Howe, G.R., St Louis, P. & Miller, A.B. Coffee and alcohol as determinants of risk of pancreas cancer: a case-control study from Toronto. *Int J Cancer* 47, 384-9 (1991).

4.1

21. Kalapothaki, V., Tzonou, A., Hsieh, C.C., Toupadaki, N., Karakatsani, A. & Trichopoulos, D. Tobacco, ethanol, coffee, pancreatitis, diabetes mellitus, and cholelithiasis as risk factors for pancreatic carcinoma. *Cancer Causes Control* 4, 375-82 (1993).

22. Warshaw, A.L. & Fernandez-del Castillo, C. Pancreatic carcinoma. *N Engl J Med* 326, 455-65 (1992).

23. Xue, F. & Michels, K.B. Diabetes, metabolic syndrome, and breast cancer: a review of the current evidence. *Am J Clin Nutr* 86, s823-35 (2007).

24. Parazzini, F., La Vecchia, C., Bocciolone, L. & Franceschi, S. The epidemiology of endometrial cancer. *Gynecol Oncol* 41, 1-16 (1991).

25. Polednak, A.P. Comorbid diabetes mellitus and risk of death after diagnosis of colorectal cancer: a population-based study. *Cancer Detect Prev* 30, 466-72 (2006).

26. Reeves, G.K., Pirie, K., Beral, V., Green, J., Spencer, E. & Bull, D. Cancer incidence and mortality in relation to body mass index in the Million Women Study: cohort study. *Bmj* 335, 1134 (2007).

27. Wardle, J., Waller, J. & Jarvis, M.J. Sex differences in the association of socioeconomic status with obesity. *Am J Public Health* 92, 1299-304 (2002).

28. Sobal, J. & Stunkard, A.J. Socioeconomic status and obesity: a review of the literature. *Psychol Bull* 105, 260-75 (1989).

29. McLaren, L. Socioeconomic status and obesity. *Epidemiol Rev* 29, 29-48 (2007).

30. Terry, P., Lagergren, J., Hansen, H., Wolk, A. & Nyren, O. Fruit and vegetable consumption in the prevention of oesophageal and cardia cancers. *Eur J Cancer Prev* 10, 365-9 (2001).

31. Tzonou, A., Lipworth, L., Garidou, A., Signorello, L.B., Lagiou, P., Hsieh, C. & Trichopoulos, D. Diet and risk of esophageal cancer by histologic type in a low-risk population. *Int J Cancer* 68, 300-4 (1996).

32. Bueno-de-Mesquita, H.B., Ferrari, P. & Riboli, E. Plant foods and the risk of colorectal cancer in Europe: preliminary findings. *IARC Sci Publ* 156, 89-95 (2002).

33. Flood, A., Velie, E.M., Chaterjee, N., Subar, A.F., Thompson, F.E., Lacey, J.V., Jr., Schairer, C., Troisi, R. & Schatzkin, A. Fruit and vegetable intakes and the risk of colorectal cancer in the Breast Cancer Detection Demonstration Project follow-up cohort. *Am J Clin Nutr* 75, 936-43 (2002).

34. Michels, K.B., Edward, G., Joshipura, K.J., Rosner, B.A., Stampfer, M.J., Fuchs, C.S., Colditz, G.A., Speizer, F.E. & Willett, W.C. Prospective study of fruit and vegetable consumption and incidence of colon and rectal cancers. *J Natl Cancer Inst* 92, 1740-52 (2000).

35. Pietinen, P., Malila, N., Virtanen, M., Hartman, T.J., Tangrea, J.A., Albanes, D. & Virtamo, J. Diet and risk of colorectal cancer in a cohort of Finnish men. *Cancer Causes Control* 10, 387-96 (1999).

36. Terry, P., Giovannucci, E., Michels, K.B., Bergkvist, L., Hansen, H., Holmberg, L. & Wolk, A. Fruit, vegetables, dietary fiber, and risk of colorectal cancer. *J Natl Cancer Inst* 93, 525-33 (2001).

37. Voorrips, L.E., Goldbohm, R.A., van Poppel, G., Sturmans, F., Hermus, R.J. & van den Brandt, P.A. Vegetable and fruit consumption and risks of colon and rectal cancer in a prospective cohort study: The Netherlands Cohort Study on Diet and Cancer. *Am J Epidemiol* 152, 1081-92 (2000).

38. Hulshof, K.F., Brussaard, J.H., Kruizinga, A.G., Telman, J. & Lowik, M.R. Socio-economic status, dietary intake and 10 y trends: the Dutch National Food Consumption Survey. *Eur J Clin Nutr* 57, 128-37 (2003).

39. Wardle, J. & Steptoe, A. Socioeconomic differences in attitudes and beliefs about healthy lifestyles. *J Epidemiol Community Health* 57, 440-3 (2003).

40. Wallstrom, P., Wirfalt, E., Janzon, L., Mattisson, I., Elmstahl, S., Johansson, U. & Berglund, G. Fruit and vegetable consumption in relation to risk factors for cancer: a report from the Malmo Diet and Cancer Study. *Public Health Nutr* 3, 263-71 (2000).

41. Bos, V., Kunst, A.E. & Mackenbach, J.P. in Nationale gegevens over sociaal-economische sterfteverschillen op basis van informatie over kleine geografische eenheden. (Instituut Maatschappelijke Gezondheidszorg, Erasmus Universiteit, Rotterdam, 2000).

42. Bos, V., Kunst, A.E. & Mackenbach, J.P. in Sociaal-economische gezonheidsverschillen: Van verklaren naar verkleinen (ed. Stronks, K.) 8-20 (Zon/MW, Den Haag, 2001).

43. Smits, J., Keij, I. & Westert, G. Effecten van sociaal-economische status van kleine, middelgrote en grote geografische eenheden op de sterfte. *Mndstat bevolking* 11, 4-10 (2001).

44. Berkman, L.F. & Macintyre, S. The measurement of social class in health studies: old measures and new formulations. *IARC Sci Publ*, 51-64 (1997).

45. Janssen-Heijnen, M.L., Houterman, S., Lemmens, V.E., Louwman, M.W., Maas, H.A. & Coebergh, J.W. Prognostic impact of increasing age and co-morbidity in cancer patients: a population-based approach. *Crit Rev Oncol Hematol* 55, 231-40 (2005).

46. Houterman, S., Janssen-Heijnen, M.L., Hendrikx, A.J., Berg, H.A. & Coebergh, J.W. Impact of comorbidity on treatment and prognosis of prostate cancer patients: A population-based study. *Crit Rev Oncol Hematol* 58, 60-7 (2006).

47. Post, P.N., Hansen, B.E., Kil, P.J., Janssen-Heijnen, M.L. & Coebergh, J.W. The independent prognostic value of comorbidity among men aged < 75 years with localized prostate cancer: a population-based study. *BJU Int* 87, 821-6 (2001).

4.1

DECISION
CURATIVE
ROLE
SINCE 1990
data
OUTCOME

BRACHYTHERAPY
DETERMINANTS
CATEGORY
HOUSING
RECOGNISING

INTERVAL CANCER
health seeking behaviour
METASTASIS
CONTRIBUTION
COVERAGE

estimated
annual
percent
change
axillary
staging
EAPC
material resources
CHARLSON
socioeconomic position
statistical
RADIOTHERAPY
GP

SMOKING
DISCUSS
lifestyle
STUDIES
central nervous system

staging
socioeconomic status
Comprehensive Cancer Centre South

HOSPITAL
intelligence
education
hazard
ratio
Eindhoven Cancer Registry
dementia

VISITS
ATTENDANCE
EXPLANATION
RISK FACTORS
DIAGNOSIS
SEP

SOCIAL SUPPORT
mastectomy
diagnostics
distribution
CARDIOVASCULAR DISEASE

stage
HORMONAL THERAPY
ADVANCED
FEAR
HYPERTENSION
colorectal
therapy
HIGH
MENTAL

MAMMOGRAPHY
UPBRINGING
ENVIRONMENT

incidence
prostatectomy
p-value
QUESTIONNAIRE
HEALTH BEHAVIOUR

SF-36
GLOBE
PHYSICAL
SOCIOEC
occupation

NEIGHBOURHOOD
EXPOSURE
LOW
value of housing
socioeconomic
physical activity
REVIEW
colorectal
cancer
screening
comorbidities

INTERMEDIATE
TUBERCULOSIS
concomitant disease
VARIATION
CHEMORADIATION
INVITATION

INVASIVE
numbers
CONTACTS
gap
LOCALISED
logistic
regression
ACCESS TO CARE
CONSULTATION

ASSETS
PSA
WORK
SCREEN-DETECTED TUMOUR

income
percentages

THE NETHERLANDS

HEALTH INSURANCE
health awareness
HOUSEHOLD

search
DETECTIO

ALCOHOL CONSUMPTION

Chapter 4.2

Small but significant socioeconomic inequalities in axillary staging and treatment of breast cancer in the Netherlands

M.J. Aarts, V.C. Hamelinck, E. Bastiaannet, J.W.W. Coebergh, G.J. Liefers, A.C. Voogd, M. van der Sangen, W.J. Louwman

ABSTRACT

Background

The use of sentinel node biopsy (SNB), lymph node dissection, breast-conserving surgery, radiotherapy, chemotherapy and hormonal treatment for breast cancer was evaluated in relation to socioeconomic status (SES) in the Netherlands, where access to care was assumed to be equal.

Methods

Female breast cancer patients diagnosed between 1994-2008 were selected from the nation-wide population-based Netherlands Cancer Registry (N=176,505). SES was based on income, employment and education at postal code level. Multivariable models included age, year of diagnosis and stage.

Results

SNB was less often applied in high SES patients (multivariable analyses, ≤49years: odds ratio (OR) 0.70(95%CI:0.56-0.89); 50-75years: OR 0.85(0.73-0.99)). Additionally lymph node dissection was less common in low SES patients age ≥76 (OR 1.34(0.95-1.89)). SES-related differences in treatment were only significant in age 50-75. High SES women with stage T1-2 were more likely to undergo breast conserving surgery (+radiotherapy) (OR 1.15(1.09-1.22) and OR 1.16(1.09-1.22), respectively). Chemotherapy use among node-positive patients was higher in the high SES group, but not significant in multivariable analysis. Hormonal therapy was not related to SES.

Conclusion

Small but significant differences were observed in the use of SNB, lymph node dissection and breast-conserving surgery according to SES in Dutch breast cancer patients despite assumed equal access to health care.

4.2

INTRODUCTION

Breast cancer is the most common cancer in females from western countries, particularly in Western Europe.[1] Incidence rates are generally highest among women with high socioeconomic status (SES).[2-5] However, at least for the Netherlands, we observed age-specific differences in this association. In women aged 25-44 years, highest incidence rates were reported for those with high SES, while in those aged 65 years and older, rates were the lowest for those with a high SES. No socioeconomic inequalities were observed in those aged of 45-64 years.[6]

Survival from breast cancer has been reported to be generally worse in those with low SES[7, 8] although better survival rates have been observed by others.[2] In the Netherlands, an equal health care system is provided and a health insurance is compulsory for all inhabitants. However, survival disparities from breast cancer have been reported. These were partly explained by tumour size[7] and by stage differences resulting from differences in attendance to the free population screening program.[9]

Treatment disparities were present in studies from Denmark and the U.K., which have shown that deprived women had higher mastectomy rates, while the odds of receiving radiotherapy after breast conserving surgery was not associated with SES as well as chemotherapy and endocrine treatment.[10-14] Furthermore, the use of sentinel node biopsy (SNB) was higher in regions with a high educational level in the U.S.,[15] but to our knowledge this has not been studied in other countries.

Although Dutch health care is supposedly equally accessible, socioeconomic treatment disparities were reported for colon, pancreas, prostate and oesophageal cancer.[16-19] However, for breast cancer care it is not known whether there are differences in axillary staging and treatment. Therefore we investigated the association between SES and the use of SNB, lymph node dissection, breast-conserving surgery, radiotherapy, chemotherapy and hormonal treatment for breast cancer in the Netherlands.

METHODS
Patient selection
Female patients with their first primary breast cancer (invasive and *in situ*) diagnosed between 1994 and 2008 were selected from the Netherlands Cancer Registry. Patients with other tumours before their breast cancer were excluded. The nationwide Dutch network and registry of histopathology and cytopathology regularly submits reports of all diagnosed malignancies to the regional cancer registries. The national hospital discharge databank, which receives discharge diagnoses of admitted patients from all Dutch hospitals, completes case ascertainment. After notification, trained registry personnel collect data on diagnosis, staging, and treatment from the medical records, including pathology and surgery reports, about nine months after diagnosis using the registration and coding manual of the Dutch Association of Comprehensive Cancer Centres.

Stage was divided according to TNM classification at the year of diagnosis. Pathological T, N and M stage was used; clinical stage was used if pathological was missing.

4.2

In the Netherlands, the sentinel lymph node biopsy (SNB) was gradually implemented from 1998 to 2003; we therefore studied the SNB from 2003 onwards. It is registered in 6 of 9 regional registries; analyses on SNB were limited to these registries and to stage cT1,2N0M0,X.

National guidelines for treatment of breast cancer were introduced in the Netherlands in 2002.[20] Before that time, treatment was based on regional guidelines. Treatment was categorized as breast conserving surgery, external beam radiotherapy after breast conserving surgery, chemotherapy and hormonal therapy. The use of breast conserving surgery and breast conserving surgery plus external beam radiotherapy was studied among patients with stage T1,2N0M0,X breast cancer and chemotherapy and hormonal therapy in TanyN+M0,X breast cancer. The use of chemotherapy was studied from 2002 onwards, as treatment guidelines were rapidly changing before that time. The use strongly increased from 1994 to 2002 and gradually further increased afterwards. We were not able to classify chemotherapy as adjuvant or neoadjuvant.

The population-based screening program for breast cancer in the Netherlands started around 1990 and covered in 1997 all women aged 50-69 years; in 1998 the upper age limit was extended to 75.

Socioeconomic status

SES was assigned to each patient using an area-based measure according to place of residence at the time of diagnosis. The area-based SES was provided by the Netherlands Institute for Social Research and consists of numbers from income, employment and education which are provided to the institute by a private organization which collects information by telephone calls with one person per 6-digit postal code area; this person is seen as representative for his or her area. Next, numbers are aggregated to 4 digit postal code areas. Validation studies indicate that these numbers at aggregated level approach the true situation.[21] A higher score represents a high social deprivation (low SES) and a low score representing little social deprivation and consequently a high SES. Scores were divided into quintiles.

Statistical analysis

All statistical tests were two-sided and considered significant if $p \leq 0.05$. The distribution of sociodemographic and clinical characteristics were studied across the SES strata. Significance was tested with non-parametric tests (continuous variables) and χ^2-tests (categorical variables).

Analyses were stratified according to age groups ≤49, 50-75, ≥76. The odds ratios (OR) were stratified by these age categories and adjusted for age (continuously), year of diagnosis, SES and T-stage. After excluding patients with unknown SES (N=445) and non-carcinomas (N=1,548), data on 176,505 patients was analyzed.

4.2

RESULTS

Patients with highest SES were on average 3 years younger (p<0.0001) and had a lower stage of disease than patients with the lowest SES (*p*<0.001; Table 1).

Table 1. *Patient characteristics of breast cancer patients in the Netherlands, diagnosed 1994-2008.*

	Socioeconomic status									
	5. lowest		4.		3. intermediate		2.		1. highest	
	N	%	N	%	N	%	N	%	N	%
Period of diagnosis										
1994-1998	10234	23	10296	18	10413	20	9372	20	11689	20
1999-2003	11990	20	11616	21	11580	19	12695	19	11845	20
2004-2008	13077	18	13389	20	13308	21	13234	21	11767	20
Age at diagnosis										*
Mean	62.2		61.4		60.7		59.9		59.3	#
0-49	7673	22	8003	23	8477	24	9128	26	10101	29
50-75	20823	59	21314	60	21339	60	21104	60	20058	57
76+	6805	19	5984	17	5485	16	5069	14	5142	15
TNM Stage										*
0 (In situ)	2755	8	2934	8	3100	9	3081	9	3150	9
1	11964	34	12203	35	12384	35	12636	36	12561	36
2	14686	42	14682	42	14402	41	14437	41	14566	41
3	3601	10	3450	10	3434	10	3271	9	3144	9
4	1899	5	1644	5	1601	5	1541	4	1425	4
Unknown	396	1	388	1	380	1	335	1	455	1

* p<0.0001 (χ^2-test); # p<0.0001 (t-test).

The use of the SNB procedure for stage cT1,2N0M0,X breast cancer increased from 74% in 2003 to 88% in 2008. In general, high SES patients less often received SNB, with 1-3% lower rates in high versus low SES patients aged 75 and younger, but not statistically significant (Table 2). These differences were significant in multivariable analyses (age ≤ 49: odds ratio (OR) 0.70 (95%CI: 0.56-0.89); 0.85 (95%CI: 0.73-0.99) in 50-75 years). In the oldest age group no consistent pattern on the use of SNB appeared. Compared to high SES, rates of lymph node dissection in addition to SNB were slightly higher in low SES patients in the youngest age group (36% versus 39%, not statistically significant), and lower in low SES patients in the oldest group (27% in high SES versus 22% in low SES, p=0.01). In multivariable analyses, among the patients aged 76 or older receiving SNB, those with high SES more often received lymph node dissection compared to those with low SES, although not statistically significant for the highest SES group (OR 1.34 (95%CI: 0.95-1.89)).

Table 2. *The use of the sentinel node procedure and additional lymph node dissection for breast cancer patients in the Netherlands, diagnosed 2003-2008, stage cT1,2N0M0,X.*

Age	Socioeconomic status	N_{total}	Sentinel node biopsy					Lymph node dissection in patients with sentinel node biopsy				
			% SNB	P-value	OR#	95%CI	Trend	% LND	P-value	OR	95%CI	Trend
≤49	1. highest	1262	84.0	0.1	**0.70**	0.56 0.89	0.053	36.4	0.7	0.90	0.76 1.08	0.7
	2.	1305	85.4		0.80	0.63 1.02		36.6		0.91	0.76 1.08	
	3. intermediate	1401	85.9		0.84	0.66 1.06		36.4		0.90	0.75 1.07	
	4.	1431	86.2		0.87	0.69 1.11		37.1		0.91	0.76 1.08	
	5. lowest	1173	87.8		1.00			38.9		1.00		
50-75	1. highest	2635	87.2	0.2	**0.85**	0.73 0.99	0.2	28.2	0.6	0.94	0.84 1.06	0.6
	2.	3405	87.6		0.90	0.77 1.04		30.3		1.03	0.93 1.16	
	3. intermediate	3832	88.9		0.97	0.84 1.12		29.6		1.03	0.93 1.15	
	4.	4209	88.3		0.96	0.84 1.11		29.0		0.99	0.89 1.10	
	5. lowest	3613	88.5		1.00			29.2		1.00		
≥76	1. highest	506	53.2	0.1	1.01	0.80 1.28	0.06	27.1	0.01	1.34	0.95 1.89	0.01
	2.	668	46.1		**0.79**	0.64 0.98		30.2		**1.55**	1.11 2.14	
	3. intermediate	793	52.7		1.10	0.90 1.36		31.1		**1.64**	1.21 2.21	
	4.	1008	49.8		0.94	0.77 1.14		29.3		**1.51**	1.13 2.01	
	5. lowest	966	50.9		1.00			21.5		1.00		

OR: odds ratio, adjusted for age, year of diagnosis, T-stage and histology; 95%CI: 95% confidence interval; LND: lymph node dissection; SNB: sentinel node biopsy; P-values are from χ^2-test; Trend refers to P-value from trend test.

4.2

Small, statistically significant socioeconomic differences were present in treatment selection in those aged 50-75 years. The use of breast conserving surgery was slightly higher in high SES patients (stage T1,2N0M0,X), i.e. 64% of patients with high SES compared to 60% in low SES (χ^2-test p<0.0001, Table 3). Nearly all of these patients received additional radiotherapy (97%), which was not significantly different between the SES groups. In multivariable analyses, the odds of breast conserving surgery remained significantly increased (OR 1.15 (95%CI: 1.09-1.22) for high versus low SES), also for breast conserving surgery plus radiotherapy (OR 1.16 (95%CI: 1.09-1.22), Table 3). In this early stage an inverse association was observed for mastectomy, with lower rates in high SES women aged 50-75 years (data not shown).

In those aged 50-75 years, the use of endocrine treatment was not related to SES, neither in univariable, nor in multivariable analyses (Table 3). Rates of chemotherapy for node positive breast cancer were highest in high SES (62% versus 55% in low SES, χ^2 p<0.0001), but were no longer significant in multivariable analyses (Table 3).

Of all therapies above mentioned, none was significantly related to SES in women younger than 50. In women of 76 and older the only significant associations were observed for breast conserving surgery, with higher rates in high SES (χ^2-test p=0.02, OR high versus low SES 1.21 (95%CI: 1.06-1.38)), and for chemotherapy, which rates were reduced in the second highest SES group (OR 0.45 (95%CI: 0.22-0.91). The use of breast conserving surgery and radiotherapy combined however was not significantly related to SES (OR 1.10 (95%CI: 0.95-1.28)).

DISCUSSION

This study shows that in the Netherlands, a country with assumed equal access to care, breast cancer patients with high SES were less likely to undergo SNB and, in the oldest group, more likely to receive additionally lymph node dissection. Furthermore, in patients aged 50-75 years the use of breast-conserving surgery and chemotherapy were significantly related to SES, although the absolute differences between the SES groups were generally small. In early stage breast cancer, the use of breast conserving surgery (+radiotherapy) was highest in patients with high SES. This could not be fully explained by patient age, year of diagnosis and T-stage. Among patients with node-positive breast cancer a higher use of chemotherapy was observed among those with high SES. This difference, however, disappeared after adjustment for stage, age and year of diagnosis.

A prior U.S. study showed higher rates of lymph node biopsy/sampling, i.e. either axillary lymph node dissection or SNB, in areas where the education level was higher, although the absolute differences were small.[15] Our data suggest a poorer staging of the axillary lymph nodes and abandoning surgery in the armpit in patients with high SES. We cannot explain this observation as we expected the rates to increase with higher SES due to – amongst others – better understanding of the importance of axillary staging. Possibly patients with high SES are more conscious of the side effects of lymph node dissection, such as lymph oedema, and therefore are more inclined not to undergo this therapy. Previously, older age was associated with reduced likelihood of receiving lymph node biopsy,[15] but mean age differed only three years in our study, suggesting that age only little affected the staging procedure. Another study stated that among women undergoing breast-conserving surgery,

4.2

Table 3. Use of therapies for breast cancer in the Netherlands according to socioeconomic status, diagnosed 1994-2008.

	Age at diagnosis																	
	≤49						50-75						≥76					
	%	P-value	OR	95%CI		Trend	%	P-value	OR	95%CI		Trend	%	P-value	OR	95%CI		Trend
Breast conserving surgery, T1,2N0M0,X *																		
1. highest SES	60.9	0.8	0.95	0.86	1.04	0.7	64.1	<.0001	**1.15**	1.09	1.22	<.0001	24.0	0.02	**1.21**	1.06	1.38	0.02
2.	61.2		0.97	0.88	1.07		63.8		**1.09**	1.03	1.16		22.6		1.10	0.96	1.26	
3. intermediate	60.6		0.95	0.86	1.05		62.3		1.04	0.99	1.10		20.8		0.98	0.86	1.13	
4.	60.2		0.94	0.85	1.03		61.8		1.03	0.98	1.09		21.5		1.04	0.91	1.19	
5. lowest SES	61.5		1.00				60.4		1.00				20.6		1.00			
Breast conserving surgery + radiotherapy, T1,2N0M0,X *																		
1. highest SES	58.9	0.8	0.96	0.87	1.05	0.8	62.3	<.0001	**1.16**	1.09	1.22	<.0001	18.3	0.5	1.10	0.95	1.28	0.5
2.	59.6		0.99	0.90	1.09		61.9		**1.10**	1.04	1.16		17.8		1.05	0.90	1.22	
3. intermediate	59.1		0.97	0.88	1.07		60.5		1.05	0.99	1.11		16.6		0.96	0.83	1.11	
4.	58.3		0.95	0.86	1.05		60.0		1.04	0.99	1.10		17.1		1.02	0.88	1.17	
5. lowest SES	59.3		1.00				58.4		1.00				16.7		1.00			
Hormonal therapy, TanyN+M0,X $																		
1. highest SES	48.3	0.3	1.08	0.98	1.20	0.2	71.5	0.9	1.02	0.94	1.10	0.9	79.8	0.2	0.93	0.79	1.11	0.2
2.	50.4		1.11	1.00	1.23		71.3		1.01	0.93	1.09		78.9		0.93	0.79	1.10	
3. intermediate	48.4		1.01	0.91	1.12		71.7		1.00	0.93	1.08		81.0		1.04	0.88	1.22	
4.	48.4		1.02	0.91	1.13		71.5		0.98	0.90	1.06		77.9		0.87	0.74	1.01	
5. lowest SES	49.3		1.00				72.1		1.00				80.3		1.00			

Table 3 continues on next page

4.2

Continuation of table 3

4.2

		Age at diagnosis																
	≤49						50-75						≥76					
	%	P-value	OR	95%CI		Trend	%	P-value	OR	95%CI		Trend	%	P-value	OR	95%CI		Trend
Chemotherapy, TanyN+M0,X &																		
1. highest SES	93.2	0.3	0.95	0.73	1.24	0.3	61.7	<.0001	1.11	0.98	1.26	0.5	2.4	0.2	1.08	0.56	2.09	0.1
2.	93.3		0.97	0.75	1.27		58.8		1.03	0.91	1.17		1.3		**0.45**	0.22	0.91	
3. intermediate	94.1		1.10	0.83	1.45		57.2		1.01	0.89	1.14		1.9		0.62	0.32	1.19	
4.	92.4		0.83	0.63	1.08		56.1		1.02	0.90	1.15		1.8		0.67	0.36	1.25	
5. lowest SES	93.8		1.00				55.3		1.00				2.9		1.00			

*OR: odds ratio; 95%CI: 95% confidence interval; SES: socioeconomic status; p-value refers to χ^2-test; Trend refers to p-value for trend; * OR adjusted for age (continuously), year of diagnosis, T-stage (T2N0 versus T1N0); $ OR adjusted for age (continuously), year of diagnosis, T-stage (T2N+, T3N+, T4N+ versus T1N+); & from 2002 onwards. OR adjusted for age (continuously), year of diagnosis, T-stage (T1N+, T3N+, T4N+ versus T2N+).*

those with comorbid conditions were less likely to receive axillary dissection.[22] Since cancer patients with high SES have fewer comorbidities,[23] higher rates of axillary dissection would be expected among high SES patients. We had no information on comorbidities in this study, but it probably has not contributed to the lower rates of SNB in high SES patients in our study population. Besides, in the U.S., patients treated in hospitals with higher patient volumes were more likely to receive lymph node biopsy.[15] Possibly this has affected our results as well. Also in the Netherlands staging procedures and type of surgery depended on hospital characteristics such as volume, with reducing differences over time.[24] It should be noted however that absolute differences in our study were small and that statistical significance may have resulted from the large number of patients.

Our results on treatment selection are in line with and the order of magnitude is fairly similar to studies from Denmark and the U.K. These studies have shown that women with a lower SES had higher mastectomy rates [10-12] and lower breast conserving surgery rates,[12-14] although an age-dependent association has been observed as well.[25] Adjustment for stage explained higher mastectomy rates in low SES,[10] whereas the association remained significant after stratification by tumour size [12] and stage (our study, early stage (data not shown)). This implies that type of surgery chosen for the SES groups is not fully explained by stage and age in early stage disease. Because of higher prevalence of concomitant diseases in patients with low SES,[23] type of surgery is expected to be less invasive due to poor general condition in low SES patients. In fact we observed higher invasive surgery (mastectomy) rates in low SES. Presence of comorbidities might also be indicative for mastectomy to avoid the effects of radiotherapy, but this has not been studied before. An Northern Italian study found that presence of comorbidities reduced the odds of receiving radiotherapy after breast conserving surgery.[26] Besides, that study also reported no educational differences in treatment of early stage breast cancer after adjustment for comorbidities and hospital characteristics.[26] As discussed previously, hospital characteristics were affecting treatment selection including type of surgery and use of radiotherapy in the Netherlands as well,[24, 27, 28] but we could not take these into account in our analyses. Nor were we able to investigate the contributions of ER status or grade; but previously these factors were reported to be not associated to SES.[10] More active involvement of the patient in decision making led to higher mastectomy rates,[29] but the effects in the Netherlands remain to be studied.

In our study, in accordance with the Dutch treatment guidelines,[30] nearly all patients undergoing breast-conserving surgery received additional radiotherapy (97%) and no differences were observed between the SES groups. Our results are in line with a study from the UK, in which the odds of receiving adjuvant radiotherapy was not associated with deprivation.[13] Compared to the U.S., our rates of adjuvant radiotherapy are high (97% versus 73%).[31] Furthermore, in the U.S. large SES-differences were observed, with adjuvant radiotherapy rates of 67% in patients with low SES versus 78% in those with high SES in the period 1991-2002, which were not explained by stage, hormone receptor status, grade, chemotherapy, comorbidity and surgeon characteristics.[32] Similar differences were observed in another U.S. study investigating adjuvant radiotherapy rates according to race, which reported 74% in whites versus 65% in blacks,[31] which remained also significant after adjustment for demographic, clinical (including comorbidities) and socioeconomic covariates.

4.2

Previous studies have reported inconsistent results with respect to the associations between SES and adjuvant radiotherapy, chemotherapy and endocrine treatment,[12, 13, 33] with higher rates in high SES in some studies but no association in others.[13, 33, 34] Low educational level was associated with reduced doses of chemotherapy, while presence of comorbidities was not associated.[35] No data were available on chemotherapy doses from the Netherlands Cancer Registry. Besides, we have used the pathological staging supplemented with clinical TNM in case postoperative data were missing. Since we were not able to classify chemotherapy as adjuvant or neoadjuvant, the staging may be not completely correct for the patients who received neoadjuvant chemotherapy.

Higher education predicted hormonal therapy use in older U.S. breast cancer survivors.[36] For those on hormonal therapy, wealthier women and women with insurance coverage for some or all medication costs were more likely to receive an aromatase inhibitor, which is prescribed by the American Society for Clinical Oncology (ASCO).[36] Due to the Dutch obligatory health insurance for every inhabitant, insurance status is unlikely to affect treatment selection. This is in line with our finding that hormonal therapy was not related to SES in our study.

Unfortunately, patient preferences in itself could not be taken into account in this study. For example, the choice of mastectomy depends on the interplay between surgeon's recommendations and patients' preferences for treatment.[37] The role of patient decision-making[38] is likely to be influenced by health literacy, i.e. "The degree to which individuals have the capacity to obtain, process, and understand basic health information and services needed to make appropriate health decisions".[39] Low health literacy may lead to treatment options that are not fully understood, and therefore some patients may not receive the most appropriate treatment for their medical condition.[40] As SES can be linked with education, those with low SES are expected to be more vulnerable to low health literacy. A solution towards solving this might be to focus more on clear and adapted communication by health care providers. In contrast, some patients do not want to be very involved in decision making.[41, 42]

Our study findings might be influenced by several limitations. First, we had no information on the presence of comorbidities, which may have affected therapy selection. Secondly, data on grade, ER-status and PR-status were not available, which might have affected our results. Thirdly, we had no information on hospital characteristics, which affected therapy selection in Italy and the Netherlands, however in the latter study regional and hospital variation reduced over time.[24, 26] Fourthly, in this study we have used a measure of SES based on 6-digit postal code of the residential area. Our results may therefore be subject to the ecological fallacy. Furthermore, our findings may be explained by some residual confounding. Although this measure of SES is not based on individual data on income, education, or occupation, it covers a relatively small geographical area and thus is likely to represent a reliable approximation of individual SES. Previous studies in the Netherlands have proven that socioeconomic differences based on neighbourhood data tend to reflect socioeconomic differences accurately at the individual level.[43-45] Furthermore, since it is based on several outcomes, it also applies to older women (born before 1955), although whose occupation or education does not always properly reflect their social class.[46]

4.2

Nevertheless, we have used population-based nationwide data, including *all* breast cancer patients from the Netherlands. We have thus provided a complete overview of the association of SES and the staging and treatment selection of breast cancer, which has not been done before.

CONCLUSION

Small but significant differences were observed in the use of SNB, lymph node dissection and breast-conserving surgery according to SES in Dutch breast cancer patients despite the assumed equal access to health care.

ACKNOWLEDGEMENTS

4.2

REFERENCES

1. Ferlay, J., Shin, H.R., Bray, F., Forman, D., Mathers, C. & Parkin, D.M. GLOBOCAN 2008, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 10 [Internet]., available from: http://globocan.iarc.fr , accessed on: 15-02-2011 (International Agency for Research on Cancer, Lyon, 2010).

2. Faggiano, F., Partanen, T., Kogevinas, M. & Boffetta, P. Socioeconomic differences in cancer incidence and mortality. *IARC Sci Publ*, 65-176 (1997).

3. Spadea, T., D'Errico, A., Demaria, M., Faggiano, F., Pasian, S., Zanetti, R., Rosso, S., Vicari, P. & Costa, G. Educational inequalities in cancer incidence in Turin, Italy. *Eur J Cancer Prev* 18, 169-78 (2009).

4. Carlsen, K., Hoybye, M.T., Dalton, S.O. & Tjonneland, A. Social inequality and incidence of and survival from breast cancer in a population-based study in Denmark, 1994-2003. *Eur J Cancer* 44, 1996-2002 (2008).

5. National Cancer Intelligence Network. in Cancer incidence by deprivation. England, 1995-2004 (London, 2009).

6. Aarts, M.J., van der Aa, M.A., Coebergh, J.W. & Louwman, W.J. Reduction of socioeconomic inequality in cancer incidence in the South of the Netherlands during 1996-2008. *Eur J Cancer* 46, 2633-46 (2010).

7. Bastiaannet, E., de Craen, A.J., Kuppen, P.J., Aarts, M.J., van der Geest, L.G., van de Velde, C.J., Westendorp, R.G. & Liefers, G.J. Socioeconomic differences in survival among breast cancer patients in the Netherlands not explained by tumor size. *Breast Cancer Res Treat* 127, 721-7 (2011).

8. Schrijvers, C.T., Mackenbach, J.P., Lutz, J.M., Quinn, M.J. & Coleman, M.P. Deprivation and survival from breast cancer. *Br J Cancer* 72, 738-43 (1995).

9. Aarts, M.J., Voogd, A.C., Duijm, L.E.M., Coebergh, J.W. & Louwman, M. Socioeconomic inequalities in attending the mass screening for breast cancer in the south of the Netherlands - associations with stage at diagnosis and survival. *Breast Cancer Res Treat* 128, 517-25 (2011).

10. Henley, N.C., Hole, D.J., Kesson, E., Burns, H.J., George, W.D. & Cooke, T.G. Does deprivation affect breast cancer management? *Br J Cancer* 92, 631-3 (2005).

11. Norredam, M., Groenvold, M., Petersen, J.H. & Krasnik, A. Effect of social class on tumour size at diagnosis and surgical treatment in Danish women with breast cancer. *Soc Sci Med* 47, 1659-63 (1998).

12. Taylor, A. & Cheng, K.K. Social deprivation and breast cancer. *J Public Health Med* 25, 228-33 (2003).

13. Downing, A., Prakash, K., Gilthorpe, M.S., Mikeljevic, J.S. & Forman, D. Socioeconomic background in relation to stage at diagnosis, treatment and survival in women with breast cancer. *Br J Cancer* 96, 836-40 (2007).

14. Raine, R., Wong, W., Scholes, S., Ashton, C., Obichere, A. & Ambler, G. Social variations in access to hospital care for patients with colorectal, breast, and lung cancer between 1999 and 2006: retrospective analysis of hospital episode statistics. *Bmj* 340, b5479 (2010).

15. Halpern, M.T., Chen, A.Y., Marlow, N.S. & Ward, E. Disparities in receipt of lymph node biopsy among early-stage female breast cancer patients. *Ann Surg Oncol* 16, 562-70 (2009).

16. Aarts, M.J., Koldewijn, E.L., Poortmans, P.M.P., Coebergh, J.W. & Louwman, M. Impact of socioeconomic status on prostate cancer treatment and survival in the Southern Netherlands. (submitted).

17. Lemmens, V.E., van Halteren, A.H., Janssen-Heijnen, M.L., Vreugdenhil, G., Repelaer van Driel, O.J. & Coebergh, J.W. Adjuvant treatment for elderly patients with stage III colon cancer in the southern Netherlands is affected by socioeconomic status, gender, and comorbidity. *Ann Oncol* 16, 767-72 (2005).

18. van Oost, F.J., Luiten, E.J., van de Poll-Franse, L.V., Coebergh, J.W. & van den Eijnden-van Raaij, A.J. Outcome of surgical treatment of pancreatic, peri-ampullary and ampullary cancer diagnosed in the south of The Netherlands: a cancer registry based study. *Eur J Surg Oncol* 32, 548-52 (2006).

19. Bus, P., Aarts, M.J., Lemmens, V.E.P.P., Van Oijen, M.G.H., Creemers, G.J., Nieuwenhuijzen, G.A.P., Van Baal, J.W.P.M. & Siersema, P.D. The effect of socioeconomic status on staging and treatment decisions in esophageal cancer. (submitted).

4.2

20. Working Group Treatment Breast Cancer. Guideline treatment breast cancer. [Richtlijn behandeling mammacarcinoom] in Dutch. (ed. Nationaal Borstkanker Overleg Nederland) (Van Zuiden Communications, 2002).

21. Tesser, P., Van Praag, C., Van Dugteren, F., Herweijer, L. & Van der Wouden, H. in Rapportage minderheden 1995 (ed. Sociaal en Cultureel Planbureau/VUGA) (Rijswijk/Den Haag, 1995).

22. Louwman, W.J., Janssen-Heijnen, M.L., Houterman, S., Voogd, A.C., van der Sangen, M.J., Nieuwenhuijzen, G.A. & Coebergh, J.W. Less extensive treatment and inferior prognosis for breast cancer patient with comorbidity: a population-based study. *Eur J Cancer* 41, 779-85 (2005).

23. Louwman, W.J., Aarts, M.J., Houterman, S., van Lenthe, F.J., Coebergh, J.W. & Janssen-Heijnen, M.L. A 50% higher prevalence of life-shortening chronic conditions among cancer patients with low socioeconomic status. *Br J Cancer* 103, 1742-1748 (2010).

24. van Steenbergen, L.N., van de Poll-Franse, L.V., Wouters, M.W., Jansen-Landheer, M.L., Coebergh, J.W., Struikmans, H., Tjan-Heijnen, V.C. & van de Velde, C.J. Variation in management of early breast cancer in the Netherlands, 2003-2006. *Eur J Surg Oncol* 36 Suppl 1, S36-43 (2010).

25. Thomson, C.S., Hole, D.J., Twelves, C.J., Brewster, D.H. & Black, R.J. Prognostic factors in women with breast cancer: distribution by socioeconomic status and effect on differences in survival. *J Epidemiol Community Health* 55, 308-15 (2001).

26. Rosato, R., Sacerdote, C., Pagano, E., Di Cuonzo, D., Baldi, I., Bordon, R., Ponti, A., Bertetto, O., Segnan, N., Merletti, F., Vineis, P. & Ciccone, G. Appropriateness of early breast cancer management in relation to patient and hospital characteristics: a population based study in Northern Italy. *Breast Cancer Res Treat* 117, 349-56 (2009).

27. Vulto, J.C., Louwman, W.J., Poortmans, P.M. & Coebergh, J.W. Hospital variation in referral for primary radiotherapy in South Netherlands, 1988-1999. *Eur J Cancer* 41, 2722-7 (2005).

28. Siesling, S., van de Poll-Franse, L.V., Jobsen, J.J., Repelaer van Driel, O.J. & Voogd, A.C. Explanatory factors for variation in the use of breast conserving surgery and radiotherapy in the Netherlands, 1990-2001. *Breast* 16, 606-14 (2007).

29. Katz, S.J., Lantz, P.M., Janz, N.K., Fagerlin, A., Schwartz, K., Liu, L., Deapen, D., Salem, B., Lakhani, I. & Morrow, M. Patient involvement in surgery treatment decisions for breast cancer. *J Clin Oncol* 23, 5526-33 (2005).

30. Oncoline. in www.oncoline.nl.

31. Smith, G.L., Shih, Y.C., Xu, Y., Giordano, S.H., Smith, B.D., Perkins, G.H., Tereffe, W., Woodward, W.A. & Buchholz, T.A. Racial disparities in the use of radiotherapy after breast-conserving surgery: a national Medicare study. *Cancer* 116, 734-41 (2010).

32. Hershman, D.L., Buono, D., McBride, R.B., Tsai, W.Y., Joseph, K.A., Grann, V.R. & Jacobson, J.S. Surgeon characteristics and receipt of adjuvant radiotherapy in women with breast cancer. *J Natl Cancer Inst* 100, 199-206 (2008).

33. Macleod, U., Ross, S., Twelves, C., George, W.D., Gillis, C. & Watt, G.C. Primary and secondary care management of women with early breast cancer from affluent and deprived areas: retrospective review of hospital and general practice records. *Bmj* 320, 1442-5 (2000).

34. Bhargava, A. & Du, X.L. Racial and socioeconomic disparities in adjuvant chemotherapy for older women with lymph node-positive, operable breast cancer. *Cancer* 115, 2999-3008 (2009).

35. Griggs, J.J., Culakova, E., Sorbero, M.E., van Ryn, M., Poniewierski, M.S., Wolff, D.A., Crawford, J., Dale, D.C. & Lyman, G.H. Effect of patient socioeconomic status and body mass index on the quality of breast cancer adjuvant chemotherapy. *J Clin Oncol* 25, 277-84 (2007).

36. Yen, T.W., Czypinski, L.K., Sparapani, R.A., Guo, C., Laud, P.W., Pezzin, L.E. & Nattinger, A.B. Socioeconomic factors associated with adjuvant hormone therapy use in older breast cancer survivors. *Cancer* 117, 398-405 (2011).

37. Hawley, S.T. Involving patients in the decision-making process regarding breast cancer treatment: implications for surgery utilization. *Womens Health (Lond Engl)* 6, 161-4 (2010).

38. Smith, D.P., King, M.T., Egger, S., Berry, M.P., Stricker, P.D., Cozzi, P., Ward, J., O'Connell, D.L. & Armstrong, B.K. Quality of life three years after diagnosis of localised prostate cancer: population based cohort study. *Bmj* 339, b4817 (2009).

4.2

39. National Network of Libraries of Medicine. in Health Literacy (ed. Glasman, P.) (Bethesda, 2010).

40. Merriman, B., Ades, T. & Seffrin, J.R. Health literacy in the information age: communicating cancer information to patients and families. *CA Cancer J Clin* 52, 130-3 (2002).

41. Lantz, P.M., Janz, N.K., Fagerlin, A., Schwartz, K., Liu, L., Lakhani, I., Salem, B. & Katz, S.J. Satisfaction with surgery outcomes and the decision process in a population-based sample of women with breast cancer. *Health Serv Res* 40, 745-67 (2005).

42. Levinson, W., Kao, A., Kuby, A. & Thisted, R.A. Not all patients want to participate in decision making. A national study of public preferences. *J Gen Intern Med* 20, 531-5 (2005).

43. Smits, J., Keij, I. & Westert, G.P. Effecten van sociaal-economische status van kleine, middelgrote en grote geografische eenheden op de sterfte [in Dutch]. *Maandstatistiek van de bevolking* 11, 4-10 (2001).

44. Bos, V., Kunst, A.E. & Mackenbach, J. in Verslag aan de Programmacommissie Sociaal-economische gezondheidsverschillen II (Instituut Maatschappelijke Gezondheidszorg, Erasmus Universiteit, Rotterdam, 2000).

45. Bos, V., Kunst, A.E. & Mackenbach, J.P. in Sociaal-economische gezondheidsverschillen: Van verklaren naar verkleinen (ed. Stronks, K.) 8-20 (Zon/MW, Den Haag, 2001).

46. Berkman, L.F. & Macintyre, S. The measurement of social class in health studies: old measures and new formulations. *IARC Sci Publ*, 51-64 (1997).

4.2

Chapter 4.3

The impact of socioeconomic status on prostate cancer treatment and survival in the Southern Netherlands

M.J. Aarts, E.L. Koldewijn, P.M.P. Poortmans, J.W.W. Coebergh, W.J. Louwman

ABSTRACT

Aim

To investigate if socioeconomic status (SES) played a role in the selection of prostate cancer treatment and overall survival.

Methods

Treatment and survival by SES of all newly diagnosed prostate cancer patients (1998-2008) from the population-based Eindhoven Cancer Registry (n=11,086) were studied.

Results

Younger patients (<75) with early stage disease, including PSA-detected stage cT1c, with low SES underwent prostatectomy and brachytherapy less often (differences: 10-16% and 0-7%) compared to those with high SES, but underwent more external beam radiotherapy, hormonal therapy and watchful waiting policy (6-9%, 5-7% and 3-7%). This was partially related to the prevalence of comorbidity. Ten-year survival for localised and advanced disease was superior in high SES patients (67% vs 44% and 29% vs 20%), both related to treatment and comorbidity. Multivariable adjusted death rates remained significantly elevated for patients with low SES, especially cT1c, age<60 ($HR_{low\_vs\_high\_SES}$: 4.2 (1.3-13.7)).

Conclusion

SES affected treatment selection and overall survival for patients with prostate cancer in the Southern-Netherlands, where treatment guidelines exist and health care is fully covered. Presence of comorbidities only partly contributed to these differences. The relation with other SES-associated factors, e.g. ability to understand medical information or to cope with health problems, remains to be explored.

4.3

INTRODUCTION

Prostate cancer is the most common cancer in men and the incidence rate has been increasing during the last decade, which is ascribed largely to PSA testing.[1] This increase was observed in males of 45 years and older, most markedly in high socioeconomic status (SES) groups.[2] It is likely that higher prostate cancer awareness in high SES[3] led to increased use of PSA testing and accompanying increasing incidence rates.

In addition, awareness may also lead to different therapies. For prostate cancer radical surgery and/or external beam radiotherapy are found to be more commonly used in patients with high SES.[4-8] This has not yet been studied for prostate cancer in the Netherlands, a country with supposedly equal access to care and full health insurance coverage. However, socioeconomic disparities in referral were observed for pancreatic cancer surgery with a higher referral rate to university hospitals for patients with high SES.[9] Similarly, low SES patients received less often adjuvant chemotherapy for colon cancer stage III[10] and oesophageal cancer.[11] In the latter study also lower rates of oesophagectomy were reported.[11] Therefore treatment disparities for prostate cancer might be also present within the Netherlands.

Presence of comorbidities affects treatment selection in prostate cancer.[12] As concomitant medical conditions are more common in cancer patients with low SES,[13] they may therefore (partly) explain the socioeconomic differences in therapy for prostate cancer.[4, 14] While the presence of comorbidity used to have little influence on the use of radical prostatectomy in the early 1990s,[15] the interaction of comorbidities and socioeconomic differences towards treatment selection remains to be explored. In a recent study, we observed that the presence of concomitant medical conditions explained 22% of the relative socioeconomic inequalities in prostate cancer survival.[13]

Thus, in this paper we explore and describe the influence of SES in selection of prostate cancer treatment and survival in the Southern Netherlands. We also address these associations in the PSA-detected group of stage cT1c. In addition, we studied the interaction with the presence of comorbidities as well.

PATIENTS AND METHODS
Study population
The Eindhoven Cancer Registry records data on all patients newly diagnosed with cancer in the south-eastern part of the Netherlands, a representative area with 2.4 million inhabitants (~15% of the Dutch population) covered by 10 general public hospitals and 2 public radiotherapy departments. Trained registry personnel actively collected data on diagnosis, stage, treatment and survival from the medical records after notification by pathologists and medical registration offices. Exposure to PSA screening in Southern Netherlands was modest since 1993.[16]

In this study, we included all patients newly diagnosed with prostate cancer between 1998 and 2008. Clinical stage was used according to TNM edition 4.2 (year(s) of diagnosis: 1998), 5 (1999-2002) and 6 (2003-2008). Localised disease includes stage 1 and 2; advanced disease

stages 3 and 4. Other and unknown (n=499) stages were excluded. The cT1c-category was defined as cT1cN0,XM0,X as introduced to classify PSA-detected prostate cancer in 1993.

Comorbidity was coded according to a slightly adapted version of the Charlsons comorbidity index.[17] Chronic obstructive pulmonary diseases, cardio- and cerebrovascular diseases, peripheral arterial disease, other malignancies, and diabetes mellitus, connective tissue diseases, rheumatoid arthritis, kidney, bowel, and liver diseases, dementia, tuberculosis and other chronic infections were recorded. Comorbidity was defined as diseases that were present at the time of cancer diagnosis. Patients receiving no active treatment such as prostatectomy, external beam radiotherapy, brachytherapy, chemotherapy, hormonal or other therapy, were classified as watchful waiting. Patients who had only a transurethral resection of the prostate (TURP) were included in the watchful waiting group.

Socioeconomic status

The SES of the patient was defined at neighbourhood level based on the six-digit postal code of the residence area, combining mean household income (1998) and mean economic value of the house/apartment (2000), derived from individual tax data provided at an aggregated level (Statistics Netherlands[18]). Each postal code area contains on average 17 households. Postal codes were assigned to three SES categories: low (1st–3rd deciles), intermediate (4th–7th) and high (8th–10th). Given the low level of migration in the Netherlands, this SES measure is assumed to be valid for 10 years before and after the base year (2000). Patients with unknown SES and postal codes of care-providing institutions were excluded.

Statistics

The effect of SES on treatment selection was studied by multivariable logistic regression analyses. Analyses were performed using SAS 9.1. P-values were two-sided and values <0.05 were considered significant. Cut-of for follow up was 1 January 2010. Overall 10-year survival rates were calculated. Cox' regression models were used to compute multivariable rates (Hazard Ratio=HR) and 95% confidence intervals (95%C.I.). Analyses (logistic regression analyses and Cox' regression models) were stratified according to stage (localised, advanced) and age (≤59, 60-74, ≥75) because of interaction. Interaction was defined by including interaction terms in the logistic regression model and Cox' regression model (P<0.05). We additionally adjusted for age, year of diagnosis (both as continuous variables) and presence of comorbid conditions (0 versus 1, ≥2, unknown). In Cox' regression models, dummy variables for therapy were included when at least 10% of the patients received the therapy, i.e. for localised stage age groups ≤59 and 60-74: prostatectomy, external beam radiotherapy, brachytherapy, hormonal therapy, watchful waiting; localised stage ≥75 years: external beam radiotherapy, hormonal therapy, watchful waiting; advanced stage all age groups: external beam radiotherapy and hormonal therapy. We additionally adjusted for age, year of diagnosis (both continuous) and presence of comorbid conditions (0 versus 1, ≥2, unknown). Prostatectomy, external beam radiotherapy and brachytherapy were considered radical therapies, and hormonal therapy and watchful waiting were considered non-radical therapies. Other (including surgical procedures other than prostatectomy) and unknown therapies were considered separate groups.

4.3

RESULTS

We found 12,316 prostate cancer patients in the Eindhoven Cancer Registry. After excluding patients with unknown SES (n=266) or postal codes of care-providing institutions (n=465), a total of 11,086 patients could be included in this study.

Patients with low SES were older, had 14% more comorbidities and higher stage of disease compared to those with high SES (Table 1). During the 11-year study period, a declining proportion of patients was diagnosed with localised disease (from 77% to 68%) in all SES groups. In contrast, more patients were diagnosed with stage cT1c (PSA-detected), increasing from 17% in 1998 to 35% in 2003 and remaining more or less stable thereafter. This pattern was present in all SES groups, slightly more in high SES (non-significant).

Table 1. *Description of prostate cancer patients according to socioeconomic status, diagnosed 1998-2008 in the Southern Netherlands.*

	Socioeconomic status						
	Low		Intermediate		High		
	N	%	N	%	N	%	*p*-value
Age (years)							
Mean	71.2		68.9		67.9		
59 or younger	224	9	599	13	640	16	<0.0001
60-74	1415	55	2734	62	2580	63	
75 and older	915	36	1107	25	872	21	
Year of incidence*							
1998-2001	789		1146		1036		
2002-2005	1012		1751		1637		
2006-2008	753		1543		1419		
Stage (clinical)							
Localised	1781	70	3177	72	3026	74	<0.0001
cT1c (PSA-detected)	693	27	1332	30	1339	33	<0.0001
Advanced	773	30	1263	28	1066	26	
Number of comorbidities							
≤59 years							
0	101	45	292	49	356	56	0.009
1	67	38	156	26	132	21	
≥2	24	11	42	7	44	7	
Unknown	32	14	109	18	108	17	
60-74 years							
0	392	28	885	32	962	37	<0.0001
1	423	30	858	31	746	29	
≥2	388	27	606	22	455	18	
Unknown	212	15	385	14	417	16	
≥75 years							
0	169	18	237	21	188	22	0.09
1	284	31	334	30	267	31	
≥2	359	39	402	36	291	33	
Unknown	103	11	134	12	126	14	

* First 2 periods included 4 years.

4.3

In general, patients younger than 75 with high SES and with localised disease more often received radical therapies like brachytherapy (0-7% higher) and prostatectomy (10-16%), while external beam radiotherapy and hormonal therapy were less common (6-9% and 5-7%, respectively) (Table 2). These patterns, except for hormonal therapy, were also present in the cT1c-category. In patients older than 75 and in patients with advanced stage no significant differences were observed, only a 8% higher rate of external beam radiotherapy and higher rates of hormonal therapy in combination with other therapies (data not shown) in patients aged 60-74 with high SES.

Most of these patterns remained significant in multivariable analyses, which were stratified by age group and clinical stage because of interaction (only shown for localised stage and age group <75). Compared to high SES, patients with low SES had reduced multivariable adjusted odds ratios of receiving prostatectomy and brachytherapy (only in age group 60-74), which remained significant in the final model including comorbidity (Table 3). In contrast, low SES had increased rates of external beam radiotherapy, hormonal therapy and watchful waiting, but these were only statistically significant for men of 59 and younger for external beam radiotherapy ($OR_{low\_vs\_high\_SES}$=1.8 (95%CI: 1.1-2.9)) and watchful waiting (1.6 (1.0-2.6)). Adjustment for comorbidity only little reduced the difference in odds ratios between low and high SES, suggesting that comorbidity contributes little to the SES-differences in treatment selection.

Within the cT1c-category, low SES patients had reduced multivariable adjusted rates of prostatectomy and brachytherapy (data not shown). In the final model (including year of diagnosis, age and comorbidity), only brachytherapy remained significantly associated in men of 60-74 years ($OR_{low\_vs\_high\_SES}$=0.7 (0.5-0.9)). Compared to high SES patients, low SES patients had increased odds ratios of external beam radiotherapy, hormonal therapy and watchful waiting. In the final model, only external beam radiotherapy remained significantly increased (59 and younger: $OR_{low\_vs\_high\_SES}$=2.3 (1.0-5.1)); 60-74 years: $OR_{low\_vs\_high\_SES}$=1.3 (1.0-1.8)).

Overall 10-year survival rates were significantly related to SES, i.e. 44% in low SES versus 67% in high SES patients with localised stage and 20% versus 29% with advanced stage (both p-values <0.0001). Because of interaction, multivariable survival analyses were stratified by stage and age. Those with low SES had an increased risk of death for most stages and age groups (Table 4). The SES gradient in risk of death was largest in those with localised disease, especially in those younger than 60 with cT1c disease: hazard ratio (HR) of death of low versus high SES in final model 4.6 (1.5-14.4). In men aged 60-74 with stage cT1c, relative risks of death were similar to the entire group of localised stage aged 60-74 (data not shown). Inclusion of all specific therapies in the multivariable model had a larger impact on the HRs of death of low versus high SES than comorbidity had, except for males of 75 and older. Nevertheless, risks remained significantly increased after adjustment for comorbidity and therapy in males with localised disease aged 60-74 (HR 1.5 (1.2-1.7)), and in males of 60-74 years and 75 and older with advanced disease (HR 1.2 (1.0-1.5) and 1.4 (1.1-1.6), respectively).

4.3

4.3

Table 2. *Treatment of prostate cancer patients according to socioeconomic status, stage and age, diagnosed 1998-2008 in the Southern Netherlands.*

Age, treatment	Localised stage				Advanced stage				cT1c (PSA-detected) #			
	Socioeconomic status				Socioeconomic status				Socioeconomic status			
	Low (%)	Intermediate (%)	High (%)	p-value*	Low (%)	Intermediate (%)	High (%)	p-value	Low (%)	Intermediate (%)	High (%)	p-value
≤59 years												
Prostatectomy §	42	54	58	<0.01	6	8	10	0.7	47	50	54	0.5
Brachytherapy	17	18	16	0.8	2	3	3	-	18	22	24	0.5
External beam radiotherapy	21	15	12	<0.05	43	42	31	0.1	14	15	7	<0.01
Hormonal therapy	19	12	12	<0.05	87	84	81	0.7	14	7	9	0.1
Watchful waiting	19	14	12	0.1	2	0	2	-	18	15	14	0.6
60-74 years												
Prostatectomy	20	27	30	<0.001	1	2	3	0.2	19	24	26	<0.05
Brachytherapy	11	14	18	<0.001	1	2	2	0.8	18	20	25	<0.01
External beam radiotherapy	35	33	29	<0.01	36	37	44	<0.05	32	27	24	<0.01
Hormonal therapy	31	28	26	<0.05	92	92	91	0.6	20	17	17	0.5
Watchful waiting	22	19	19	0.1	1	2	1	0.5	24	24	23	0.9
≥75 years												
Prostatectomy	1	1	1	-	0	0	0	-	0	1	0	-
Brachytherapy	2	3	2	0.4	0	0	0	-	2	5	2	0.2
External beam radiotherapy	19	19	23	0.2	13	16	12	0.7	20	17	15	0.4
Hormonal therapy	44	43	43	1.0	90	88	90	0.7	42	31	34	0.1
Watchful waiting	41	43	43	0.8	7	9	8	0.5	43	52	51	0.1

* calculated with Chi-square tests; § combination of treatments possible, like external beam radiotherapy combined with adjuvant hormonal treatment for advanced stage. Maximal 6% of the patients received other or unknown therapies (data not shown); # stage cT1c is part of localised stage.

Table 3. Multivariable analyses of the treatment of prostate cancer patients according to socioeconomic status, diagnosed 1998-2008 in the Southern Netherlands.

Age at diagnosis, therapy	Socioeconomic status	N	Model adjusted for year of diagnosis and age			Model adjusted for year of diagnosis, age + comorbidity		
			OR§	95%C.I.*		OR	95%C.I.	
≤59 years								
Prostatectomy	Low	72	**0.53**	0.37	0.75	**0.57**	0.40	0.81
	Intermediate	246	0.84	0.65	1.09	0.85	0.66	1.10
	High	299	1.00			1.00		
Brachytherapy	Low	29	1.05	0.66	1.67	1.04	0.65	1.66
	Intermediate	82	1.12	0.80	1.57	1.12	0.80	1.57
	High	84	1.00			1.00		
External beam radiotherapy	Low	36	**2.00**	1.25	3.20	**1.78**	1.10	2.87
	Intermediate	68	1.36	0.93	1.98	1.31	0.89	1.93
	High	61	1.00			1.00		
Hormonal therapy	Low	312	**1.67**	1.04	2.68	1.57	0.97	2.54
	Intermediate	555	0.94	0.64	1.40	0.92	0.62	1.37
	High	500	1.00			1.00		
Watchful waiting	Low	32	**1.68**	1.05	2.69	**1.64**	1.01	2.64
	Intermediate	64	1.15	0.79	1.68	1.18	0.81	1.73
	High	63	1.00			1.00		
60-74 years								
Prostatectomy	Low	206	**0.70**	0.58	0.85	**0.75**	0.62	0.91
	Intermediate	542	0.94	0.81	1.09	0.97	0.84	1.13
	High	575	1.00			1.00		
Brachytherapy	Low	113	**0.62**	0.49	0.78	**0.62**	0.50	0.79
	Intermediate	274	**0.76**	0.64	0.90	**0.76**	0.64	0.90
	High	344	1.00			1.00		
External beam radiotherapy	Low	360	1.17	0.99	1.38	1.14	0.96	1.34
	Intermediate	663	1.14	0.99	1.31	1.13	0.98	1.29
	High	565	1.00			1.00		
Hormonal therapy	Low	259	1.11	0.93	1.32	1.06	0.89	1.27
	Intermediate	310	1.04	0.90	1.20	1.02	0.88	1.18
	High	250	1.00			1.00		
Watchful waiting	Low	224	**1.21**	1.00	1.47	1.20	0.99	1.45
	Intermediate	386	1.04	0.89	1.23	1.04	0.88	1.23
	High	359	1.00			1.00		

*§ Odds ratio (OR). Values in bold are significant; * 95%C.I.: 95% confidence interval; Data for unknown and other therapies are not shown.*

4.3

4.3

Table 4. Multivariable analyses of the survival of prostate cancer patients according to socioeconomic status, stage and age, diagnosed 1998-2008 in the Southern Netherlands.

Age	Socioeconomic status	10-y overall survival	Model adjusted for year of diagnosis and:								
			—			Comorbidity@		Therapy#		Comorbidity + Therapy#	
			Log rank	HR	95%C.I.*	HR	95%C.I.	HR	95%C.I.	HR	95%C.I.
Localised stage											
≤59 years	Low	77%	<0.05	**2.32**	1.24-4.36	**2.04**	1.08-3.87	1.82	0.96-3.43	1.72	0.90-3.31
	Intermediate	84%		1.51	0.87-2.61	1.42	0.82-2.45	1.60	0.93-2.78	1.59	0.91-2.78
	High	89%		1.0		1.0		1.0		1.0	
60-74 years	Low	53%	<0.05	**1.81**	1.51-2.15	**1.61**	1.35-1.92	**1.63**	1.36-1.94	**1.46**	1.22-1.74
	Intermediate	59%		**1.50**	1.28-1.75	**1.40**	1.19-1.65	**1.43**	1.22-1.68	**1.35**	1.15-1.59
	High	74%		1.0		1.0		1.0		1.0	
≥75 years	Low	25%	<0.05	1.16	0.98-1.37	1.15	0.97-1.36	1.14	0.96-1.34	1.13	0.96-1.34
	Intermediate	19%		1.15	0.98-1.36	1.17	0.99-1.38	1.13	0.96-1.33	1.15	0.97-1.35
	High	29%		1.0		1.0		1.0		1.0	
Advanced stage											
≤59 years	Low	30%	0.9	1.01	0.61-1.65	1.00	0.61-1.64	1.09	0.67-1.80	1.08	0.65-1.77
	Intermediate	38%		1.02	0.69-1.51	1.02	0.69-1.51	1.03	0.69-1.52	1.04	0.70-1.55
	High	41%		1.0		1.0		1.0		1.0	
60-74 years	Low	27%	<0.001	**1.36**	1.13-1.64	**1.34**	1.12-1.62	**1.23**	1.02-1.48	**1.21**	1.01-1.46
	Intermediate	32%		1.11	0.94-1.31	1.10	0.93-1.29	1.00	0.85-1.18	1.00	0.85-1.18
	High	35%		1.0		1.0		1.0		1.0	
≥75 years	Low	9%	<0.01	**1.27**	1.04-1.55	**1.23**	1.01-1.50	**1.37**	1.12-1.67	**1.35**	1.10-1.64
	Intermediate	8%		1.03	0.85-1.26	1.02	0.84-1.25	1.11	0.91-1.36	1.10	0.91-1.35
	High	13%		1.0		1.0		1.0		1.0	

§ Hazard ratio (HR); Values in bold are significant; * 95%C.I.: 95% confidence interval; @ no versus 1, 2, or unknown comorbidities; # Therapies included in the model: localised stage age groups ≤59 and 60-74: prostatectomy, external beam radiotherapy, brachytherapy, hormonal therapy, watchful waiting; localised stage ≥75 years: external beam radiotherapy, hormonal therapy, watchful waiting; advanced stage all age groups: external beam radiotherapy and hormonal therapy.

The introduction of brachytherapy for localised disease prostate cancer was related to SES. The use increased in all SES groups, with the strongest rise in high SES, but the gap between high and low SES became smaller in most recent years. This pattern was most pronounced in males aged 70-74 with localised disease (Figure 1). In the logistic regression analyses we found reduced multivariable ORs of receiving brachytherapy: OR 0.1 (0.0-0.9) in the period 1998-2001, 0.5 (0.3-1.0) in 2002-2005 and 0.5 (0.3-0.9) in 2006-2008, after adjustment for age, year of diagnosis and comorbidities. Effects on survival were investigated through multivariable Cox regression analyses. Risk of death remained increased during these periods: compared to high SES, the multivariable HR was 1.6 (1.1-2.3) in the period 1998-2001, 1.8 (1.2-2.7) from 2002-2005, and reduced to 1.4 (0.6-3.3) in the period 2006-2008, after adjustment for age, year of diagnosis, comorbidities and therapies. Also the wait and see policy became more common during the study period, but the introduction was not associated to SES.

4.3
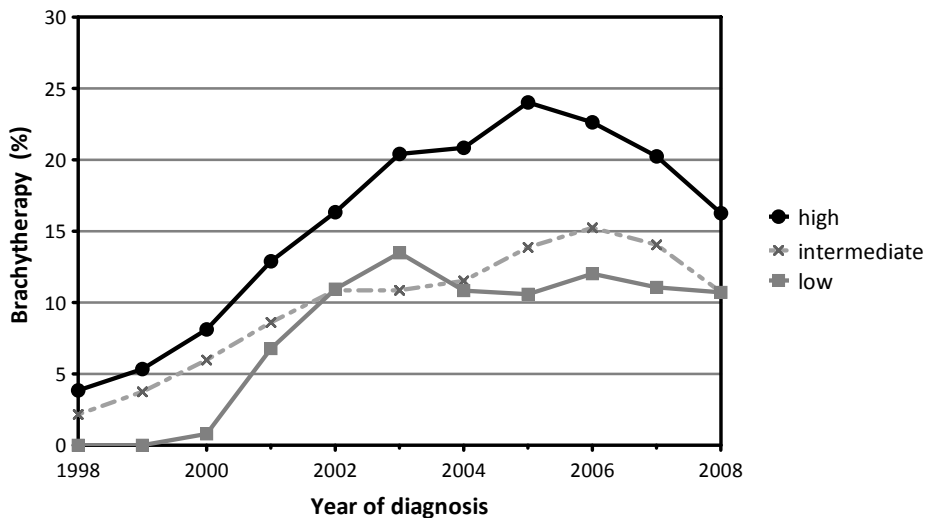
Figure 1. Introduction of brachytherapy for localised prostate cancer patients according to socioeconomic status, aged 70-74, diagnosed 1998-2008 in the Southern Netherlands. Three-year moving averages.

DISCUSSION

Even in a country where quality health care is supposedly accessible for everyone, we found that prostate cancer patients with localised disease younger than 75 with a low SES received radical therapy less often compared to high SES. This could only partially be explained by the presence of comorbidities. Treatment selection disparities, rather than comorbidities, seemed to contribute to survival differences observed for patients with localised disease up to 74 years of age, and for patients with advanced stage aged 60-74. Risks of death in low SES patients were higher, which remained present in most stages and ages after adjustment for comorbidity and therapy.

Despite different study settings and health care systems in previous studies, our results are in line with findings from Australia, England and the SEER database; low SES patients receive radical therapies less often, i.e. prostatectomy, external beam radiotherapy and/or brachytherapy[5-8, 19, 20] and more often hormonal therapy or no treatment at all compared to high SES patients.[6] A study performed in Switzerland (1995-2005) with compulsory health insurance as well, reported that men with low SES underwent prostatectomy less often and were more frequently managed by watchful waiting than men with high SES. These differences remained significant after stratification for stage at diagnosis.[21]

Differences in treatment may result from stage at diagnosis, variation between hospitals and comorbidities.[7, 12] However, we even observed treatment disparities within stages, thus these could not explain all of the socioeconomic differences in treatment selection. Previously, prostate cancer patients in large hospitals (i.e. more than 500 beds) were more often referred for radiotherapy than those in smaller hospitals in Southern Netherlands from 1988 to 1999, with large variation between hospitals.[22] Hospital variation in treatment of prostate cancer still remained in 2008 to 2010 (RHA Verhoeven, personal communication). Some therapies, e.g. brachytherapy, were performed by only one hospital for a while, we therefore decided not to include treatment hospital in our analyses.

Presence of comorbidities has not been taken into account by other research groups. In our study, we observed that comorbidities could only partly explain the influence of SES on treatment selection. Although therapy was a more important influencing factor, we could partially ascribe survival disparities to differences in comorbidities in males with localised disease younger than 75. It should be noted however that prostate cancer lethality is generally low for localised disease and that overall survival is to a larger extent affected by other factors, which may be related to SES-associated lifestyle components. This will be discussed in more detail later on.

Furthermore, differences in treatment selection could arise from differences in risk groups, as described in the national guidelines for the treatment of prostate cancer (www.oncoline. nl), which were released in 2007. However, Gleason score, PSA level (both registered since 2005) and T-stage only slightly contributed to the SES differences observed for treatment selection (data not shown).

4.3

Thus, apart from stage and comorbidity, other factors are likely to play a role in the association of SES with treatment selection and survival. For example, SES-determined patient preferences for early detection and/or treatments could not be taken into account in this study. Patient decision-making[23] is likely to be influenced by health literacy, i.e. "The degree to which individuals have the capacity to obtain, process, and understand basic health information and services needed to make appropriate health decisions".[24] Since it can be expected that high SES patients are less amenable to low health literacy, we expect them to more actively search for therapies, to be more eager to discuss and try new, experimental (more or less aggressive), or hazardous therapies. It is likely that this explains the initially highest rates of brachytherapy in high SES patients, which was introduced at the end of the nineties. Besides, brachytherapy was restrictively covered by health insurance companies until around 2003, thereby being initially only available to those who could afford this expensive therapy.

Besides, also related to health literacy, PSA testing is more common in high SES,[25, 26] confirmed by the slightly higher proportion of patients with stage cT1c in high SES patients in our study.

Treatment selection matters because it affects health-related quality of life (HRQOL), which was highest in patients treated with prostatectomy, while hormone treatment was associated with the lowest physical HRQOL.[27] Previously we showed that, up to 5 to 10 years after prostate cancer diagnosis, HRQOL was better in patients with high SES.[28] For physical HRQOL these higher scores in the high SES group were no longer significant in multivariable analyses including therapy, but mental HRQL remained significantly higher in high SES.

Previous studies reported similar survival rates for external beam radiotherapy, brachytherapy and prostatectomy in patients with localised prostate cancer, while we observed that the choice for radical treatment did (at least partly) affect the hazard ratios for overall survival. Apparently, high SES patients received radical therapy more often because of better health status, associated with better overall survival rates. By including comorbidities in Cox' regression analyses, we aimed to adjust for health status. Low SES however remained significantly increased death risk suggesting that other factors related to SES contribute to differences in survival.

The following limitations of the current study should be mentioned. Firstly, because high SES patients generally have fewer concomitant diseases, they are likely to be operated more often than low SES patients, also leading to better staging and likely SES-specific stage migration. We were not able to control for this in our analyses. Secondly, the Eindhoven Cancer Registry only records therapies given or planned within 6 months of diagnosis. We do not think that this leads to an underestimation since generally the final treatment is chosen relatively soon after diagnosis. Thirdly, the indicator of SES is based on the postal code of the residential area and is thus subject to ecological fallacy. However, as this aggregate covers on average only 17 households, it likely represents a reliable approximation of individual SES. Furthermore, routinely collected income tax data have been found to provide reliable estimates of household income in the Netherlands and it has been proven that socioeconomic differences based on neighbourhood data tend to reflect socioeconomic differences accurately at the

4.3

individual level.[29-31] Fourthly, we assumed that the SES indicator of a certain postal code did not change during the 10 years before and after 2000. This is supported by the similarity of results obtained for survival with another SES indicator during the period 1983–2002.[32] Fifthly, we had no data available on causes of death, thus we were not able to calculate prostate cancer specific death rates. Finally, unfortunately, no SES-specific life tables are available in the Netherlands to estimate prostate cancer specific survival according to SES. Using general life tables may lead to an underestimation of the relative survival rates in low SES and to an overestimation in high SES patients. Previously, we also found a higher rate of comorbidity among prostate cancer patients (70% in low SES vs 58% in high SES), which contributed largely (22%) to the lower survival rates for low SES groups.[13] By adjusting for comorbidities we (at least) partly adjusted for higher risk of death among low SES patients. Even when SES specific mortality is taken into account, high educated prostate cancer patients had approximately 12% better survival after 5 years in Denmark.[33] It therefore seems unlikely that we have largely overestimated the socioeconomic differences in survival.

Nevertheless, the results of this study form an important contribution to the limited information available on the association of SES and the treatment of and survival after prostate cancer diagnosis, especially in the PSA-detected group. Furthermore, the contribution of comorbidity has not been studied before. We have used population-based data, including *all* prostate cancer patients from the Southern-Netherlands.

CONCLUSION
Despite full coverage by health insurance, low threshold equal access to health care and the presence of national treatment guidelines, we found treatment and survival inequalities among prostate cancer patients in the Southern-Netherlands. Survival rates were lowest in low SES which was partially related to more non-radical treatments and to a lesser extent to the presence of comorbidities. The relation with other SES-related factors, e.g. the ability to understand and make decisions based on the medical information supplied, or patients' preferences, remains to be explored.

ACKNOWLEDGEMENTS

4.3

REFERENCES

1. Cremers, R.G.H.M., Karim-Kos, H.E., Houterman, S., Verhoeven, R.H.A., Schroder, F.H., Van der Kwast, T.H., Kil, P.J.M., Coebergh, J.W.W. & Kiemeney, L.A.L.M. Prostate cancer: trends in incidence, survival and mortality in the Netherlands, 1989-2006. *Eur J Cancer* 46, 2077-2087 (2010).

2. Aarts, M.J., van der Aa, M.A., Coebergh, J.W. & Louwman, W.J. Reduction of socioeconomic inequality in cancer incidence in the South of the Netherlands during 1996-2008. *Eur J Cancer* 46, 2633-46 (2010).

3. Fitzpatrick, P., Corcoran, N. & Fitzpatrick, J.M. Prostate cancer: how aware is the public? *Br J Urol* 82, 43-8 (1998).

4. Kane, C.J., Lubeck, D.P., Knight, S.J., Spitalny, M., Downs, T.M., Grossfeld, G.D., Pasta, D.J., Mehta, S.S. & Carroll, P.R. Impact of patient educational level on treatment for patients with prostate cancer: data from CaPSURE. *Urology* 62, 1035-9 (2003).

5. Krupski, T.L., Kwan, L., Afifi, A.A. & Litwin, M.S. Geographic and socioeconomic variation in the treatment of prostate cancer. *J Clin Oncol* 23, 7881-8 (2005).

6. Fairley, L., Baker, M., Whiteway, J., Cross, W. & Forman, D. Trends in non-metastatic prostate cancer management in the Northern and Yorkshire region of England, 2000-2006. *Br J Cancer* 101, 1839-45 (2009).

7. Lyratzopoulos, G., Barbiere, J.M., Greenberg, D.C., Wright, K.A. & Neal, D.E. Population based time trends and socioeconomic variation in use of radiotherapy and radical surgery for prostate cancer in a UK region: continuous survey. *Bmj* 340, c1928 (2010).

8. Berglund, A., Garmo, H., Robinson, D., Tishelman, C., Holmberg, L., Bratt, O., Adolfsson, J., Stattin, P. & Lambe, M. Differences according to socioeconomic status in the management and mortality in men with high risk prostate cancer. *Eur J Cancer* 48, 75-84 (2012).

9. van Oost, F.J., Luiten, E.J., van de Poll-Franse, L.V., Coebergh, J.W. & van den Eijnden-van Raaij, A.J. Outcome of surgical treatment of pancreatic, peri-ampullary and ampullary cancer diagnosed in the south of The Netherlands: a cancer registry based study. *Eur J Surg Oncol* 32, 548-52 (2006).

10. Lemmens, V.E., van Halteren, A.H., Janssen-Heijnen, M.L., Vreugdenhil, G., Repelaer van Driel, O.J. & Coebergh, J.W. Adjuvant treatment for elderly patients with stage III colon cancer in the southern Netherlands is affected by socioeconomic status, gender, and comorbidity. *Ann Oncol* 16, 767-72 (2005).

11. van Vliet, E.P., Eijkemans, M.J., Steyerberg, E.W., Kuipers, E.J., Tilanus, H.W., van der Gaast, A. & Siersema, P.D. The role of socio-economic status in the decision making on diagnosis and treatment of oesophageal cancer in The Netherlands. *Br J Cancer* 95, 1180-5 (2006).

12. Berglund, A., Garmo, H., Tishelman, C., Holmberg, L., Stattin, P. & Lambe, M. Comorbidity, treatment and mortality: a population based cohort study of prostate cancer in PCBaSe Sweden. *J Urol* 185, 833-9 (2011).

13. Louwman, W.J., Aarts, M.J., Houterman, S., van Lenthe, F.J., Coebergh, J.W. & Janssen-Heijnen, M.L. A 50% higher prevalence of life-shortening chronic conditions among cancer patients with low socioeconomic status. *Br J Cancer* 103, 1742-1748 (2010).

14. Vulto, A.J., Lemmens, V.E., Louwman, M.W., Janssen-Heijnen, M.L., Poortmans, P.H., Lybeert, M.L. & Coebergh, J.W. The influence of age and comorbidity on receiving radiotherapy as part of primary treatment for cancer in South Netherlands, 1995 to 2002. *Cancer* 106, 2734-2742 (2006).

15. Post, P.N., Kil, P.J., Hendrikx, A.J., Janssen-Heijnen, M.L., Crommelin, M.A. & Coebergh, J.W. Comorbidity in patients with prostate cancer and its relevance to treatment choice. *BJU Int* 84, 652-6 (1999).

16. Post, P.N., Kil, P.J., Crommelin, M.A., Schapers, R.F. & Coebergh, J.W. Trends in incidence and mortality rates for prostate cancer before and after prostate-specific antigen introduction. A registry-based study in southeastern Netherlands, 1971-1995. *European Journal of Cancer* 34, 705-9 (1998).

17. Charlson, M.E., Pompei, P., Ales, K.L. & MacKenzie, C.R. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 40, 373-83 (1987).

18. Van Duin, C. & Keij, I. Sociaal-economische status indicator op postcodeniveau [in Dutch]. *Maandstatistiek van de bevolking* 50, 32-35 (2002).

4.3

19. Hall, S.E., Holman, C.D., Wisniewski, Z.S. & Semmens, J. Prostate cancer: socio-economic, geographical and private-health insurance effects on care and survival. *BJU Int* 95, 51-8 (2005).

20. Byers, T.E., Wolf, H.J., Bauer, K.R., Bolick-Aldrich, S., Chen, V.W., Finch, J.L., Fulton, J.P., Schymura, M.J., Shen, T., Van Heest, S. & Yin, X. The impact of socioeconomic status on survival after cancer in the United States : findings from the National Program of Cancer Registries Patterns of Care Study. *Cancer* 113, 582-91 (2008).

21. Rapiti, E., Fioretta, G., Schaffar, R., Neyroud-Caspar, I., Verkooijen, H.M., Schmidlin, F., Miralbell, R., Zanetti, R. & Bouchardy, C. Impact of socioeconomic status on prostate cancer diagnosis, treatment, and prognosis. *Cancer* 115, 5556-5565 (2009).

22. Vulto, J.C., Louwman, W.J., Poortmans, P.M. & Coebergh, J.W. Hospital variation in referral for primary radiotherapy in South Netherlands, 1988-1999. *Eur J Cancer* 41, 2722-7 (2005).

23. Smith, D.P., King, M.T., Egger, S., Berry, M.P., Stricker, P.D., Cozzi, P., Ward, J., O'Connell, D.L. & Armstrong, B.K. Quality of life three years after diagnosis of localised prostate cancer: population based cohort study. *Bmj* 339, b4817 (2009).

24. National Network of Libraries of Medicine. in Health Literacy (ed. Glasman, P.) (Bethesda, 2010).

25. Nijs, H.G., Essink-Bot, M.L., DeKoning, H.J., Kirkels, W.J. & Schroder, F.H. Why do men refuse or attend population-based screening for prostate cancer? *J Public Health Med* 22, 312-6 (2000).

26. Scales, C.D., Jr., Antonelli, J., Curtis, L.H., Schulman, K.A. & Moul, J.W. Prostate-specific antigen screening among young men in the United States. *Cancer* 113, 1315-23 (2008).

27. Mols, F., van de Poll-Franse, L.V., Vingerhoets, A.J., Hendrikx, A., Aaronson, N.K., Houterman, S., Coebergh, J.W. & Essink-Bot, M.L. Long-term quality of life among Dutch prostate cancer survivors: results of a population-based study. *Cancer* 107, 2186-96 (2006).

28. Aarts, M.J., Mols, F., Thong, M.S., Louwman, M., Coebergh, J.W. & Van de Poll-Franse, L.V. Long-term Prostate Cancer Survivors With Low Socioeconomic Status Reported Worse Mental Health-related Quality of Life in a Population-based Study. *Urology* 76, 1224-30 (2010).

29. Bos, V., Kunst, A.E. & Mackenbach, J. in Verslag aan de Programmacommissie Sociaal-economische gezondheidsverschillen II (Instituut Maatschappelijke Gezondheidszorg, Erasmus Universiteit, Rotterdam, 2000).

30. Smits, J., Keij, I. & Westert, G.P. Effecten van sociaal-economische status van kleine, middelgrote en grote geografische eenheden op de sterfte [in Dutch]. *Maandstatistiek van de bevolking* 11, 4-10 (2001).

31. Bos, V., Kunst, A.E. & Mackenbach, J.P. in Sociaal-economische gezondheidsverschillen: Van verklaren naar verkleinen (ed. Stronks, K.) 8-20 (Zon/MW, Den Haag, 2001).

32. Louwman, W.J., van de Poll-Franse, L.V., Fracheboud, J., Roukema, J.A. & Coebergh, J.W. Impact of a programme of mass mammography screening for breast cancer on socio-economic variation in survival: a population-based study. *Breast Cancer Res Treat* 105, 369-75 (2007).

33. Marsa, K., Johnsen, N.F., Bidstrup, P.E., Johannesen-Henry, C.T. & Friis, S. Social inequality and incidence of and survival from male genital cancer in a population-based study in Denmark, 1994-2003. *Eur J Cancer* 44, 2018-29 (2008).

4.3

Chapter 4.4

The effect of socioeconomic status on staging and treatment decisions in esophageal cancer

P. Bus, M.J. Aarts, V.E.P.P. Lemmens, M.G. van Ooijen, G.J. Creemers,
G.A. Nieuwenhuijzen, J.W. van Baal, P.D. Siersema

ABSTRACT

Background

Optimal treatment choice for patients with esophageal cancer (EC) is complex and largely determined by tumor characteristics, comorbidity, and age.

Goals

This study describes the role of patient characteristics, among which is socioeconomic status (SES), in EC treatment.

Study

Patients diagnosed with primary EC between 1990 and 2008 in the southern part of the Netherlands were identified using the Eindhoven Cancer Registry. Multivariable logistic and proportional hazard regression analyses were used to identify determinants of treatment and survival.

Results

We included 1,914 patients, and 37% underwent intentionally curative treatment. Low-SES patients were diagnosed at older age (16% vs. 9%, age more than or equal to 80) and with more advanced tumor stages (13% vs. 10%, stage T4) than high-SES patients. Age less than 60 compared with 70 to 79 years [adjusted odds ratio 4.51; 95% confidence interval (CI) 2.98-6.84] and high compared to low SES [adjusted odds ratio 1.59; 95% CI 1.07-2.37] were independent predictors for curative treatment. Probability of death for high-SES patients undergoing palliative treatment was decreased compared with low-SES patients (hazard ratio 0.84; 95% CI 0.71-0.99).

Conclusions

SES is an important factor in treatment choice of EC. As health care is equally accessible to the whole population in The Netherlands, this suggests that both patient-related and physician-related factors are involved in this phenomenon.

4.4

INTRODUCTION

Esophageal cancer (EC) is the eighth most common cancer worldwide and the sixth malignancy on the list of estimated cancer deaths.[1] Symptoms, such as dysphagia and retrosternal pain, occur at a relatively late stage of this malignancy; the tumor spreads, however, at an early stage to lymph nodes and solid organs. EC is therefore a highly lethal tumor with a 5-year survival rate of 15% to 20%.[2, 3]

For adequate EC treatment, various options are available. Early-stage tumors can be removed by endoscopic techniques, that is, endoscopic mucosal resection in combination with an ablative treatment modality.[4] These relatively new techniques are, however, not yet fully implemented in daily clinical practice. More advanced EC can be treated by transhiatal or transthoracic esophagectomy often combined with neoadjuvant radiation and/or chemotherapy.[5] Furthermore, there is an increasing use of chemoradiotherapy as treatment option with a curative intent for esophageal squamous-cell carcinoma.

Elderly patients with multiple comorbidities, such as cardiovascular or pulmonary disease, may not be candidates for surgery and are therefore often not eligible for curative treatment options.[6] These patients mostly undergo a palliative treatment, such as (intraluminal) radiation therapy, stent placement, or dilation to relieve dysphagia. Hence, the choice of treatment is not only based on tumor characteristics, such as tumor stage, but also on patient characteristics, such as age and comorbidity.

Some studies have shown that socioeconomic status (SES) may be involved in the decision making of cancer treatment.[7, 8] Pancreatic cancer patients with a low SES were found to be less likely to undergo surgical treatment.[7] In patients with EC, it was reported that high-SES patients underwent esophagectomy more frequently, compared to low-SES patients.[8] This study, however, was based on a relatively small group of patients from a single institution. Besides treatment choice, cancer patients with a low SES also have a less favourable prognosis as compared to high-SES patients, as was previously demonstrated for breast, colon, kidney, and pancreatic cancer.[9-12]

In the current study, we investigated patient and tumor characteristics of newly diagnosed EC patients from 11 centers in the southern part of the Netherlands, a country with equal access to health care and full health care insurance coverage. We also analyzed differences in treatment and survival, while taking into account SES and other relevant characteristics.

PATIENTS AND METHODS
Data collection
Data from the population-based Eindhoven Cancer Registry, maintained by the Comprehensive Cancer Center South, were studied. This registry records data with regard to patient and tumor characteristics of all patients that have a newly diagnosed malignancy in the southern part of the Netherlands, which represents about 15% of the total Dutch population (2.4 million people).

For this study, patients diagnosed with primary EC in the period 1990 to 2008 were included. Tumor localization was categorized into anatomical subsites: distal third, middle third, proximal third, or unknown or overlapping subsites of the esophagus (other). Two periods were defined in order to study cohort effects, 1990 to 2000 and 2001 to 2008. Tumor stage was based on the clinical TNM classification, according to the fourth, fifth, and sixth International Union Against Cancer editions, as appropriate.[13-15] TNM stage was determined by physical examination, endoscopy, endoscopic ultrasound, computed tomography of the neck, thorax or abdomen, or surgical exploration.

SES was determined at the neighborhood level using postal codes, combining mean household income and mean value of housing, as provided by Statistics Netherlands (CBS, Rijswijk, The Netherlands). This was derived from individual fiscal data that are made available on an aggregated level. Postal codes were then assigned to one of 3 predefined SES categories: low (first to third decile), intermediate (fourth to seventh decile) and high (eighth to tenth decile).

Clinically relevant comorbidities were registered according to a slightly modified version of the Charlson Comorbidity index, such as previous malignancies, chronic obstructive pulmonary diseases, cardiovascular diseases, digestive tract diseases, urinary tract diseases, connective tissue diseases, dementia, Parkinson disease, diabetes, and infectious diseases.[16]

Study outcomes

The primary outcomes of this study were treatment choice and survival. Choice of treatment was either curative or palliative, with curative treatment being defined as surgery with or without (neo) adjuvant radiation and/or chemotherapy or definite radiation and/or chemotherapy in patients with T1-3N0-1M0 disease. Radiation and/or chemotherapy for T4N0-1M1 tumors, diagnostic procedures, other treatment or no treatment were regarded as palliative. Follow-up for overall survival was complete until January 2009.

Statistical analyses

Statistical analysis was performed with the Statistical Package for Social Sciences for Windows (version 15; SPSS Inc., Chicago, IL). The X^2 test was used to test differences in categorical variables between patients in the different treatment and SES groups. $P < 0.05$ were regarded as statistically significant. Univariable and multivariable logistic regression analysis was performed to determine factors influencing treatment choice. All variables that showed a statistically significant association or a $P < 0.2$ in the univariable analysis were included in the final multivariable model, estimating odds ratios (ORs) with 95% confidence intervals (CI) and P values. Survival analyses were performed using the Kaplan-Meier method, and comparisons between groups assessed by the log-rank test. Cox proportional hazards regression analysis was performed to investigate the effect of treatment and SES on overall survival before and after adjustment for confounding factors. Overall survival was calculated from the time of diagnosis to either death or end of follow-up (January 2009).

4.4

RESULTS

Population characteristics

Between January 1, 1990 and December 31, 2008, a total of 1914 patients were diagnosed with primary EC in the southern part of the Netherlands. The majority of the patients was male (n=1403; 73%). Fifty-five percent (n=1051) of the patients had an adenocarcinoma; the remainder was diagnosed with squamous-cell carcinoma. Of the whole group of EC patients, 37% underwent a curative treatment. Treatment modalities in the curative group consisted of surgery (59%), surgery with neoadjuvant radiation and/or chemotherapy (15%), surgery with adjuvant radiation and/or chemotherapy (3%), definite radiation therapy (14%), chemotherapy (1%), or a combination of chemotherapy and radiation therapy (8%). Treatment modalities in the palliative group consisted of chemotherapy (6%), radiation therapy (45%), a combination of radiation and chemotherapy (6%), metastasectomy (7%) and treatment to relieve dysphagia or no treatment (37%).

Low-SES patients were diagnosed at an older age (mean age of 68 y vs. 65 y for intermediate and 65 y for high SES; $P<0.001$) (Table 1). Low-SES patients were more often diagnosed with a T4 carcinoma: 13% versus 10% for an intermediate SES and 10% for a high SES ($P<0.01$). Moreover, these patients more often had an unknown tumor stage (Tx; 66% vs. 61% for intermediate SES and 58% for a high SES). In the low-SES group, 59% of the patients had 1 or more comorbidities, compared with 57% in the intermediate SES and 53% in the high-SES group ($P<0.05$). Patients with low SES were less likely to undergo a curative treatment (30% vs. 37% for intermediate SES and 44% for high SES; $P<0.01$). There was no statistically significant difference in tumor histology between the SES groups.

Treatment choice

Comparison of characteristics between curative-treated and palliative-treated patients showed that patients with a curative treatment more often had a tumor in the distal third of the esophagus, were younger, had fewer comorbidities, and had a higher SES (Table 2). High SES was identified as an independent predictor of undergoing a curative treatment [adjusted (adj.) OR 1.59; 95% CI, 1.07-2.37], compared with low SES. In contrast, older age at diagnosis (80 y and above) was associated with a lower OR of undergoing curative treatment (adj. OR 0.20; 95% CI, 0.10-0.39) compared to patients who were 70 to 79 year old. Patients with 2 or more comorbidities were less likely to undergo a curative treatment (adj. OR, 0.54; 95% CI 0.36-0.80) compared to patients without comorbidities. A more distal tumor location was associated with a higher OR of undergoing a curative treatment, while a proximal location was associated with a lower OR (distal vs. mid-esophagus: adj. OR 1.60; 95% CI, 1.03-2.49 and proximal vs. mid-esophagus: adj. OR 0.42; 95% CI, 0.21-0.85).

High-SES patients in the palliative group more often underwent a combination of chemotherapy and radiotherapy than patients with a low SES (8% vs. 3%; $P<0.01$). Moreover, high-SES patients in the palliative treatment group underwent less frequently no therapy at all, compared to low-SES patients (33% vs. 39%; $P<0.01$).

4.4

Table 1. *Differences in the characteristics between the 3 SES groups.*

Characteristics	Low SES (n=576) (%)	Intermediate SES (n=780) (%)	High SES (n=558) (%)	P
Age (y)				
<60	135 (23)	262 (34)	181 (32)	
60-69	170 (30)	246 (32)	174 (31)	<0.01
70-79	179 (31)	207 (27)	155 (28)	
≥80	92 (16)	65 (8)	48 (9)	
Sex (%)				
Male	391 (68)	598 (77)	414 (74)	<0.01
Female	185 (32)	182 (23)	144 (26)	
Tumor type				
SCC	283 (49)	344 (44)	236 (42)	0.053
EAC	293 (51)	436 (56)	322 (58)	
Tumor localisation				
Proximal third	53 (9)	58 (7)	42 (8)	
Middle third	123 (21)	141 (18)	98 (18)	<0.05
Distal third	367 (64)	555 (71)	380 (68)	
Other	33 (6)	26 (3)	38 (7)	
Differentiation grade				
Well/moderate	231 (40)	289 (37)	207 (37)	
Poor	204 (35)	289 (37)	224 (40)	0.320
Missing	141 (25)	202 (26)	127 (23)	
Period				
1990-2000	241 (42)	252 (32)	195 (35)	<0.01
2001-2008	335 (58)	528 (68)	363 (65)	
Treatment				
Palliative	403 (70)	492 (63)	311 (56)	<0.01
Curative	173 (30)	288 (37)	247 (44)	
T				
1	13 (2)	28 (4)	18 (3)	
2	25 (4)	33 (4)	38 (7)	
3	89 (16)	163 (21)	125 (22)	<0.01
4	72 (13)	78 (10)	53 (10)	
X	377 (66)	478 (61)	324 (58)	
N				
0	181 (31)	235 (30)	187 (34)	
1	203 (35)	302 (39)	239 (43)	<0.01
X	192 (33)	243 (31)	132 (24)	

4.4

Continuation of table 1.

M				
0	320 (56)	387 (50)	319 (57)	
1	160 (28)	274 (35)	174 (31)	<0.01
X	96 (17)	119 (15)	65 (12)	
No. comorbidities				
0	153 (27)	251 (32)	184 (33)	
1	151 (26)	220 (28)	154 (28)	
≥2	190 (33)	228 (29)	142 (25)	<0.05
Missing	82 (14)	81 (10)	78 (14)	

EAC indicates esophageal adenocarcinoma; SCC, squamous-cell carcinoma; SES, socioeconomic status.

Table 2. *Differences in characteristics between the palliative and curative treatment groups and the likelihood of receiving curative treatment by means of logistic regression analysis.*

Characteristics	Palliative treatment (n=1206) (%)	Curative treatment (n=708) (%)	Univariable OR (95% CI)	Multivariable OR (95% CI)
Age (y)				
<60	303 (25)	275 (39)	**1.95** (1.53-2.48)	**4.51** (2.98-6.84)
60-69	348 (29)	242 (34)	**1.49** (1.17-1.91)	**2.45** (1.65-3.64)
70-79	369 (31)	172 (24)	1.0	1.0
≥ 80	186 (15)	19 (3)	**0.22** (0.13-0.36)	**0.20** (0.10-0.39)
Sex (%)				
Male	880 (73)	523 (74)	1.0	1.0
Female	326 (27)	185 (26)	0.96 (0.77-1.18)	1.05 (0.73-1.51)
Tumor type				
SCC	562 (47)	301 (43)	1.0	1.0
EAC	644 (53)	407 (57)	1.18 (0.98-1.42)	1.14 (0.80-1.63)
Tumor localisation				
Proximal third	119 (10)	34 (5)	**0.61** (0.39-0.94)	**0.42** (0.21-0.85)
Middle third	246 (20)	116 (16)	1.0	1.0
Distal third	772 (64)	530 (75)	**1.46** (1.14-1.86)	**1.60** (1.03-2.49)
Other	69 (6)	28 (4)	0.86 (0.53-1.41)	1.03 (0.44-2.42)
T				
1	9 (1)	50 (7)	1.0	1.0
2	18 (1)	78 (11)	0.78 (0.33-1.87)	2.23 (0.57-8.81)
3	96 (8)	281 (40)	0.53 (0.25-1.11)	1.22 (0.37-3.98)
4	192 (16)	11 (2)	**0.01** (0.004-0.03)	**0.01** (0.001-0.02)
X	891 (74)	288 (41)	**0.06** (0.03-0.12)	**0.05** (0.02-0.16)

Table 2 continues on next page

4.4

Continuation of table 2.

N				
0	278 (23)	325 (46)	1.0	1.0
1	484 (40)	260 (37)	**0.46** (0.37-0.57)	**0.43** (0.28-0.64)
X	444 (37)	123 (17)	**0.24** (0.18-0.31)	**0.47** (0.32-0.70)
M				
0	456 (38)	570 (80)	1.0	1.0
1	560 (46)	48 (7)	**0.07** (0.05-0.09)	**0.02** (0.01-0.04)
X	190 (16)	90 (13)	**0.38** (0.29-0.50)	**0.51** (0.32-0.80)
SES				
Low	403 (33)	173 (24)	1.0	1.0
Intermediate	492 (41)	288 (41)	**1.36** (1.08-1.72)	1.26 (0.87-1.83)
High	311 (26)	247 (35)	**1.85** (1.45-2.36)	**1.59** (1.07-2.37)
Period				
1990-2000	448 (37)	240 (34)	1.0	1.0
2001- 2008	758 (63)	468 (66)	1.15 (0.95-1.40)	1.03 (0.74-1.42)
No. comorbidities				
0	349 (29)	239 (34)	1.0	1.0
1	331 (27)	194 (27)	0.86 (0.67-1.09)	0.78 (0.54-1.13)
≥ 2	373 (31)	187 (26)	**0.73** (0.58-0.93)	**0.54** (0.36-0.80)
Missing	153 (13)	88 (12)	-	-

Missing cases in multivariate analysis n=241, due to missing number of comorbidities. For the multivariable analysis, we adjusted for all variables in the table. CI indicates confidence interval; EAC, esophageal adenocarcinoma; OR, odds ratio; SCC, squamous cell carcinoma; SES, socioeconomic status.

Treatment outcome

Survival analysis was based on all patients, with a total of 1581 patients (83%) having died at the end of follow-up. Median survival of the entire cohort was 7 months (mean 14.7 mo; 95% CI, 13.6-15.8). Patients with a curative treatment had a longer median survival (14 mo; mean 25.9; 95% CI, 23.5-28.3) than those with a palliative treatment (5 mo; mean 8.1; 95% CI, 7.4-8.9). No significant differences in survival time were found between the different SES groups either within the curative or palliative treatment groups (Figures 1a and 1b).

Hazard ratios (HR) for survival were calculated and are shown in Table 3. High SES was associated with a lower mortality risk in the palliative treatment group (adj. HR 0.84; 95% CI, 0.71-0.99), but no effect was found in the curative group. Moreover, patients younger than 60 years had a lower mortality risk in the palliative group (adj. HR 0.77; 95% CI, 0.64-0.93), whereas age played no statistically significant role in the curative treatment group. The presence of at least 1 comorbidity had a negative prognostic impact on survival in the curative group (adj. HR 1.34; 95% CI, 1.05-1.70 for comorbidity and adj. HR 1.45; 95% CI, 1.11-1.89 for 2 or more comorbidities).

4.4

Table 3. *Proportional hazards regression analysis according to intent of treatment: survival.*

Characteristics	Curative treatment (HR 95% CI)		Palliative treatment (HR 95% CI)	
	Univariable	Multivariable	Univariable	Multivariable
Age (y)				
<60	0.85 (0.67–1.07)	0.80 (0.61-1.06)	0.95 (0.81-1.11)	**0.77** (0.64-0.93)
60-69	0.91 (0.72–1.16)	0.81 (0.61-1.06)	1.05 (0.90-1.22)	0.93 (0.78-1.10)
70-79	1.0	1.0	1.0	1.0
≥80	1.70 (0.99–2.92)	1.65 (0.92-2.98)	1.03 (0.85-1.24)	1.12 (0.92-1.37)
Sex				
Male	1.0	1.0	1.0	1.0
Female	0.89 (0.72–1.10)	0.79 (0.62-1.01)	0.94 (0.83-1.08)	0.99 (0.86-1.16)
Histology				
SCC	1.0	1.0	1.0	1.0
EAC	**0.76** (0.64–0.92)	0.80 (0.63-1.03)	0.91 (0.81-1.02)	0.87 (0.75-1.01)
Sublocalisation				
Proximal third	1.10 (0.72-1.68)	1.21 (0.74-1.97)	0.82 (0.66-1.04)	0.87 (0.68-1.13)
Middle third	1.0	1.0	1.0	1.0
Distal third	**0.77** (0.61-0.98)	0.94 (0.69-1.27)	0.94 (0.81-1.09)	0.99 (0.82-1.18)
Other	0.91 (0.55-1.49)	1.02 (0.57-1.83)	**1.36** (1.04-1.79)	**1.40** (1.04-1.90)
Comorbidity				
0	1.0	1.0	1.0	1.0
1	**1.30** (1.03-1.63)	**1.34** (1.05-1.70)	1.11 (0.95-1.30)	1.12 (0.95-1.31)
≥ 2	1.22 (0.96-1.55)	**1.45** (1.11-1.89)	1.01 (0.87-1.18)	1.05 (0.89-1.23)
T-status				
1	1.0	1.0	1.0	1.0
2	1.22 (0.74-2.02)	0.96 (0.54-1.68)	1.29 (0.53-3.13)	1.67 (0.47-5.95)
3	**1.70** (1.11-2.60)	1.21 (0.73-1.99)	1.31 (0.61-2.83)	1.67 (0.52-5.37)
4	1.92 (0.94-4.12)	1.56 (0.64-3.81)	1.65 (0.78-3.52)	2.67 (0.84-8.49)
X	1.34 (0.88-2.05)	1.19 (0.73-1.95)	1.67 (0.79-3.51)	2.41 (0.77-7.56)
N-status				
0	1.0	1.0	1.0	1.0
1	**1.57** (1.28-1.93)	**1.49** (1.15-1.94)	**1.45** (1.24-1.70)	1.20 (1.00-1.43)
X	1.24 (0.97-1.59)	1.22 (0.91-1.64)	**1.70** (1.45-1.91)	**1.50** (1.26-1.78)
M-status				
0	1.0	1.0	1.0	1.0
1	**2.14** (1.51-3.02)	**2.11** (1.44-3.11)	**1.81** (1.59-2.07)	**2.09** (1.78-2.46)
X	1.26 (0.96-1.65)	1.19 (0.87-1.62)	**1.38** (1.16-1.65)	1.22 (1.00-1.49)
SES				
Low	1.0	1.0	1.0	1.0
Medium	1.0 (0.79-1.26)	1.03 (0.79-1.33)	0.90 (0.78-1.03)	0.86 (0.74-1.00)
High	1.13 (0.89-1.43)	1.17 (0.90-1.53)	0.88 (0.76-1.03)	**0.84** (0.71-0.99)
Period				
1990-2000	1.0	1.0	1.0	1.0
2001-2008	**0.68** (0.56-0.82)	**0.61** (0.49-0.77)	0.95 (0.84-1.07)	0.91 (0.80-1.05)

Missing cases in multivariate analysis n=241. For the multivariable analysis we adjusted for all variables in the table. CI indicates confidence interval; EAC, esophageal adenocarcinoma; HR, hazard ratio; SCC, squamous cell carcinoma; SES, socioeconomic status.

4.4

A. Curative

B. Palliative

4.4
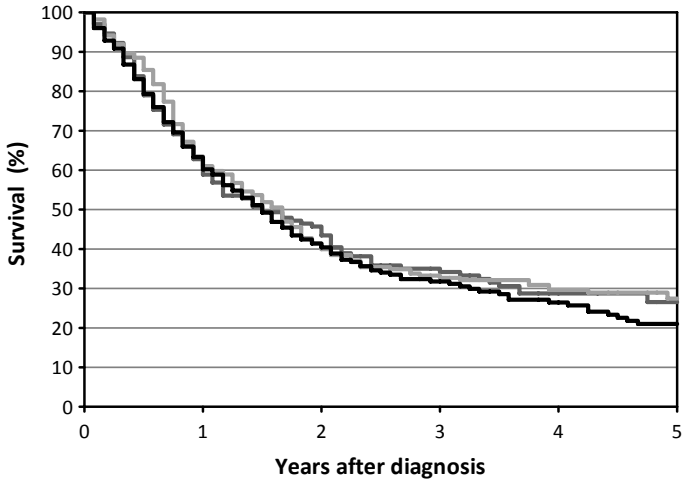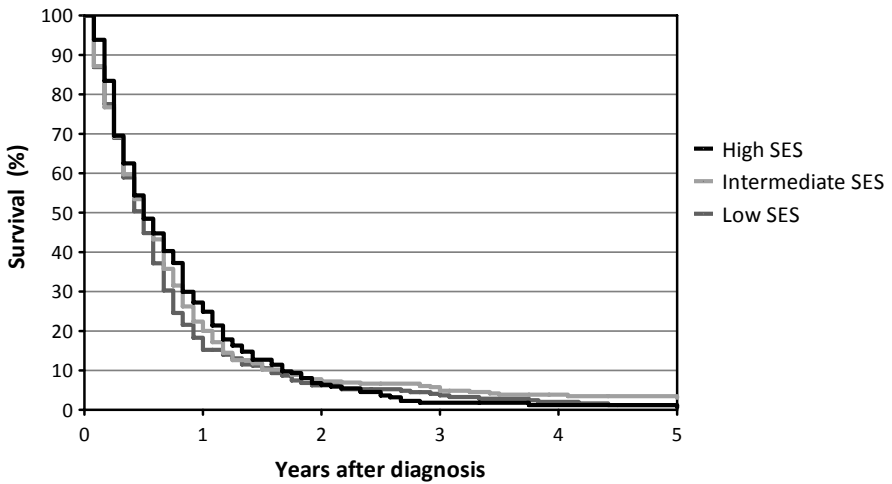
Figure 1. *A, Survival analysis for the different SES groups within the curative treatment and (B) palliative treatment group. SES indicates socioeconomic status.*

DISCUSSION

In this study, we determined the role of patient characteristics and tumor characteristics on treatment choice and survival in EC patients. We found that low-SES patients were diagnosed at a higher age, at a more advanced tumor stage, and had more comorbidities. Moreover, high-SES patients had a higher likelihood of undergoing a curative treatment, even after adjustment for comorbidity, tumor stage, and age. High SES also had a positive effect on life expectancy in the palliative group, after adjustment for age, tumor stage, histology and localization.

Our results confirm prior studies in which an effect of SES was found on treatment choice in EC patients.[8, 17] In 1 study, it was found that low-SES patients more frequently underwent stent placement, while high-SES patients were more often treated with chemotherapy or underwent esophageal resection.[8] Others have suggested that belonging to a minority group, no tumor staging, and one or more comorbidities influenced the likelihood of undergoing a curative treatment.[18] This study was conducted in the United States where health care is not equally accessible. In the Netherlands, however, there is similar access to health care for all income groups, with equal high coverage of health care insurance and compensation of treatment costs. On the basis of this, one would not expect a difference in the likelihood of undergoing a curative treatment for EC. However, treatment disparities across the SES groups have been reported previously for esophageal, pancreatic and colorectal cancer in the Netherlands.[8, 17, 19] Our study confirms the role of SES in EC treatment; however, our database contained patients from 11 different hospitals and 5 extra years of patient inclusion. Moreover, our SES scale is more specific, as we calculated with fewer households (17 vs. 4000 inhabitants in the previous study) and added the house value for a more stable calculation. Thus, 5 years later, SES is still an important factor in determining treatment options.

It has previously been found that low-SES patients have an increased delay between symptom awareness and visiting primary health care in case of upper gastrointestinal tumors, including EC.[20, 21] This could explain the differences between SES groups in our study. However, other factors might also be involved as, adjusted for age and tumor stage, low SES was still associated with a lower likelihood of undergoing a curative treatment. For example, a less "healthy" lifestyle can be involved. It has been found that low-SES patients are more often smokers, obese and have more comorbidities, factors that are known to influence the development and treatment of EC.[22-24] Moreover, it has previously been reported that cancer patients with a low SES more often have 1 or more serious comorbidities, compared with high SES.[24] Our information on comorbidities showed that low-SES patients more often had 2 or more comorbidities.

The difference in relative risk of death between low-SES and high-SES patients in the palliative treatment group was remarkable and may be explained by the fact that a higher percentage of high-SES patients were treated with a combination of radiotherapy and chemotherapy compared with low-SES patients. Differences in treatment and survival between different SES groups have been reported for various cancer types, both in Europe and the United States. Swedish women with breast cancer and a high SES have a higher mortality risk, while in the Netherlands and the United States, a decreased mortality was found in this group.[25-27] Low-

4.4

SES patients with colorectal cancer were found to have a poor survival compared with high-SES patients, both in Europe and the United States.[11, 28] Pancreatic cancer patients with a low SES had a higher mortality rate in the United States, whereas SES had no effect on pancreatic cancer mortality in Germany.[7, 29] Although the observed differences between the United States and Europe are often explained by the absence of a multipayer health care system in the United States, these data suggests that differences in outcome for several cancer types in Europe are most likely also due to decisional factors that are at least partly related to SES.

Even though high-SES patients more often received a curative treatment in our study, this is not reflected in the survival curves. This suggests that treatment with a curative intent is not always beneficial and/or that high-SES patients may have received a curative treatment while they did not meet the specific requirements for this, for example tumor stage and age.

The odds for receiving a curative treatment were not significantly different between the 2 studied periods (1990 to 2000 vs. 2001 to 2008). However, the relative risk for death was lower in the second period in patients receiving a curative treatment. This suggests that esophagectomy mortality decreased over time, mostly due to higher hospital volumes.[30]

Our study has several strengths and limitations. Our database contains both pathological and clinical data of all patients diagnosed in a well-confined region. In contrast, we did not have information on smoking, weight, race, or education. Race has been shown to be an important factor, next to SES, in the mortality of patients with breast, prostate and colorectal cancer.[31] In the Netherlands, however, race is not thought to be involved, since health care is equally available for all inhabitants, irrespective to SES or race. In addition, a recent study about colon cancer treatment in the United States concluded that race was not affecting treatment outcome, if patients received similar treatment.[32]

It can be imagined that education plays a role in health care-seeking behaviour and treatment choice. However, studies that evaluated patient delay in presenting with upper gastrointestinal cancer symptoms to their physician showed inconclusive data regarding the role of education.[33, 34] Another limitation is the high number of unknown TNM stages, which was caused by insufficient tumor staging and was mainly found in the period 1990 to 2000, in patients older than 80 years and in patients with low SES. This is, unfortunately, a reflection of the daily clinical practice as was especially the case in the 1990s, the patient's incapability to undergo staging procedures, or the limited added value of elaborate staging procedures in patients with extensive disease and/or low life expectancy. In addition, the high proportion of patients with unknown TNM stage may be related to the population-based nature of this study, which included patients who did not undergo a resection as well, still the vast majority of patients with esophageal cancer.

Overall, this study shows that even in a country with equal access to health care, SES is involved in treatment choice and survival of EC. Further studies are needed to provide more insight in the causes of these inequalities. It remains to be determined whether the effect of SES is mainly caused by patient-related or physician-related factors and how these factors can be modified.

4.4

REFERENCES

1. Ferlay, J., Shin, H.R., Bray, F., Forman, D., Mathers, C. & Parkin, D.M. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *Int J Cancer* 127, 2893-917 (2010).

2. Jemal, A., Siegel, R., Xu, J. & Ward, E. Cancer statistics, 2010. *CA Cancer J Clin* 60, 277-300 (2010).

3. Schlansky, B., Dimarino, A.J., Jr., Loren, D., Infantolino, A., Kowalski, T. & Cohen, S. A survey of oesophageal cancer: pathology, stage and clinical presentation. *Aliment Pharmacol Ther* 23, 587-93 (2006).

4. Tantau, M., Mosteanu, O., Pop, T., Tantau, A. & Mester, G. Endoscopic therapy of Barrett's esophagus and esophageal adenocarcinoma. *J Gastrointestin Liver Dis* 19, 213-7 (2010).

5. Kaklamanos, I.G., Walker, G.R., Ferry, K., Franceschi, D. & Livingstone, A.S. Neoadjuvant treatment for resectable cancer of the esophagus and the gastroesophageal junction: a meta-analysis of randomized clinical trials. *Ann Surg Oncol* 10, 754-61 (2003).

6. Pultrum, B.B., Bosch, D.J., Nijsten, M.W., Rodgers, M.G., Groen, H., Slaets, J.P. & Plukker, J.T. Extended esophagectomy in elderly patients with esophageal cancer: minor effect of age alone in determining the postoperative course and survival. *Ann Surg Oncol* 17, 1572-80 (2010).

7. Cheung, M.C., Yang, R., Byrne, M.M., Solorzano, C.C., Nakeeb, A. & Koniaris, L.G. Are patients of low socioeconomic status receiving suboptimal management for pancreatic adenocarcinoma? *Cancer* 116, 723-33 (2010).

8. van Vliet, E.P., Eijkemans, M.J., Steyerberg, E.W., Kuipers, E.J., Tilanus, H.W., van der Gaast, A. & Siersema, P.D. The role of socio-economic status in the decision making on diagnosis and treatment of oesophageal cancer in The Netherlands. *Br J Cancer* 95, 1180-5 (2006).

9. Quaglia, A., Lillini, R., Casella, C., Giachero, G., Izzotti, A. & Vercelli, M. The combined effect of age and socio-economic status on breast cancer survival. *Crit Rev Oncol Hematol* 77, 210-20 (2010).

10. Booth, C.M., Li, G., Zhang-Salomons, J. & Mackillop, W.J. The impact of socioeconomic status on stage of cancer at diagnosis and survival: a population-based study in Ontario, Canada. *Cancer* 116, 4160-7 (2010).

11. Aarts, M.J., Lemmens, V.E.P.P., Louwman, W.J., Kunst, A.E. & Coebergh, J.W.W. Socioeconomic status and changing inequalities in colorectal cancer? A review of the associations with risk, treatment and outcome. *Eur J Cancer* 46, 2681-95 (2010).

12. Hussain, S.K., Lenner, P., Sundquist, J. & Hemminki, K. Influence of education level on cancer survival in Sweden. *Ann Oncol* 19, 156-62 (2008).

13. Hermanek, P. & Sobin, L. (eds.) International Union Against Cancer (UICC): TNM Classification of Malignant Tumors. (Springer-Verlag, Berlin, Heidelberg, New York, 1987).

14. Sobin, L. & Wittekind, C. UICC International Union against Cancer. TNM Classification of malignant tumours, ed 5th Geneva, Switzerland: Wiley-Liss. (1997).

15. Sobin, L. & Wittekind, C. (eds.) UICC International Union against Cancer. TNM Classification of malignant tumours, ed 6th Geneva, Switzerland: Wiley-Liss (2002).

16. Charlson, M.E., Pompei, P., Ales, K.L. & MacKenzie, C.R. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 40, 373-83 (1987).

17. van Oost, F.J., Luiten, E.J., van de Poll-Franse, L.V., Coebergh, J.W. & van den Eijnden-van Raaij, A.J. Outcome of surgical treatment of pancreatic, peri-ampullary and ampullary cancer diagnosed in the south of The Netherlands: a cancer registry based study. *Eur J Surg Oncol* 32, 548-52 (2006).

18. Merrill, R.M., Merrill, A.V. & Mayer, L.S. Factors associated with no surgery or radiation therapy for invasive cervical cancer in Black and White women. *Ethn Dis* 10, 248-56 (2000).

19. Lemmens, V.E., van Halteren, A.H., Janssen-Heijnen, M.L., Vreugdenhil, G., Repelaer van Driel, O.J. & Coebergh, J.W. Adjuvant treatment for elderly patients with stage III colon cancer in the southern Netherlands is affected by socioeconomic status, gender, and comorbidity. *Ann Oncol* 16, 767-72 (2005).

4.4

20. Macdonald, S., Macleod, U., Campbell, N.C., Weller, D. & Mitchell, E. Systematic review of factors influencing patient and practitioner delay in diagnosis of upper gastrointestinal cancer. *Br J Cancer* 94, 1272-80 (2006).

21. Berkman, N.D., Davis, T.C. & McCormack, L. Health literacy: what is it? *J Health Commun* 15 Suppl 2, 9-19 (2010).

22. Cook, M.B., Kamangar, F., Whiteman, D.C., Freedman, N.D., Gammon, M.D., Bernstein, L., Brown, L.M., Risch, H.A., Ye, W., Sharp, L., Pandeya, N., Webb, P.M., Wu, A.H., Ward, M.H., Giffen, C., Casson, A.G., Abnet, C.C., Murray, L.J., Corley, D.A., Nyren, O., Vaughan, T.L. & Chow, W.H. Cigarette smoking and adenocarcinomas of the esophagus and esophagogastric junction: a pooled analysis from the international BEACON consortium. *J Natl Cancer Inst* 102, 1344-53 (2010).

23. Steffen, A., Schulze, M.B., Pischon, T., Dietrich, T., Molina, E., Chirlaque, M.D., Barricarte, A., Amiano, P., Quiros, J.R., Tumino, R., Mattiello, A., Palli, D., Vineis, P., Agnoli, C., Misirli, G., Boffetta, P., Kaaks, R., Rohrmann, S., Bueno-de-Mesquita, H.B., Peeters, P.H., May, A.M., Spencer, E.A., Allen, N.E., Bingham, S., Tjonneland, A., Halkjaer, J., Overvad, K., Stegger, J., Manjer, J., Lindkvist, B., Hallmanns, G., Stenling, R., Lund, E., Riboli, E., Gonzalez, C.A. & Boeing, H. Anthropometry and esophageal cancer risk in the European prospective investigation into cancer and nutrition. *Cancer Epidemiol Biomarkers Prev* 18, 2079-89 (2009).

24. Louwman, W.J., Aarts, M.J., Houterman, S., van Lenthe, F.J., Coebergh, J.W. & Janssen-Heijnen, M.L. A 50% higher prevalence of life-shortening chronic conditions among cancer patients with low socioeconomic status. *Br J Cancer* 103, 1742-1748 (2010).

25. Bastiaannet, E., de Craen, A.J., Kuppen, P.J., Aarts, M.J., van der Geest, L.G., van de Velde, C.J., Westendorp, R.G. & Liefers, G.J. Socioeconomic differences in survival among breast cancer patients in the Netherlands not explained by tumor size. *Breast Cancer Res Treat* 127, 721-7 (2011).

26. Weires, M., Bermejo, J.L., Sundquist, K., Sundquist, J. & Hemminki, K. Socio-economic status and overall and cause-specific mortality in Sweden. *BMC Public Health* 8, 340 (2008).

27. Sprague, B.L., Trentham-Dietz, A., Gangnon, R.E., Ramchandani, R., Hampton, J.M., Robert, S.A., Remington, P.L. & Newcomb, P.A. Socioeconomic status and survival after an invasive breast cancer diagnosis. *Cancer* 117, 1542-1551 (2011).

28. Le, H., Ziogas, A., Lipkin, S.M. & Zell, J.A. Effects of socioeconomic status and treatment disparities in colorectal cancer survival. *Cancer Epidemiol Biomarkers Prev* 17, 1950-62 (2008).

29. Kuhn, Y., Koscielny, A., Glowka, T., Hirner, A., Kalff, J.C. & Standop, J. Postresection survival outcomes of pancreatic cancer according to demographic factors and socio-economic status. *Eur J Surg Oncol* 36, 496-500 (2010).

30. Finks, J.F., Osborne, N.H. & Birkmeyer, J.D. Trends in hospital volume and operative mortality for high-risk surgery. *N Engl J Med* 364, 2128-37 (2011).

31. Byers, T.E., Wolf, H.J., Bauer, K.R., Bolick-Aldrich, S., Chen, V.W., Finch, J.L., Fulton, J.P., Schymura, M.J., Shen, T., Van Heest, S. & Yin, X. The impact of socioeconomic status on survival after cancer in the United States : findings from the National Program of Cancer Registries Patterns of Care Study. *Cancer* 113, 582-91 (2008).

32. Sabounchi, S., Keihanian, S. & Anand, B.S. Impact of Race on Colorectal Cancer. *Clin Colorectal Cancer* (2011).

33. Porta, M., Gallen, M., Belloc, J. & Malats, N. Predictors of the interval between onset of symptoms and first medical visit in patients with digestive tract cancer. *Int J Oncol* 8, 941-9 (1996).

34. Mariscal, M., Llorca, J., Prieto, D. & Delgado-Rodriguez, M. Determinants of the interval between the onset of symptoms and diagnosis in patients with digestive tract cancers. *Cancer Detect Prev* 25, 420-9 (2001).

4.4

DECISION

CURATIVE

ROLE

SINCE 1990

data

BRACHYTHERAPY

DETERMINANTS

CATEGORY

HOUSING

RECOGNISING

OUTCOME

INTERVAL CANCER

health seeking behaviour

METASTASIS

CHARLSON

CONTRIBUTION

COVERAGE

estimated annual percent change

axillary staging

EAPC

material resources

socioeconomic position

RADIOTHERAPY

GP

statistical

SMOKING

STUDIES

HOSPITAL

staging

lifestyle

central nervous system

Comprehensive Cancer Centre South

intelligence

education

hazard ratio

Eindhoven Cancer Registry

dementia

stage

HORMONAL THERAPY

VISITS

ATTENDANCE

EXPLANATION

SOCIAL SUPPORT

socioeconomic status

DISCUSS

RISK FACTORS

diagnostics

mastectomy

DIAGNOSIS

distribution

CARDIOVASCULAR DISEASE

SEP

therapy

HIGH

MENTAL

ADVANCED

FEAR

HYPERTENSION

colorectal

UPBRINGING

ENVIRONMENT

MAMMOGRAPHY

incidence

prostatectomy

p-value

QUESTIONNAIRE

HEALTH BEHAVIOUR

SF-36

GLOBE

NEIGHBOURHOOD

EXPOSURE

LOW

PHYSICAL

SOCIOEC

ALCOHOL CONSUMPTION

INTERMEDIATE

value of housing

socioeconomic

physical activity

REVIEW

colorectal cancer screening

comorbidities

occupation

TUBERCULOSIS

concomitant disease

VARIATION

CHEMORADIATION

INVITATION

INVASIVE

numbers

CONTACTS

gap

LOCALISED

logistic regression

ACCESS TO CARE

CONSULTATION

ASSETS

PSA

WORK

SCREEN-DETECTED TUMOUR

income

percentages

THE NETHERLANDS

HEALTH INSURANCE

health awareness

HOUSEHOLD

search

DETECTIO

Chapter 4.5

Educational inequalities in cancer survival: a role for comorbidities and health behaviours?

M.J. Aarts, C.B.M. Kamphuis, W.J. Louwman, J.W.W. Coebergh, J.P. Mackenbach, F.J. van Lenthe

ABSTRACT

Aim

To study the contribution of comorbidities and health behaviours to socioeconomic inequalities in cancer survival in the Netherlands.

Methods

The GLOBE study sent postal questionnaires to individuals in the Netherlands in 1991, resulting in 18,973 respondents (response 70 %). Questions were asked on education, health and health-related behaviours. Participants were linked for cancer diagnosis (1991-2008), comorbidity and survival (up to 2010) with the population-based Eindhoven Cancer Registry, resulting in 2,576 tumours.

Results

Five-year crude survival was best in high educated patients as compared to low educated patients: 48% versus 32% in males, 67% versus 47% in females. Generally, survival was better in patients with few comorbidities, high physical activity levels, and light or excessive alcohol consumption, while the association for smoking was not consistent. Except for lung cancer, high educated patients had reduced risks of death in multivariable analyses (hazard ratios (HR) range: 0.4-0.8). Survival was affected by comorbidity (HR$_{\geq 2 \text{ versus } 0 \text{ comorbidities}}$ range: 1.1-2.7) and lifestyle behaviours (HR range: 0.5-2.2). Being high educated remained associated with reduced risk of death (HR range: 0.4-0.8) after inclusion of comorbidities and lifestyle behaviours in the model, except for lung cancer (HR 1.0).

Conclusion

Generally, high educated cancer patients had better survival. Although presence of comorbidities and poor lifestyle behaviours affected survival from cancer, these did not explain educational inequalities in survival. The role of other factors for inequalities in cancer survival, such as social support, capacity to obtain, process and understand health information and services, needs to be explored.

4.5

INTRODUCTION

Many studies report highest cancer mortality rates among those with low socioeconomic position (SEP).[1-4] This disadvantage may be the result of higher cancer incidence in low SEP groups. Indeed, people from lower socioeconomic strata have more or less consistent excess risks for respiratory cancers, cancers of the head and neck and upper gastrointestinal tract, liver and cervix uteri.[1, 5-7] Risks for cancers of the colon, breast and ovary and malignant melanoma are generally lower in those with a low SEP.[1, 5-7] Some of these cancers have found to be related to unhealthy behaviours. Part of the increased risks of developing lung and breast cancer can be explained by smoking, alcohol intake and physical activity.[8] Recently, smoking was thought to explain 19% of all new cancer cases in the U.K., whereas deficient intake of fruits and vegetables, occupational exposures, overweight and obesity and infectious agents explained 4-7% of cancer incidence.[9]

Increased cancer mortality rates among people with lower SEP may not only result from increased incidence, but also from poorer survival from cancer in lower SEP. Survival rates from cancer are generally better for patients with high SEP,[4, 5, 10-12] which has been ascribed partly to lower prevalence of other chronic diseases (comorbidities) in high SEP cancer patients.[13, 14] The presence of these comorbidities is affected by lifestyle (for example smoking is related to the occurrence of COPD and cardiovascular disease), and lifestyle likely influences the socioeconomic inequalities in cancer survival as well. Because unhealthy behaviours are not necessarily reflected in quantifiable comorbidity scores, lifestyle may further explain socioeconomic inequalities in cancer survival. Previous studies on this topic reported small effects of smoking, physical activity and alcohol consumption upon socioeconomic differences in survival from respiratory-related cancers, colorectal cancers and all cancers combined in New Zealand and Sweden.[15, 16] The explanatory role of lifestyle in socioeconomic inequalities in cancer survival has not been studied for other cancers separately, nor the additional effect of comorbidities.

The prospective GLOBE study was designed to investigate several explanations for socioeconomic inequalities in health in the Netherlands. Linkage of information from study participants to the Eindhoven Cancer Registry enabled us to study the presence of socioeconomic inequalities in cancer survival and the contribution of three cancer-related behavioural risk factors (alcohol consumption, smoking and physical activity) and comorbidities.

METHODS
Population
The prospective GLOBE study started in 1991, and aimed to investigate the contribution of explanatory factors to socio-economic inequalities in health. GLOBE is the Dutch acronym for 'Health and Living Conditions of the Population of Eindhoven and Surroundings'. A detailed description of the purpose and design of the GLOBE study, and main results after the first ten years are presented elsewhere.[17, 18] In short, in 1991 a postal questionnaire was sent to non-institutionalised Dutch persons between 15 and 75 years of age, living in or near the city of Eindhoven, to which 18,973 individuals responded (70.1%). The questionnaire included measures of SEP, self-reported health, health-related behaviour (e.g. smoking, alcohol

4.5

consumption, physical activity), material circumstances (housing, income), psychosocial characteristics (marital status, vitality), health-care utilisation, and childhood circumstances.

Cancer survival

The population-based Eindhoven Cancer Registry has collected data on new cancer patients since 1955 according to international guidelines.[19] Trained registry personnel actively collects data on diagnosis and treatment. The registry also records serious co-morbidity at diagnosis according to an adaptation of the list of Charlson.[20] Since 1988, the registry has covered an area in the south-east of the Netherlands with a population of over 2 million inhabitants, including the area in which GLOBE participants resided. Follow-up was complete for cancer patients until 31 December 2009. Non-cancer patients who moved out the area were lost to follow-up.

Questionnaire information from respondents and cancer registry records were linked in a two-step procedure. First, a combination of the respondent's sex, date of birth and the first two characters of his or her last name at birth were used as a linking key. In a second step, uncertain matches were checked by visual inspection of the Eindhoven Cancer Registry, using identifiable data (such as initials, full last names, and address). We included patients diagnosed from 1991 to 2008. Patients who indicated in the questionnaire that they had suffered from 'malignant disease or cancer' in the past were excluded from the present study (n=70, mainly cancers of the breast, colon and lung and basal cell carcinomas), as patients could have changed to a more healthy lifestyle in response to their disease. Only if at least 5 patients were at risk of dying per subgroup for any given time since diagnosis, survival rates are shown. For males we studied the three most common cancers: colon, non-small cell lung and prostate cancers. Due to the small number of females in higher educational levels, we were only able to study inequalities in breast cancer.

Educational level

Educational level was indicated by highest attained level of education, with students classified according to their current training, using a closed question in the baseline questionnaire. Four different groups were created: (1) primary school only; (2) lower vocational school and lower secondary school; (3) intermediate vocational school and intermediate/higher secondary school; and (4) higher vocational school and university. In The Netherlands educational level is recognised as a good indicator of SEP.[21] Because of relatively small numbers of patients in the high educated group, we decided to use the low educated group as reference group.

Behavioural variables

Self-reported current smoking behaviour was categorised into four groups: never; former smoker; current smoker; unknown. On the basis of questions on the average number of days per week that individuals used alcohol and the average number of glasses consumed per day, individuals were categorised into five groups for alcohol consumption: total abstainers; light; moderate; excessive; unknown drinkers (for details see [22]). Leisure physical activity was calculated from the number of hours spent on gardening, cycling, walking and physical exercise (none or little; moderate; much; unknown, for details see [23]).

4.5

Cox regression analyses were performed to assess the effects of comorbidities and behavioural variables on risk of death. We first adjusted for age, year of diagnosis (both continuously) and stage at diagnosis (pathological TNM supplemented with clinical TNM in case of missing stage; except prostate for which clinical stage was used). Subsequently we adjusted for presence of comorbidities, categorised into: 0; 1; 2 or more; unknown . We additionally added alcohol, physical activity and smoking, resulting in the final model.

RESULTS

Between 1991 and 2008, 2,576 first primary tumours were diagnosed within the GLOBE population of 18,973 individuals (Table 1). The percentage of patients with a low educational level varied considerably per tumour localisation; 41% of male small cell lung cancer patients and 39% of female patients with non-melanoma skin cancer or with unknown primary localisation only attended primary school, compared with 19% and 18% of the male and female melanoma patients.

No consistent socioeconomic patterns were present in mean age or stage distribution of the cancer patients (data not shown). The prevalence of comorbidities was slightly higher among low educated cancer patients (Table 2). Furthermore, among the low educated patients, a higher proportion smoked and were abstainers. Levels of physical activity were highest among the highest educated.

Survival was best in patients with high educational level, in both males and females (Figure 1). Crude five-year survival was 48% in males with high educational level compared to 32% in low education, and 67% and 47% in females, respectively. In colon and prostate cancer, males with low educational level had poorer survival, while crude survival from non-small cell lung cancer was lowest in high educated patients. Breast cancer survival was best in highly educated women (5 year survival 87%) and poorest in low educated women (69%).

Survival from colon, prostate and breast cancer was better among patients with no or one comorbidity than with two or more comorbidities, and in patients with high compared to low levels of physical activity, except for lung cancer (Table 3). Among prostate and breast cancer patients, survival was better for those with light or excessive alcohol consumption than for total abstainers or moderate consumers.

Risk of death for colon, prostate and breast cancer was lower in patients with high compared to low education, although only significant for prostate cancer, in multivariable models adjusting for age, year of diagnosis, and stage at diagnosis (Hazard ratios (HR) range: 0.4-1.2, Table 4 and online supplements). Presence of comorbidities predicted poor survival especially in prostate cancer (≥2 compared to no comorbidities: hazard ratio (HR) 2.7 (95%CI: 1.6-4.5); online supplement). Effects of lifestyle on cancer survival were moderate. In general, patients consuming no or little amounts of alcohol had reduced risks of death compared to moderate consumers (HR range: 0.6-1.1), while those with excessive consumption had increased risks (HRs 1.0-1.6, breast: 0.5), but none of these associations were statistically significant. Patients with high physical activity levels had mostly reduced risks of death, while those with no/little activity had only increased risks in prostate cancer (HR 2.2, 95%CI

4.5

1.3-3.7). Being a former or current smoker was associated with reduced hazard of death in lung cancer compared to never smokers (HR 0.5), but increased risks in prostate (HR 1.7-1.9) and breast cancer (HR 1.2-1.8).

In the final multivariable model, associations between education and survival and between behaviour and survival remained of similar magnitude (Table 5 and online supplement). Having high education was still associated with reduced risk of death, with even slightly stronger reduction of some of the hazards (low versus high education HR range 0.4-1.0, Table 5 versus Table 4).

Table 1. *Percentage of patients by tumour site (10 most common and basal cell carcinoma) and educational level, patients in the longitudinal GLOBE study, Eindhoven, the Netherlands, diagnosed 1991-2008.*

		Educational level				
	Total	1. Low	2.	3.	4. High	other/ unknown
	N	%	%	%	%	%
Males						
Oesophagus (incl cardia stomach)	46	20	48	11	17	4
Colon	127	20	29	28	19	3
Rectum	62	27	34	16	19	3
Non-small cell lung cancer	225	35	30	20	8	6
Small cell lung cancer	69	41	36	10	13	0
Skin, melanoma	52	19	25	21	35	0
Skin, non-melanoma (SCC*)	69	28	29	19	20	4
Prostate	286	25	26	21	23	5
Urinary bladder	107	32	22	24	20	3
Primary localisation unknown	46	33	22	22	17	7
Total (excl basal cell carcinoma)	*1435*	*27*	*30*	*21*	*18*	*4*
Skin, basal cell carcinoma	186	25	28	19	23	5
Females						
Colon	115	32	40	10	7	10
Rectum	40	35	38	20	3	5
Pancreas	26	35	54	12	0	0
Non-small cell lung cancer	65	34	49	12	0	5
Skin, melanoma	38	18	58	18	5	0
Skin, non-melanoma (SCC)	44	39	48	7	2	5
Breast	371	26	51	15	5	4
Corpus uteri	60	37	48	7	8	0
Ovary	39	23	44	18	13	3
Primary localisation unknown	41	39	37	5	10	10
Total (excl basal cell carcinoma)	*1141*	*31*	*47*	*13*	*5*	*5*
Skin, basal cell carcinoma	161	25	45	21	2	7

*SCC: squamous cell carcinoma

4.5

Table 2. *Distribution of comorbidity at diagnosis and behaviours at baseline (1991) by educational level in the longitudinal GLOBE study, Eindhoven, The Netherlands. Includes males with prostate, non-small cell lung or colon cancer and females with breast cancer, diagnosed 1991-2008.*

	Educational level			
	1.Low	**2**	**3**	**4. High**
Number of patients	271	365	199	127
Comorbidities	(%)	(%)	(%)	(%)
None	28	43	36	39
1	26	27	28	28
2 or more	32	19	23	23
Unknown	13	10	14	11
Smoking				
Never	22	22	17	11
Former	29	35	40	57
Current	45	42	41	32
Unknown	5	2	2	0
Alcohol				
Total abstainers	34	20	12	7
Light	33	45	39	39
Moderate	13	20	32	43
Excessive	9	10	15	7
Unknown	11	5	3	4
Physical activity				
None/little	21	18	16	9
Moderate	58	57	50	51
Much	15	23	31	37
Unknown	6	2	4	2

4.5
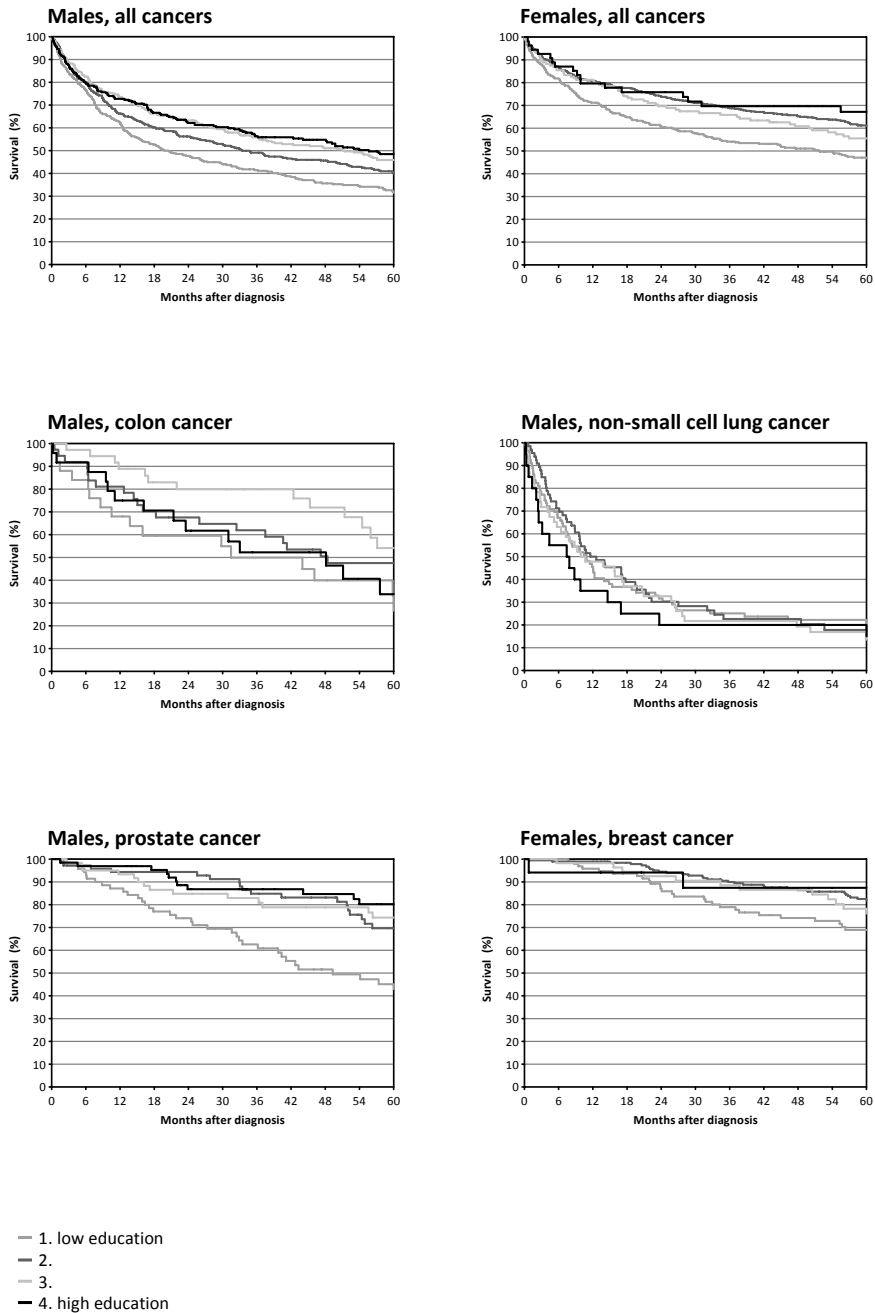
Figure 1. *Crude survival from cancer by tumour site and sex, according to educational level, patients in the longitudinal GLOBE study, Eindhoven, The Netherlands, diagnosed 1991-2008.*

4.5

Table 3. *Crude survival according to number of comorbidities at diagnosis and behaviours at baseline (1991) per tumour type in the longitudinal GLOBE study, Eindhoven, The Netherlands. Includes males with prostate, lung or colon cancer and females with breast cancer, diagnosed 1991-2008.*

	Colon	Non-small cell lung	Prostate	Breast
Mean age at diagnosis	68.7	67.3	70.1	63.5
	3 y survival (%)	1 y survival (%)	3 y survival (%)	3 y survival (%)
Comorbidities at diagnosis				
None	75	40	85	88
1	50	51	84	86
2 or more	59	46	64	80
Unknown	69	50	83	87
Smoking				
Never	51	#	81	87
Former	65	48	80	84
Current	63	46	76	87
Unknown	#	#	86	92
Alcohol				
Total abstainers	56	45	69	83
Light	72	45	82	90
Moderate	59	32	79	80
Excessive	55	61	90	94
Unknown	#	75	67	88
Physical activity				
None/little	67	59	57	88
Moderate	57	47	82	85
Much	83	31	88	90
Unknown	#	50	#	64

 # less than 5 patients in this group, data not shown.

4.5

Table 4. *Multivariable risk of death according to tumour type for cancer patients in the longitudinal GLOBE study, Eindhoven, The Netherlands. Includes males with prostate, non-small cell lung or colon cancer and females with breast cancer, diagnosed 1991-2008.*

	Colon			Non-small cell lung			Prostate			Breast		
	HR	95%CI		HR	95%CI		HR	95%CI		HR	95%CI	
Age	**1.0**	1.0	1.1	**1.0**	1.0	1.1	**1.1**	1.1	1.1	**1.0**	1.0	1.1
Year of diagnosis	1.0	0.9	1.1	1.0	0.9	1.0	1.0	0.9	1.0	1.0	1.0	1.1
Stage												
1	1.0			1.0			1.0			1.0		
2	0.8	0.4	1.8	2.1	1.0	4.6	1.2	0.7	2.3	**1.9**	1.2	3.0
3	1.7	0.8	3.6	**3.0**	1.9	4.5	**1.4**	0.6	3.4	**2.7**	1.4	5.0
4	**4.1**	1.9	9.0	**6.2**	3.8	10.1	**4.3**	2.3	8.2	**9.9**	4.8	20.4
Unknown	**13.4**	3.3	54.9	1.3	0.8	2.1	**3.8**	1.5	9.6	1.1	0.2	8.1
Education												
1. Low	1.0			1.0			1.0			1.0		
2.	0.6	0.3	1.2	0.9	0.6	1.2	**0.5**	0.3	0.9	0.8	0.5	1.2
3.	**0.4**	0.2	0.8	1.1	0.8	1.6	0.6	0.4	1.1	1.0	0.6	1.8
4. High	0.8	0.4	1.6	1.2	0.7	2.0	**0.4**	0.2	0.7	0.7	0.3	2.1

HR: hazard ratio, 95%CI: 95% confidence interval. Values in bold are significant. Models are adjusted for all variables listed.

4.5

Table 5. *Multivariable risk of death according to tumour type for cancer patients in the longitudinal GLOBE study, Eindhoven, The Netherlands. Includes males with prostate, non-small cell lung or colon cancer and females with breast cancer, diagnosed 1991-2008.*

	Colon			Non-small cell lung			Prostate			Breast		
	HR	95%CI		HR	95%CI		HR	95%CI		HR	95%CI	
Age	**1.0**	1.0	1.1	**1.0**	1.0	1.1	**1.1**	1.0	1.1	**1.0**	1.0	1.1
Year of diagnosis	1.0	0.9	1.0	**1.0**	0.9	1.0	**0.9**	0.9	1.0	1.0	1.0	1.1
Stage												
1	1.0			1.0			1.0			1.0		
2	0.6	0.2	1.4	2.1	0.9	4.6	1.6	0.8	3.0	**1.9**	1.2	3.0
3	1.4	0.6	3.3	**3.3**	2.1	5.3	1.5	0.6	3.8	**2.5**	1.3	4.9
4	**3.5**	1.5	8.4	**7.8**	4.5	13.5	**5.7**	2.8	11.7	**14.8**	6.4	34.3
Unknown	**22.3**	4.5	111.2	1.3	0.7	2.2	**6.0**	2.3	15.8	1.1	0.1	8.7
Education												
1. Low	1.0			1.0			1.0			1.0		
2.	0.6	0.3	1.1	0.7	0.5	1.1	**0.5**	0.3	0.9	0.8	0.5	1.3
3.	**0.3**	0.1	0.6	0.9	0.6	1.3	0.6	0.3	1.0	1.0	0.6	1.9
4. High	0.6	0.3	1.3	1.0	0.5	1.7	**0.4**	0.2	0.7	0.6	0.2	1.9
Comorbidities												
0	1.0			1.0			1.0			1.0		
1	**2.7**	1.3	5.8	1.3	0.9	2.1	**1.8**	1.1	3.1	1.4	0.9	2.3
2 or more	1.2	0.6	2.7	1.2	0.8	1.8	**3.0**	1.7	5.2	1.5	0.8	2.8
Unknown	0.9	0.4	2.3	1.2	0.6	2.1	1.7	0.8	3.6	1.8	0.9	3.3
Alcohol												
Abstainer	0.6	0.2	1.3	0.6	0.4	1.0	0.7	0.4	1.5	0.9	0.5	1.6
Light	**0.5**	0.3	1.0	0.8	0.5	1.3	0.9	0.6	1.5	0.8	0.4	1.4
Moderate	1.0			1.0			1.0			1.0		
Excessive	1.2	0.5	2.7	1.0	0.6	1.8	1.1	0.6	2.3	0.6	0.2	1.9
Unknown	-			0.5	0.2	1.1	1.4	0.5	3.5	0.7	0.3	1.7
Physical activity												
No/little	1.0	0.5	1.9	0.9	0.6	1.4	**2.2**	1.3	3.8	0.7	0.4	1.2
Moderate	1.0			1.0			1.0			1.0		
Much	1.0	0.5	2.0	1.5	1.0	2.2	1.1	0.7	1.8	0.6	0.3	1.0
Unknown	5.0	0.9	27.8	0.9	0.4	1.9	2.9	1.1	7.5	0.8	0.3	1.9
Smoking												
Never	1.0			1.0			1.0			1.0		
Former	0.9	0.3	2.2	0.5	0.1	1.6	1.7	0.6	4.6	**1.9**	1.2	3.1
Current	0.8	0.3	2.2	0.4	0.1	1.5	2.2	0.9	5.9	1.2	0.8	2.0
Unknown	-			0.2	0.0	1.2	0.6	0.1	3.1	1.3	0.4	4.1

HR: hazard ratio, 95%CI: 95% confidence interval. Values in bold are significant. Models are adjusted for all variables listed.

4.5

DISCUSSION

In this study we investigated educational differences in cancer survival and the contribution of comorbidity and lifestyle to survival. In general, those with high education had best survival. Comorbidity was a strong predictor of death, especially in colon and prostate cancer patients, while the strengths of the effects of alcohol consumption, smoking and physical activity were variable between the cancers. The mostly increased risk of death in low educated cancer patients could not be explained by higher prevalence of comorbidities or poorer lifestyle.

Our results confirm previous studies that also pointed to better survival for patients with high SEP for a variety of cancers, including breast, prostate, colon and lung.[4, 5, 11, 12, 14, 24] Not surprisingly, the difference between high and low SEP in survival was limited for lung cancer, which is rather lethal and the effects of comorbidities and lifestyle are expected to be minor.

The reasons for socioeconomic inequalities in cancer survival are not exactly known yet, but differences in stage at diagnosis, treatment, and lifestyle related factors such as physical activity, obesity and dietary patterns have been proposed. Some previous studies took into account stage at diagnosis, which was reported not to fully explain better survival in high SEP patients with prostate (depending on age), breast (only in screen-detected tumours), and in some studies on colorectal cancer.[4, 11, 14, 24] In our analyses we adjusted for stage and comorbidities at diagnosis, and investigated the additional effects of alcohol consumption, physical activity and smoking on educational inequalities in cancer survival. We assumed that by adjusting for comorbidity we also adjusted partly for lifestyle. Comparing the models with comorbidity, behaviour and the final model shows that associations of lifestyle hardly changed by inclusion of comorbidity and vice versa (online supplement). This may suggest that comorbidities reflect high-risk behaviours well.

Previously we have shown that comorbidities explained some of the socioeconomic variation in breast, colorectal and prostate cancer survival.[13, 14, 24] Although comorbidity in itself was reported a significant prognostic factor in the multivariable analyses,[25] it did not explain the educational difference in cancer survival. We expect this to result from the rather weak association between education and comorbidities.

Furthermore, treatment could contribute to the socioeconomic inequalities in cancer survival. Small treatment disparities were present across the educational levels (data not shown), but small numbers hampered inclusion in multivariable analyses.
Few studies investigated the role of lifestyle in socioeconomic inequalities in cancer survival. A Danish study showed that comorbidity, and to a lesser extent lifestyle, reduced the variation in colorectal cancer survival associated with SEP, while factors related to disease or treatment were not contributing to the variation.[26] Also smoking status prior cancer diagnosis was an important predictive factor for socioeconomic variation in cancer survival in Norwegian women, whereas in breast cancer no association with smoking status, alcohol consumption, stage or comorbidity was found.[27] In men smoking and alcohol consumption did not explain socioeconomic variation in Swedish overall cancer survival.[15] In New Zealand socioeconomic variation in colorectal cancer survival could not be explained by smoking status, alcohol intake and physical activity.[16] Previously the role of alcohol was suggested

4.5

to substantially influence socioeconomic inequalities in male cancer mortality (being the product of incidence and survival) in some, but not other European countries.[28] The Netherlands were not taken into account.

Other factors that could contribute to the better survival in high educated cancer patients are healthier lifestyle in general (other than we could measure), or a better capacity to obtain, process and understand health information and services (so-called "health literacy"). These have been reported to be associated with SEP.[3, 29]

Among breast cancer patients, we performed stratified analyses to investigate the effect of screening in postmenopausal women. Results for postmenopausal women, i.e. those aged 50 and over, were of similar magnitude as all ages combined (data not shown). Numbers of premenopausal women were too small to analyse separately.

For prostate cancer we stratified the analyses according to tumour stage, to unravel possible screening effects. Overall, results were similar to the total group of prostate cancer patients. Compared to those with advanced stage, effects of smoking and physical activity were stronger in those with localised disease (see online supplement Tables 3A and 3B). Presence of comorbidities strongly affected risk of death in those with advanced disease (≥2 compared to no comorbidities: HR 5.0 (95%CI 1.7-14.6)).

Our study findings might be influenced by several methodological limitations. We have excluded subjects with prevalent cancer at baseline (i.e. 1991) in order to eliminate possible selection effects. The validity of the self-reported prevalence of cancer in the study population that filled in the 1991 questionnaire was checked, and some underreporting was found among those with a lower educational level.[30] Furthermore, we assumed that lifestyle prior to cancer diagnosis was indicative to lifestyle after diagnosis. However, this can be debated as the experience of cancer diagnosis and treatment may serve as a critical cue for an individual to make positive health behaviour changes.[31]

Reporting of smoking habits, alcohol consumption and physical activity may be inaccurate and is often understated or overstated in case of physical activity, although a recent study reported that this was not true for nicotine consumption.[32-34] Reporting on these items may differ across the SEP groups, thereby introducing differential bias. This may dilute the effect of lifestyle and may (partly) explain why lifestyle hardly affected the educational differences in cancer survival.

A disadvantage of using education is that it better reflects SEP in some age cohorts than in others.[35] Those born before 1950 may not have attained the educational level that could be expected based on their potential abilities. This effect is probably stronger for women, since education of young women beyond primary school or lower vocational school has become more common since the 1960s. The effect of possible misclassification of SEP by using educational level may explain why our results are not in accordance with previous studies that reported strong associations of the prevalence of comorbidities and SEP, which explained inequalities in cancer survival.[13, 14]

4.5

A strength of this study is that the follow-up of the original sample on vital status has been nearly complete (99.8%). Additionally, the completeness of the Eindhoven Cancer Registry is expected to be at least 95%,[36] thus only few new cancer cases diagnosed within the registration area would not be included in the cancer registry. Furthermore, the area covered by the Eindhoven Cancer Registry is much larger than the area covered by the GLOBE study, so participants who moved outside the area of the GLOBE study, but still within the area of the Eindhoven Cancer Registry, could also be included in the present study. Those moving outside the GLOBE-study area were in a previous study found to be mainly high educated individuals with few comorbidities and high levels of physical activity, which might have influenced our results. However, these were mostly young individuals who have a low chance of developing cancer.[37] Finally, the two-step linkage procedure ascertained the appropriate identification of cancer patients within the GLOBE cohort. This makes it unlikely that the results have been biased by incompleteness of data on cancer diagnosis.

To conclude, high educated cancer patients had reduced risks of death. Although presence of comorbidities and poor lifestyle behaviours affected survival from cancer, these did not explain educational inequalities in survival. The role of other factors, such as social support, capacity to obtain, process and understand health information and services, and access to health care, needs to be explored.

4.5

REFERENCES

1. Faggiano, F., Partanen, T., Kogevinas, M. & Boffetta, P. Socioeconomic differences in cancer incidence and mortality. *IARC Sci Publ*, 65-176 (1997).

2. Menvielle, G., Leclerc, A., Chastang, J.F., Melchior, M. & Luce, D. Changes in socioeconomic inequalities in cancer mortality rates among French men between 1968 and 1996. *Am J Public Health* 97, 2082-7 (2007).

3. Mackenbach, J.P., Stirbu, I., Roskam, A.J., Schaap, M.M., Menvielle, G., Leinsalu, M. & Kunst, A.E. Socioeconomic inequalities in health in 22 European countries. *N Engl J Med* 358, 2468-81 (2008).

4. Aarts, M.J., Lemmens, V.E.P.P., Louwman, W.J., Kunst, A.E. & Coebergh, J.W.W. Socioeconomic status and changing inequalities in colorectal cancer? A review of the associations with risk, treatment and outcome. *Eur J Cancer* 46, 2681-95 (2010).

5. Dalton, S.O., Schuz, J., Engholm, G., Johansen, C., Kjaer, S.K., Steding-Jessen, M., Storm, H.H. & Olsen, J.H. Social inequality in incidence of and survival from cancer in a population-based study in Denmark, 1994-2003: Summary of findings. *Eur J Cancer* 44, 2074-85 (2008).

6. National Cancer Intelligence Network. in Cancer incidence by deprivation. England, 1995-2004 (London, 2009).

7. Aarts, M.J., van der Aa, M.A., Coebergh, J.W. & Louwman, W.J. Reduction of socioeconomic inequality in cancer incidence in the South of the Netherlands during 1996-2008. *Eur J Cancer* 46, 2633-46 (2010).

8. Louwman, W.J., van Lenthe, F.J., Coebergh, J.W. & Mackenbach, J.P. Behaviour partly explains educational differences in cancer incidence in the south-eastern Netherlands: the longitudinal GLOBE study. *Eur J Cancer Prev* 13, 119-25 (2004).

9. Parkin, D.M., Boyd, L. & Walker, L.C. The fraction of cancer attributable to lifestyle and environmental factors in the UK in 2010. Summary and conclusions. *Br J Cancer* 105, S77-S81 (2011).

10. Schrijvers, C.T., Coebergh, J.W., van der Heijden, L.H. & Mackenbach, J.P. Socioeconomic variation in cancer survival in the southeastern Netherlands, 1980-1989. *Cancer* 75, 2946-53 (1995).

11. Woods, L.M., Rachet, B. & Coleman, M.P. Origins of socio-economic inequalities in cancer survival: a review. *Ann Oncol* 17, 5-19 (2006).

12. Kogevinas, M. & Porta, M. Socioeconomic differences in cancer survival: a review of the evidence. *IARC Sci Publ*, 177-206 (1997).

13. Louwman, W.J., Aarts, M.J., Houterman, S., van Lenthe, F.J., Coebergh, J.W. & Janssen-Heijnen, M.L. A 50% higher prevalence of life-shortening chronic conditions among cancer patients with low socioeconomic status. *Br J Cancer* 103, 1742-1748 (2010).

14. Aarts, M.J., Koldewijn, E.L., Poortmans, P.M.P., Coebergh, J.W. & Louwman, M. Impact of socioeconomic status on prostate cancer treatment and survival in the Southern Netherlands. (submitted).

15. Rosengren, A. & Wilhelmsen, L. Cancer incidence, mortality from cancer and survival in men of different occupational classes. *Eur J Epidemiol* 19, 533-40 (2004).

16. Kelsall, H.L., Baglietto, L., Muller, D., Haydon, A.M., English, D.R. & Giles, G.G. The effect of socioeconomic status on survival from colorectal cancer in the Melbourne Collaborative Cohort Study. *Soc Sci Med* 68, 290-7 (2009).

17. Mackenbach, J.P. Socioeconomic inequalities in health in The Netherlands: impact of a five year research programme. *Bmj* 309, 1487-91 (1994).

18. van Lenthe, F.J., Schrijvers, C.T., Droomers, M., Joung, I.M., Louwman, M.J. & Mackenbach, J.P. Investigating explanations of socio-economic inequalities in health: the Dutch GLOBE study. *Eur J Public Health* 14, 63-70 (2004).

19. Parkin, D.M., Bray, F., Ferlay, J. & Pisani, P. Global cancer statistics, 2002. *CA Cancer J Clin* 55, 74-108 (2005).

20. Charlson, M.E., Pompei, P., Ales, K.L. & MacKenzie, C.R. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 40, 373-83 (1987).

4.5

21. van Berkel-van Schaik, A.B. & Tax, B. in Naar een standaardoperationalisatie van sociaal-economische status voor epidemiologisch en sociaal-medisch onderzoek. (Towards a standard operationalisation of socioeconomic status for epidemiological and sociomedical research). (Ministerie van WCC, Rijswijk, 1990).

22. van Lenthe, F.J., Avendano, M., van Beeck, E.F. & Mackenbach, J.P. Childhood and adulthood socioeconomic position and the hospital-based incidence of hip fractures after 13 years of follow-up: the role of health behaviours. *J Epidemiol Community Health* 65, 980-5 (2011).

23. Slingerland, A.S., van Lenthe, F.J., Jukema, J.W., Kamphuis, C.B., Looman, C., Giskes, K., Huisman, M., Narayan, K.M., Mackenbach, J.P. & Brug, J. Aging, retirement, and changes in physical activity: prospective cohort findings from the GLOBE study. *Am J Epidemiol* 165, 1356-63 (2007).

24. Aarts, M.J., Voogd, A.C., Duijm, L.E.M., Coebergh, J.W. & Louwman, M. Socioeconomic inequalities in attending the mass screening for breast cancer in the south of the Netherlands - associations with stage at diagnosis and survival. *Breast Cancer Res Treat* 128, 517-25 (2011).

25. Janssen-Heijnen, M.L., Houterman, S., Lemmens, V.E., Louwman, M.W., Maas, H.A. & Coebergh, J.W. Prognostic impact of increasing age and co-morbidity in cancer patients: a population-based approach. *Crit Rev Oncol Hematol* 55, 231-40 (2005).

26. Frederiksen, B.L., Osler, M., Harling, H., Ladelund, S. & Jorgensen, T. Do patient characteristics, disease, or treatment explain social inequality in survival from colorectal cancer? *Soc Sci Med* (2009).

27. Braaten, T., Weiderpass, E., Kumle, M. & Lund, E. Explaining the socioeconomic variation in cancer risk in the Norwegian Women and Cancer Study. *Cancer Epidemiol Biomarkers Prev* 14, 2591-7 (2005).

28. Menvielle, G., Kunst, A.E., Stirbu, I., Borrell, C., Bopp, M., Regidor, E., Heine Strand, B., Deboosere, P., Lundberg, O., Leclerc, A., Costa, G., Chastang, J.F., Esnaola, S., Martikainen, P. & Mackenbach, J.P. Socioeconomic inequalities in alcohol related cancer mortality among men: to what extent do they differ between Western European populations? *Int J Cancer* 121, 649-55 (2007).

29. Smith, S.G., Wolf, M.S. & von Wagner, C. Socioeconomic status, statistical confidence, and patient-provider communication: an analysis of the Health Information National Trends Survey (HINTS 2007). *J Health Commun* 15 Suppl 3, 169-85 (2010).

30. Schrijvers, C.T., Stronks, K., van de Mheen, D.H., Coebergh, J.W. & Mackenbach, J.P. Validation of cancer prevalence data from a postal survey by comparison with cancer registry records. *Am J Epidemiol* 139, 408-14 (1994).

31. Patterson, R.E., Neuhouser, M.L., Hedderson, M.M., Schwartz, S.M., Standish, L.J. & Bowen, D.J. Changes in diet, physical activity, and supplement use among adults diagnosed with cancer. *J Am Diet Assoc* 103, 323-8 (2003).

32. Adams, S.A., Matthews, C.E., Ebbeling, C.B., Moore, C.G., Cunningham, J.E., Fulton, J. & Hebert, J.R. The effect of social desirability and social approval on self-reports of physical activity. *Am J Epidemiol* 161, 389-98 (2005).

33. Hebert, J.R., Clemow, L., Pbert, L., Ockene, I.S. & Ockene, J.K. Social desirability bias in dietary self-report may compromise the validity of dietary intake measures. *Int J Epidemiol* 24, 389-98 (1995).

34. Yeager, D.S. & Krosnick, J.A. The validity of self-reported nicotine product use in the 2001-2008 National Health and Nutrition Examination Survey. *Med Care* 48, 1128-32 (2010).

35. Berkman, L.F. & Macintyre, S. The measurement of social class in health studies: old measures and new formulations. *IARC Sci Publ*, 51-64 (1997).

36. Schouten, L.J., Hoppener, P., van den Brandt, P.A., Knottnerus, J.A. & Jager, J.J. Completeness of cancer registration in Limburg, The Netherlands. *Int J Epidemiol* 22, 369-376 (1993).

37. van Lenthe, F.J., Martikainen, P. & Mackenbach, J.P. Neighbourhood inequalities in health and health-related behaviour: results of selective migration? *Health Place* 13, 123-37 (2007).

4.5

4.5

Table 1. Multivariable risk of death for colon cancer patients in the longitudinal GLOBE study, Eindhoven, The Netherlands. Includes males, diagnosed 1991-2008.

	Model 0			Model 0+education			Model 0+comorb			Model 0+behaviour			Model 0+all		
	HR	95%CI		HR	95%CI		HR	95%CI		HR	95%CI		HR	95%CI	
Age	**1.1**	1.0	1.1	**1.0**	1.0	1.1	1.0	1.0	1.1	**1.1**	1.0	1.1	**1.0**	1.0	1.1
Year of diagnosis	1.0	1.0	1.1	1.0	0.9	1.1	1.0	0.9	1.0	1.0	0.9	1.1	1.0	0.9	1.0
Stage															
1	1.0			1.0			1.0			1.0			1.0		
2	1.0	0.5	2.1	0.8	0.4	1.8	0.9	0.4	2.1	0.8	0.4	1.8	0.6	0.2	1.4
3	1.9	0.9	4.1	1.7	0.8	3.6	1.8	0.8	3.9	2.0	0.9	4.5	1.4	0.6	3.3
4	**4.8**	2.3	10.2	**4.1**	1.9	9.0	**4.5**	2.0	10.4	**4.8**	2.1	10.6	**3.5**	1.5	8.4
Unknown	10.3	2.7	39.6	**13.4**	3.3	54.9	**10.5**	2.7	40.8	**13.0**	2.9	58.9	**22.3**	4.5	111.2
Education															
1. Low				1.0									1.0		
2.				0.6	0.3	1.2							0.6	0.3	1.1
3.				**0.4**	0.2	0.8							**0.3**	0.1	0.6
4. High				0.8	0.4	1.6							0.6	0.3	1.3
Comorbidities															
0							1.0						1.0		
1							**2.2**	1.1	4.4				**2.7**	1.3	5.8
2 or more							1.5	0.7	3.1				1.2	0.6	2.7
Unknown							0.9	0.4	2.3				0.9	0.4	2.3
Alcohol															
Abstainer										0.7	0.3	1.5	0.6	0.2	1.3
Light										0.6	0.3	1.1	**0.5**	0.3	1.0
Moderate										1.0			1.0		
Excessive										1.6	0.7	3.6	1.2	0.5	2.7
Physical activity															
No/little										0.9	0.5	1.7	1.0	0.5	1.9
Moderate										1.0			1.0		
Much										0.8	0.4	1.6	1.0	0.5	2.0
Unknown										6.7	1.4	32.1	5.0	0.9	27.8
Smoking															
Never										1.0			1.0		
Former										0.9	0.4	2.3	0.9	0.3	2.2
Current										0.8	0.3	2.1	0.8	0.3	2.2
Unknown										-			-		

HR: hazard ratio, 95%CI: 95% confidence interval. Values in bold are significant.

Table 2. *Multivariable risk of death for non-small cell lung cancer patients in the longitudinal GLOBE study, Eindhoven, The Netherlands. Includes males, diagnosed 1991-2008.*

	Model 0		Model 0+education		Model 0+comorb		Model 0+behaviour		Model 0+all	
	HR	95%CI	HR	95%CI	HR	95%CI	HR	95%CI	HR	95%CI
Age	1.0	1.0 1.1	1.0	1.0 1.1	1.0	1.0 1.1	1.1	1.0 1.1	1.0	1.0 1.1
Year of diagnosis	1.0	0.9 1.0	1.0	0.9 1.0	1.0	0.9 1.0	1.0	0.9 1.0	1.0	0.9 1.0
Stage										
1	1.0		1.0		1.0		1.0		1.0	
2	2.1	0.9 4.5	2.1	1.0 4.6	2.1	1.0 4.6	2.0	0.9 4.4	**2.1**	0.9 4.6
3	**2.9**	1.9 4.4	**3.0**	1.9 4.5	**2.9**	1.9 4.4	**3.1**	2.0 4.8	**3.3**	2.1 5.3
4	**6.1**	3.8 9.9	**6.2**	3.8 10.1	**6.2**	3.8 10.1	**7.2**	4.2 12.2	**7.8**	4.5 13.5
Unknown	1.2	0.7 2.0	**1.3**	0.8 2.1	**1.3**	0.7 2.1	**1.2**	0.7 2.0	**1.3**	0.7 2.2
Education										
1. Low			1.0						1.0	
2.			0.9	0.6 1.2					0.7	0.5 1.1
3.			1.1	0.8 1.6					0.9	0.6 1.3
4. High			1.2	0.7 2.0					1.0	0.5 1.7
Comorbidities										
0					1.0				1.0	
1					1.1	0.7 1.6			1.3	0.9 2.1
2 or more					1.1	0.7 1.6			1.2	0.8 1.8
Unknown					1.0	0.6 1.7			1.2	0.6 2.1
Alcohol										
Abstainer							**0.6**	0.4 1.1	**0.6**	0.4 1.0
Light							0.8	0.5 1.2	0.8	0.5 1.3
Moderate							1.0		1.0	
Excessive							1.0	0.6 1.7	1.0	0.6 1.8
Unknown							0.6	0.3 1.3	0.5	0.2 1.1
Physical activity										
No/little							0.9	0.6 1.3	0.9	0.6 1.4
Moderate							1.0		1.0	
Much							1.4	0.9 2.2	1.5	1.0 2.2
Unknown							1.0	0.5 2.0	0.9	0.4 1.9
Smoking										
Never							1.0		1.0	
Former							0.5	0.2 1.8	0.5	0.1 1.6
Current							0.5	0.2 1.6	0.4	0.1 1.5
Unknown							0.3	0.1 1.3	0.2	0.0 1.2

HR: hazard ratio, 95%CI: 95% confidence interval. Values in bold are significant.

4.5

Table 3. *Multivariable risk of death for prostate cancer patients in the longitudinal GLOBE study, Eindhoven, The Netherlands. Includes males, diagnosed 1991–2008.*

	Model 0		Model 0+education		Model 0+comorb		Model 0+behaviour		Model 0+all	
	HR	95%CI	HR	95%CI	HR	95%CI	HR	95%CI	HR	95%CI
Age	**1.1**	1.1 1.0	**1.1**	1.1 1.1	**1.1**	1.0 1.1	**1.1**	1.1 1.1	**1.1**	1.0 1.1
Year of diagnosis	1.0	0.9 1.0	1.0	0.9 1.0	**0.9**	0.9 1.0	1.0	0.9 1.0	**0.9**	0.9 1.0
Stage										
1	1.0		1.0		1.0		1.0		1.0	
2	1.1	0.6 2.1	1.2	0.7 2.3	1.5	0.8 2.7	1.1	0.6 2.2	1.6	0.8 3.0
3	1.2	0.5 2.8	1.4	0.6 3.4	1.5	0.6 3.7	0.9	0.4 2.2	1.5	0.6 3.8
4	**4.4**	2.4 8.4	**4.3**	2.3 8.2	**6.5**	3.3 12.7	**4.1**	2.1 8.1	**5.7**	2.8 11.7
Unknown	**3.5**	1.4 8.8	**3.8**	1.5 9.6	**4.6**	1.8 11.7	**4.4**	1.7 11.4	**6.0**	2.3 15.8
Education										
1. Low			1.0						1.0	
2.			**0.5**	0.3 0.9					**0.5**	0.3 0.9
3.			0.6	0.4 1.1					0.6	0.3 1.0
4. High			**0.4**	0.2 0.7					**0.4**	0.2 0.7
Comorbidities										
0					1.0				1.0	
1					1.5	0.9 2.6			**1.8**	1.1 3.1
2 or more					**2.7**	1.6 4.5			**3.0**	1.7 5.2
Unknown					1.4	0.7 2.8			1.7	0.8 3.6
Alcohol										
Abstainer							1.1	0.6 2.1	0.7	0.4 1.5
Light							0.9	0.6 1.5	0.9	0.6 1.5
Moderate							1.0		1.0	
Excessive							1.3	0.7 2.7	1.1	0.6 2.3
Unknown							1.7	0.7 4.2	1.4	0.5 3.5
Physical activity										
No/little							**2.2**	1.3 3.7	**2.2**	1.3 3.8
Moderate							1.0		1.0	
Much							0.8	0.5 1.3	1.1	0.7 1.8
Unknown							**2.9**	1.2 7.2	**2.9**	1.1 7.5
Smoking										
Never							1.0		1.0	
Former							1.7	0.6 4.4	1.7	0.6 4.6
Current							1.9	0.7 5.0	2.2	0.9 5.9
Unknown							1.0	0.2 5.1	0.6	0.1 3.1

HR: hazard ratio, 95%CI: 95% confidence interval. Values in bold are significant.

4.5

Table 3A. *Multivariable risk of death for prostate cancer patients with localised stage in the longitudinal GLOBE study, Eindhoven, The Netherlands. Includes males, diagnosed 1991-2008.*

	Model 0			Model 0+education			Model 0+comorb			Model 0+behaviour			Model 0+all		
	HR	95%CI		HR	95%CI		HR	95%CI		HR	95%CI		HR	95%CI	
Age	**1.1**	1.0	1.1	**1.1**	1.0	1.1	**1.1**	1.0	1.1	**1.1**	1.0	1.1	**1.1**	1.0	1.1
Year of diagnosis	**0.9**	0.8	1.0	**0.9**	0.8	1.0	**0.9**	0.8	1.0	**0.9**	0.8	1.0	**0.9**	0.8	1.0
Stage															
1	1.0			1.0			1.0			1.0			1.0		
2	1.7	0.9	3.5	1.9	1.0	3.9	2.0	1.0	4.0	1.6	0.8	3.4	2.1	1.0	4.5
Education															
1. Low				1.0									1.0		
2.				0.6	0.3	1.1							**0.4**	0.2	0.8
3.				0.6	0.3	1.3							0.6	0.3	1.2
4. High				**0.4**	0.2	0.8							**0.3**	0.1	0.7
Comorbidities															
0							1.0						1.0		
1							1.2	0.6	2.3				1.3	0.6	2.6
2 or more							1.7	0.9	3.3				**2.1**	1.0	4.3
Unknown							0.8	0.3	2.0				0.9	0.3	2.3
Alcohol															
Abstainer										1.1	0.4	2.7	0.6	0.2	1.9
Light										0.8	0.4	1.5	0.8	0.4	1.4
Moderate										1.0			1.0		
Excessive										0.9	0.4	2.3	0.7	0.3	2.0
Unknown										3.1	0.7	14.5	3.9	0.8	19.3
Physical activity															
No/little										**2.6**	1.2	5.4	**2.4**	1.1	5.3
Moderate										1.0			1.0		
Much										0.7	0.3	1.4	0.8	0.4	1.6
Unknown										-			-		
Smoking															
Never										1.0			1.0		
Former										2.5	0.6	11.3	3.3	0.7	16.5
Current										3.0	0.7	13.1	4.0	0.8	18.5
Unknown										0.5	0.0	8.5	0.2	0.0	3.7

HR: hazard ratio, 95%CI: 95% confidence interval. Values in bold are significant.

4.5

Table 3B. *Multivariable risk of death for prostate cancer patients with advanced stage in the longitudinal GLOBE study, Eindhoven, The Netherlands. Includes males, diagnosed 1991-2008.*

	Model 0 HR	Model 0 95%CI		Model 0+education HR	Model 0+education 95%CI		Model 0+comorb HR	Model 0+comorb 95%CI		Model 0+behaviour HR	Model 0+behaviour 95%CI		Model 0+all HR	Model 0+all 95%CI	
Age	**1.1**	1.0	1.1	**1.1**	1.0	1.1	**1.1**	1.0	1.1	**1.1**	1.0	1.1	**1.1**	1.0	1.1
Year of diagnosis	1.0	0.9	1.1	1.0	0.9	1.1	0.9	0.9	1.0	1.0	0.9	1.1	0.9	0.8	1.0
Stage															
3	**0.3**	0.1	0.6	**0.3**	0.1	0.6	**0.2**	0.1	0.5	**0.2**	0.1	0.6	**0.3**	0.1	0.6
4	1.0			1.0			1.0			1.0			1.0		
Education															
1. Low				1.0									1.0		
2.				0.7	0.3	1.6							0.8	0.3	2.3
3.				0.8	0.3	1.9							0.6	0.2	1.8
4. High				0.4	0.2	1.1							0.4	0.1	1.3
Comorbidities															
0							1.0						1.0		
1							1.8	0.7	4.3				2.7	0.9	7.9
2 or more							**3.4**	1.4	8.5				**5.0**	1.7	14.6
Unknown							1.4	0.4	5.3				1.9	0.3	10.2
Alcohol															
Abstainer										0.8	0.2	2.5	0.9	0.3	2.8
Light										0.9	0.4	2.1	1.0	0.4	2.8
Moderate										1.0			1.0		
Excessive										1.4	0.5	3.9	1.6	0.5	4.9
Unknown										1.3	0.4	4.5	1.2	0.3	4.6
Physical activity															
No/little										1.6	0.6	4.3	1.4	0.5	3.8
Moderate										1.0			1.0		
Much										0.8	0.3	1.6	1.2	0.5	3.1
Unknown										2.5	0.8	7.8	3.2	0.9	11.0
Smoking															
Never										1.0			1.0		
Former										0.9	0.2	3.9	0.7	0.1	3.9
Current										0.9	0.2	3.8	1.1	0.2	5.6
Unknown										0.7	0.1	7.7	0.4	0.0	4.6

HR: hazard ratio, 95%CI: 95% confidence interval. Values in bold are significant.

4.5

Table 4. Multivariable risk of death for breast cancer patients in the longitudinal GLOBE study, Eindhoven, The Netherlands. Includes females, diagnosed 1991-2008.

	Model 0			Model 0+education			Model 0+comorb			Model 0+behaviour			Model 0+all		
	HR	95%CI		HR	95%CI		HR	95%CI		HR	95%CI		HR	95%CI	
Age	**1.0**	1.0	1.1	**1.0**	1.0	1.1	**1.0**	1.0	1.0	**1.0**	1.0	1.1	**1.0**	1.0	1.1
Year of diagnosis	1.0	1.0	1.1	1.0	1.0	1.1	1.0	1.0	1.1	1.0	1.0	1.1	**1.0**	1.0	1.1
Stage															
1	1.0			1.0			1.0			1.0			1.0		
2	**1.9**	1.2	3.0	**1.9**	1.2	3.0	**1.8**	1.2	2.9	**2.0**	1.3	3.1	**1.9**	1.2	3.0
3	2.7	1.4	5.0	2.7	1.4	5.0	2.6	1.4	4.9	2.5	1.3	4.8	2.5	1.3	4.9
4	**9.8**	4.7	20.1	**9.9**	4.8	20.4	**10.9**	5.2	22.8	**13.0**	5.8	29.2	**14.8**	6.4	34.3
Unknown	1.0	0.1	7.6	1.1	0.2	8.1	0.9	0.1	6.9	1.2	0.2	9.0	1.1	0.1	8.7
Education															
1. Low				1.0									1.0		
2.				0.8	0.5	1.2							0.8	0.5	1.3
3.				1.0	0.6	1.8							1.0	0.6	1.9
4. High				0.7	0.3	2.1							0.6	0.2	1.9
Comorbidities															
0							1.0						1.0		
1							1.4	0.8	2.2				1.4	0.9	2.3
2 or more							1.6	0.9	2.9				1.5	0.8	2.8
Unknown							1.7	0.9	3.1				1.8	0.9	3.3
Alcohol															
Abstainer										0.9	0.5	1.6	0.9	0.5	1.6
Light										0.7	0.4	1.2	0.8	0.4	1.4
Moderate										1.0			1.0		
Excessive										0.5	0.2	1.8	0.6	0.2	1.9
Unknown										0.7	0.3	1.6	0.7	0.3	1.7
Physical activity															
No/little										0.7	0.4	1.2	0.7	0.4	1.2
Moderate										1.0			1.0		
Much										0.6	0.3	1.0	0.6	0.3	1.0
Unknown										0.7	0.3	1.9	0.8	0.3	1.9
Smoking															
Never										1.0			1.0		
Former										**1.8**	1.1	2.8	**1.9**	1.2	3.1
Current										1.2	0.8	2.0	1.2	0.8	2.0
Unknown										1.3	0.4	4.0	1.3	0.4	4.1

HR: hazard ratio, 95%CI: 95% confidence interval. Values in bold are significant.

4.5

DECISION

CURATIVE

ROLE

SINCE 1990

data

RECOGNISING

OUTCOME

BRACHYTHERAPY

DETERMINANTS

CATEGORY

HOUSING

health seeking behaviour

METASTASIS

CONTRIBUTION

COVERAGE

INTERVAL CANCER

material resources

CHARLSON

socioeconomic position

RADIOTHERAPY

GP

estimated annual percent change

axillary staging

EAPC

SMOKING

statistical

STUDIES

central nervous system

HOSPITAL

staging

socioeconomic status

DISCUSS

lifestyle

Eindhoven Cancer Registry

dementia

Comprehensive Cancer Centre South

stage

HORMONAL THERAPY

intelligence

education

hazard ratio

HYPERTENSION

RISK FACTORS

mastectomy

diagnostics

DIAGNOSIS

distribution

CARDIOVASCULAR DISEASE

SEP

VISITS

ATTENDANCE

EXPLANATION

SOCIAL SUPPORT

FEAR

colorectal

therapy

HIGH

MENTAL

ADVANCED

UPBRINGING

ENVIRONMENT

MAMMOGRAPHY

prostatectomy

p-value

QUESTIONNAIRE

incidence

HEALTH BEHAVIOUR

SF-36

GLOBE

PHYSICAL

SOCIOEC

NEIGHBOURHOOD

LOW

value of housing

socioeconomic

physical activity

REVIEW

colorectal cancer screening

comorbidities

occupation

EXPOSURE

INTERMEDIATE

concomitant disease

VARIATION

CHEMORADIATION

INVITATION

TUBERCULOSIS

ALCOHOL CONSUMPTION

CONTACTS

gap

logistic regression

ACCESS TO CARE

INVASIVE

numbers

PSA

LOCALISED

WORK

CONSULTATION

ASSETS

income

percentages

SCREEN-DETECTED TUMOUR

THE NETHERLANDS

HEALTH INSURANCE

health awareness

HOUSEHOLD

search

DETECTIO

Chapter 4.6

Long-term prostate cancer survivors with low socioeconomic status reported worse mental health-related quality of life in a population-based study

M.J. Aarts, F. Mols, M.S. Thong, M.W. Louwman, J.W.W. Coebergh, L.V. van de Poll-Franse

ABSTRACT

Objective

To explore whether socioeconomic status (SES) was associated with health-related quality of life (HRQL) and health care use among long-term prostate cancer survivors.

Patients and Methods

Through urologists in the Comprehensive Cancer Centre South all 5- to 10-year prostate cancer survivors known in the Eindhoven Cancer Registry without disease progression were invited to complete the 36-item Short Form Health Survey (SF-36), the Expanded Prostate Cancer Index and the Dutch sexual activities module. Multivariate linear regression assessed the effect of SES (based on home value and household income) on HRQL and health care use.

Results

Five-hundred eighty-four patients (response rate 81%) were included. Survivors with a low SES exhibited lower mental SF-36 scores (6-16 points on a 0-100 scale), independent of socio-demographic and clinical characteristics ($P<0.05$), and hardly any differences in physical SF-36 subscales, sexual function, and urinary and bowel function and bother. Presence of serious comorbidity had a stronger predictive value for HRQL than SES. Health care use did not seem to be associated with SES.

Conclusions

Prostate cancer survivors with a low SES exhibited a worse mental but not physical HRQL than those with a higher SES. Long-term health outcomes of patients with low SES may be maximized by paying extra attention to comorbid conditions.

4.6

INTRODUCTION

The absolute number of long-term prostate cancer survivors, ie, those alive at least 5 years after initial diagnosis, has been rising since the end of the 1970s owing to earlier detection and better treatments.[1] Health-related quality of life (HRQL) of prostate cancer patients is markedly affected by primary treatment, eg, radical prostatectomy has been associated with the highest physical HRQL and hormone therapy with the lowest.[2, 3] Patients with a low socioeconomic status (SES) generally underwent less aggressive therapy,[4, 5] and even after controlling for treatment, patients suffered from both a worse prognosis and worse HRQL at baseline and 2 years after primary treatment.[6] More specifically, having a low income was associated with worse mental health outcomes and greater improvements within 6 months after diagnosis.[7, 8] Although there have been several studies on SES and HRQL in short-term survivors, the association among long-term survivors remained unclear.

The association of SES with health care use among long-term prostate cancer survivors has rarely been investigated. Available studies show mixed results. A study among the general Chinese population, which also includes prostate cancer patients, showed that better HRQL predicted lower health care use.[9] Two years after diagnosis of prostate cancer, complementary and alternative medicine use was reported for 30% of the men, with an odds ratio of 1.6 for high compared to low SES,[10] but another study found no significant association with education or income.[11]

The present study assessed whether the presence of socioeconomic inequalities was associated with HRQL and health care use among long-term prostate cancer survivors.

PATIENTS AND METHODS

Setting and participants

All patients newly diagnosed with prostate cancer between 1994 and 1998 and age <75 years at diagnosis were selected from the population-based Eindhoven Cancer Registry (ECR) (Figure 1), which covers the southern part of the Netherlands (2.4 million inhabitants). Because we were interested in survivors only, patients with progression or recurrence were excluded. Data collection started in November 2004 among the 5- to 10-year survivors. A certified Medical Ethics Committee approved this study.

Data collection

Urologists sent their (former) patients a letter that explained that by returning the questionnaire they were consenting to linkage with their disease history in the ECR. After 2 months, a reminder letter with a questionnaire was sent to non-respondents.[2]

Measures

The ECR routinely collects data on tumor characteristics, including date of diagnosis, grade, stage (Tumor-Node-Metastasis clinical classification[12]), comorbidity (according to an adapted Charlson comorbidity index[13]), treatment, and patient characteristics (eg, date of birth and postal code). The questionnaire included questions on sociodemographic data, including marital status and educational level, and comorbidities.

4.6

Statistics Netherlands developed an indicator of SES for each postal code (on average, 17 households) based on aggregated individual fiscal data on the economic value of the home and household income. SES was categorized into tertiles, ie, as low (decile 1-3), medium (4-7), or high (8-10).[14] Postal codes including a care-providing institution, were excluded (N=16) because assigning a SES is difficult. The SES classes were linked to the postal codes of patients in the ECR at the time of diagnosis.

HRQL was assessed with the Dutch version of the SF-36 questionnaire,[15] incorporating two composite scales – Physical Component Summary (PCS) and Mental Component Summary (MCS) – derived from physical functioning (PF), role limitations as a result of physical health problems (RLPH), bodily pain (BP), general health perceptions (GH), vitality (VT), social functioning (SF), role limitations due to emotional problems (RLEP), and general mental health (MH). Scores were converted to a 0 to 100 scale, with higher scores indicating better functioning.[15] Clinical significant changes in HRQL were discriminated by the threshold of half a standard deviation.[16]

Urinary and bowel functioning and bother were measured with the Expanded Prostate Cancer Index (EPIC)[17] which was validated in Dutch patients.[18] Four scales were used, assessing the level of urinary functioning (5 items) and bowel functioning (7 items) and the degree of bother with urinary and bowel functions (7 items each).[17] Scores were transformed to a 0 to 100 scale, with higher scores indicating better functioning or less bother.

Sexual function and bother were assessed by a Dutch sexual activities module of 12 single items.[18] Health care use included questions on contacts with their general practitioner (GP) and visits to a medical specialist in the past 12 months.

Statistical analyses

Statistical analyses were performed using SAS version 9.1 (SES Institute, Cary, NC). Tests were two-sided and significant if $P \leq 0.05$. Significance was tested with t-tests (continuous variables) and chi-square tests (categorical variables).

The independent association of SES with the SF-36 scores was investigated with multivariate linear regression analyses. Variables that changed the beta of SES by >10% (adjusted for age at questionnaire and years since diagnosis) were included in the model, which was then used for all subscales separately. To avoid collinearity, education and partner status were excluded because of correlation with SES and marital status, respectively. Age at time of questionnaire and time since diagnosis were entered as continuous variables; tumor stages I vs II, III, IV or unknown; therapy (eg, radiotherapy versus no radiotherapy); comorbidity (no vs 1, 2 or more comorbidities); and marital status (married vs not married/divorced/widowed). The final model included: SES, stage, age at questionnaire, years since diagnosis, number of comorbidities, marital status, radiotherapy, surgery, hormonal therapy, wait and see, and other therapy. This model also tested for urinary and bowel functions and bother, and the use of health care. In multivariate analyses, we considered $P < 0.01$ statistically significant to compensate at least in part for multiple testing. P values >0.01 and <0.05 were of borderline significance.

4.6

RESULTS

Of the 964 prostate cancer survivors, 780 (81%) returned a completed questionnaire. After exclusion of those with recurrence or progression data on 584 patients could be analyzed (Figure 1).

Prostate cancer survivors with low, intermediate, and high SES were similar with respect to age, years since diagnosis, stage at diagnosis, grade, primary treatment, and work status (Table 1). At the time of questionnaire, comorbidity was more common among patients with a low SES (69%) than those with intermediate (61%) or high SES (62%) (P=0.07). At diagnosis, 51% of the patients with low SES had one or more comorbidities, compared to 50 and 45% in intermediate and high SES, respectively (P=0.5). Married prostate cancer survivors were more likely to be of intermediate or high SES (P=0.02) and highly educated persons were more likely to have a high SES (P <0.0001).
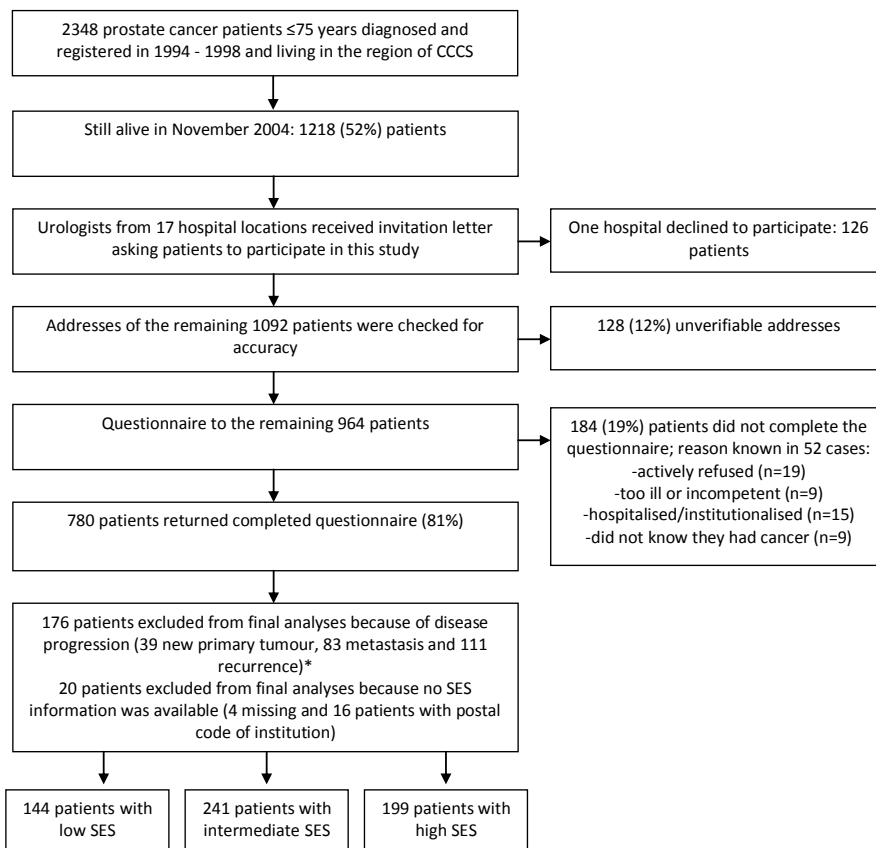
```
┌─────────────────────────────────────────────────────┐
│ 2348 prostate cancer patients ≤75 years diagnosed and│
│ registered in 1994 - 1998 and living in the region of│
│ CCCS                                                  │
└─────────────────────────────────────────────────────┘
                         │
┌─────────────────────────────────────────────────────┐
│ Still alive in November 2004: 1218 (52%) patients     │
└─────────────────────────────────────────────────────┘
                         │
┌─────────────────────────────────────┐   ┌──────────────────────────────┐
│ Urologists from 17 hospital locations│──▶│ One hospital declined to      │
│ received invitation letter asking     │   │ participate: 126 patients     │
│ patients to participate in this study │   └──────────────────────────────┘
└─────────────────────────────────────┘
                         │
┌─────────────────────────────────────┐   ┌──────────────────────────────┐
│ Addresses of the remaining 1092       │──▶│ 128 (12%) unverifiable         │
│ patients were checked for accuracy    │   │ addresses                      │
└─────────────────────────────────────┘   └──────────────────────────────┘
                         │
┌─────────────────────────────────────┐   ┌──────────────────────────────┐
│ Questionnaire to the remaining 964    │──▶│ 184 (19%) patients did not     │
│ patients                              │   │ complete the questionnaire;    │
└─────────────────────────────────────┘   │ reason known in 52 cases:      │
                         │                  │ -actively refused (n=19)       │
                         │                  │ -too ill or incompetent (n=9)  │
                         │                  │ -hospitalised/institutionalised│
                         │                  │  (n=15)                        │
                         │                  │ -did not know they had cancer  │
                         │                  │  (n=9)                         │
┌─────────────────────────────────────┐   └──────────────────────────────┘
│ 780 patients returned completed       │
│ questionnaire (81%)                   │
└─────────────────────────────────────┘
                         │
┌──────────────────────────────────────────────────────┐
│ 176 patients excluded from final analyses because of   │
│ disease progression (39 new primary tumour, 83         │
│ metastasis and 111 recurrence)*                        │
│ 20 patients excluded from final analyses because no SES│
│ information was available (4 missing and 16 patients    │
│ with postal code of institution)                       │
└──────────────────────────────────────────────────────┘
          │                  │                  │
┌──────────────┐   ┌──────────────┐   ┌──────────────┐
│ 144 patients │   │ 241 patients │   │ 199 patients │
│ with low SES │   │ with         │   │ with high    │
│              │   │ intermediate │   │ SES          │
│              │   │ SES          │   │              │
└──────────────┘   └──────────────┘   └──────────────┘
```

4.6

Figure 1. Flow chart of the data collection process.
*: patients may have combinations of disease progression. SES = socioeconomic status.

Table 1. *Sociodemographic and clinical characteristics of long-term prostate cancer survivors without recurrent disease or new primary malignancies or metastases according to socioeconomic status at the time of diagnosis.*

	N (%)			
	Low SES N=144 (25)	Intermediate SES N=241 (41)	High SES N=199 (34)	*P* value
Mean age at questionnaire (years, standard deviation)	75.1 (6.0)	74.5 (5.7)	74.0 (6.2)	#
Median age (years)	75.7	75.1	74.8	
Age distribution (years)				
50-59	1 (1)	3 (1)	5 (3)	
60-69	32 (22)	44 (18)	47 (24)	
70-79	76 (53)	160 (66)	114 (57)	
80+	35 (24)	34 (14)	33 (17)	
Time since diagnosis (years)	7.9	7.8	7.6	†
Stage at diagnosis				0.5
I	47 (33)	71 (29)	50 (25)	
II	78 (54)	136 (56)	130 (65)	
III	5 (3)	6 (2)	5 (3)	
IV	6 (4)	13 (5)	5 (3)	
Unknown	8 (6)	15 (6)	9 (5)	
Grade at diagnosis				0.2
1	54 (38)	108 (45)	67 (34)	
2	63 (44)	85 (35)	92 (46)	
3	19 (13)	34 (14)	33 (17)	
Unknown	8 (6)	14 (6)	7 (4)	
Primary treatment				
Radical prostatectomy	66 (46)	129 (54)	93 (47)	0.2
External beam radiotherapy	74 (51)	101 (42)	92 (46)	0.2
Hormonal therapy	38 (26)	65 (27)	43 (22)	0.4
Watchful waiting	12 (8)	12 (5)	13 (7)	0.4
Self-reported comorbidity at questionnaire				0.07
None	44 (31)	93 (39)	76 (38)	
1	46 (32)	82 (34)	76 (38)	
2 or more	54 (38)	66 (27)	47 (24)	
Most frequent comorbid conditions at questionnaire				
Hypertension	47 (33)	63 (26)	58 (29)	0.4
Arthritis or rheumatism	35 (24)	56 (23)	42 (21)	0.8
Asthma or COPD	25 (17)	36 (15)	23 (12)	0.3
Marital status				0.02
Married	97 (73)	190 (83)	163 (83)	
Not married/divorced	15 (11)	7 (3)	13 (7)	
Widowed	21 (16)	33 (14)	21 (11)	
Educational level*				<0.0001
Low	87 (65)	105 (46)	62 (32)	
Medium	33 (25)	81 (36)	69 (35)	
High	13 (10)	42 (18)	64 (33)	
Work status				0.10
Employed	7 (5)	6 (3)	2 (1)	
Unemployed	6 (5)	17 (7)	18 (9)	
Retired	118 (90)	207 (90)	176 (90)	

* Education: low (no or primary school); medium (lower general secondary education or vocational training); high (pre-university education, high vocational training, university).
† p-value low vs intermediate 0.6, low vs high 0.0331, intermediate vs high 0.08
 # p-value low vs intermediate 0.3, low vs high 0.1, intermediate vs high 0.4
SES = socioeconomic status.

4.6

An association with SES was observed for most of the unadjusted SF-36 subscale scores: patients with a high SES exhibited higher scores on the global physical (1.7-12.3 points) and global mental (8.8-16.0 points) subscales (Figure 2). In multivariate analyses (ie, after adjustment for tumor stage, primary therapy, time since diagnosis, age, and marital status at time of questionnaire), socioeconomic inequalities were observed on most of the mental subscales and on the mental component summary score, but on none of the physical subscales. Borderline significant differences were observed for physical functioning and bodily pain, on all of the mental subscales, and on the physical component summary score. Patients with a low SES had significantly lower scores on the SF-36 subscales role-emotional (unadjusted scores and adjusted P values: 16 points, $P=0.002$), mental health (9 points, $P=0.0003$), social functioning (10 points, $P=0.004$) and mental component summary (5 points, $P <0.0001$) than high SES and lower scores than intermediate SES on the mental component summary (4 points, $P=0.002$). Borderline significant higher scores for intermediate compared with low SES were on the subscales role-emotional (12 points, $P=0.02$), mental health (6 points, $P=0.01$) and social functioning (7 points, $P=0.04$). Those with high SES had higher scores on the subscales physical functioning (7 points, $P=0.04$), vitality (5 points, $P=0.02$), and the physical component summary (3 points, $P=0.02$) than intermediate SES. Those with intermediate SES had higher scores on the subscale bodily pain (3 points, $P=0.04$), indicating higher levels of pain than those with low SES. Differences between low and high SES were clinically relevant for the subscales mental health, social functioning, and mental component summary. The complete model explained a larger part
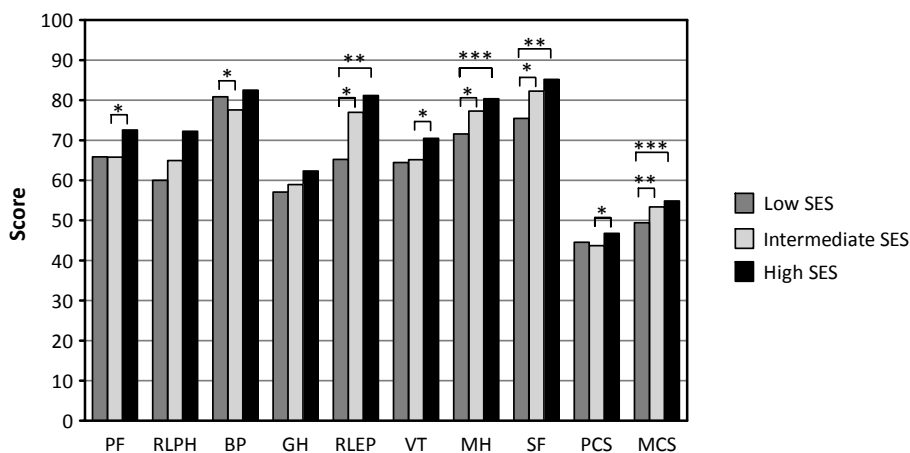

Figure 2. *SF-36 subscale scores of prostate cancer survivors according to socioeconomic status (SES). Reported scores are unadjusted. Adjustment for age at time of questionnaire, time since diagnosis, tumor stage, therapy, comorbidity, and marital status revealed significances, indicated by asterisks.*
* P<0.05, ** P <0.01, *** P <0.001. PF = physical functioning; RLPH = role limitations physical health; RLEP = role limitations emotional problems; VT = vitality; MH = mental health; SF = social functioning; P = pain; GH = general health; PCS = physical component summary; MCS = mental component summary.

of the variance of the physical SF-36 subscales (14-20%) than the mental subscales (8-12%). Comorbidity had a stronger predictive value than SES; it contributed 9% to 12% to the physical and 3% to 8% to the mental subscales, whereas SES contributed only 1% to 2% and 2% to 3%, respectively, to these subscales.

Urinary and function, bother and summary scores were similar across the SES categories, with urinary summary scores of 81, 79 and 80, and bowel summary scores of 91, 89 and 89 for low, intermediate and high SES respectively (Figure 3). None of these scores was associated to SES in the multivariate analyses, neither was erectile dysfunction: 77%, 73% and 77% of the survivors with low, intermediate, and high SES, respectively, reported problems with maintaining an erection.

In multivariate analyses, SES was not associated with the frequency of contacts with a GP, the mean number of contacts per year was 3.8 for low, 4.1 for intermediate and 3.3 for high SES patients. High SES patients reported a significantly lower number of visits to a medical specialist (2.5/y) than those with an intermediate SES (3.3/y) (multivariate P=0.0100). No differences were observed compared to the low SES group (2.9 visits/y).

COMMENT

In this study, 5- to 10-year prostate cancer survivors with high SES reported a better HRQL on 3 mental SF-36 subscales. Borderline significant differences were observed on one mental and two physical subscales. There were no socioeconomic inequalities in terms of urinary or bowel functioning and bother, or erectile problems. Furthermore, we found no differences with respect to health care usage, but high SES patients had a lower number of visits to a medical specialist compared to the intermediate SES group.
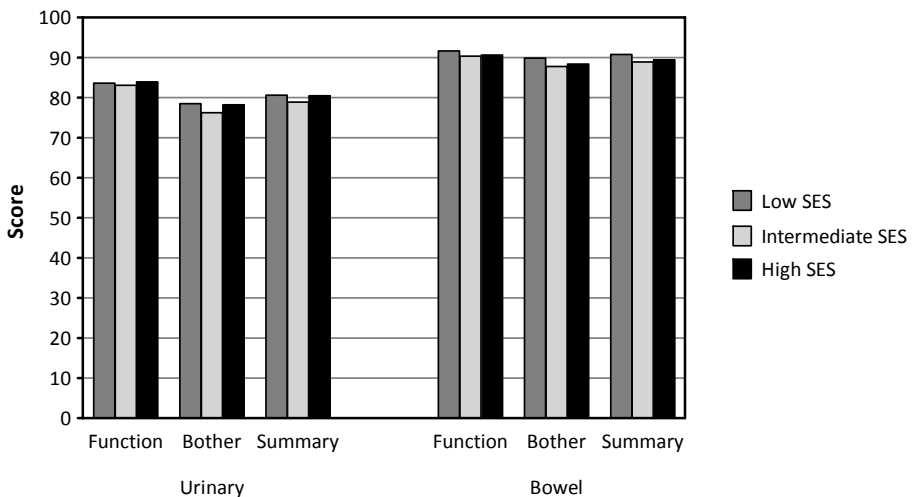

Figure 3. Urinary and bowel problems in disease-free prostate cancer survivors according to their socioeconomic status.

To our knowledge, this is one of the first studies that focused on socioeconomic inequalities in HRQL among *long-term* survivors of prostate cancer. Higher general HRQL scores among high SES patients have been shown within a short period before, during and after diagnosis of cancer in various study settings.[6, 19, 20] However, one year after diagnosis these differences disappeared[6, 19, 20] but reappeared after 1.5 to 8.5 and 5 to 10 years,[21, 22] and were likely related to treatment. Besides, a United States study on impoverished prostate cancer patients receiving free treatment reported that low income was associated with worse mental health[7] and that those with less than high school education had greater improvement in their mental well-being during treatment to 6 months after diagnosis, although no information on pretreatment scores was presented.[8]

Prostate cancer patients of high SES reported adjusted SF-36 scores that were 1 to 4 points higher than patients of other education or income, but no absolute scores were given.[21] We observed unadjusted differences in the range of 2 to 12 points, which probably resulted from the larger number of SES categories. Two years after prostate cancer diagnosis, SF-36 scores were 2 to 21 points higher than we observed, although we used a population that was 10 years older and consisted of long-term survivors.[6]

In line with our results, no association of SES with urinary function, bowel function, urinary bother, and bowel bother was reported 2 years after diagnosis.[6] However, another study found that patients with high SES had scores that were 1.6 to 1.9 points higher than those of lower SES on urinary function and bother after 1.5 to 8.5 years but no absolute scores were shown.[21]

Socioeconomic patterns may have changed during the survival time and patients with a low SES will have fewer resources and thus more concerns about work and finances. This will only have a small influence because an extensive social security system exists in The Netherlands.

Both comorbidity and cancer treatment chosen have been associated with HRQL and SES.[23, 24] Cancer patients with low SES had a 50% higher prevalence of comorbidity (M. Louwman, written communication, May 2010), which was associated with less aggressive treatment[5] and worse HRQL in prostate cancer patients.[6, 21] In our study comorbidity could not explain the socioeconomic inequalities in HRQL scores via therapy, because neither primary treatment nor comorbidity were related to SES, although those with low SES reported slightly more comorbid diseases (51% vs 45% in high SES, P=0.5). Healthy survivorship bias may have reduced the strength of the association between SES and comorbidity at diagnosis. At time of the questionnaire, similar inequalities in prevalence of comorbidity were observed (69% in low vs 62% in high SES, P=0.07). Nevertheless, comorbidity may explain part of the socioeconomic inequalities in HRQL scores. Certain lifestyle characteristics may also contribute to the association of SES with HRQL, for which we aimed to adjust by comorbidity (such as smoking which results in higher rates of lung disease). However, the socioeconomic inequalities persisted in the final model. Because comorbidity had a stronger predictive value than SES, prostate cancer patients with a low SES could benefit from more support for their chronic concomitant diseases to maximize health outcomes. The exact role of comorbidity in

4.6

socioeconomic inequalities in HRQL should be further investigated, and researchers should be aware of the possible confounding role of comorbidity.

By contrast, higher HRQL scores were reported by persons with a high SES in the general population,[25] and thus may not be specific to prostate cancer. Since no data were available on SES and HRQL of the general Dutch elderly male population, this remains unclear.

Those with a high SES had a slightly lower number of visits to a medical specialist than the intermediate SES group, which partly relates to the lower number of concomitant diseases in those with high SES. In the general male Dutch population a contrasting association was found.[26] Nevertheless, all inhabitants in the Netherlands have obligatory health insurance, making health care accessible for everyone. In addition, Dutch guidelines (http://www. oncoline.nl) recommend the number and duration of follow-up visits of prostate cancer patients up to 10 years after diagnosis.

We observed no socioeconomic inequalities in the number of contacts with a GP, whereas in the general Dutch population health care use (ie, medical specialist and GP) was highest among people with a low SES and this was strongly affected by health status.[27] We included relatively healthy survivors, resulting in small differences between survivors in health care use and urinary and bowel functions and bothers, as well as erectile dysfunction. This may also explain the low number of contacts with the GP (3.3-4.1 visits/year) compared with the general Dutch population: 4.6 and 5.7 contacts per year in males aged 65 to 75 and 75 years and older, respectively.[26]

Thus, also in a country with obligatory health insurance for all inhabitants and equal access to care, socioeconomic inequalities in mental HRQL were observed. It is not clear what causes these inequalities; however, policymakers should prevent broadening of inequalities by ensuring access to health care remains equal for everyone. In addition, doctors would be wise to anticipate to comorbid conditions among prostate cancer survivors, especially among those with low SES, to diminish SES disparities in mental HRQL and to maximize long-term outcomes.

Several limitations of this study should be noted. First, no baseline data on the patients were available and it therefore remains unclear whether the lower mental HRQL seen in patients of low SES is an underlying aspect of their lower SES or is the result of prostate cancer treatment. To address this issue, subsequent studies should include baseline measures of the HRQL of prostate cancer patients before treatment. Second, the health status of those with unverifiable addresses and nonrespondents is unknown. Therefore our results do not apply to these patients. Third, we used an indicator of SES based on the postal code of the residential area at the time of diagnosis. Long-term survivors may thus have been incorrectly classified, but SES at postal code level remains quite constant over time. In addition, especially those with poor health may have moved and they are less likely to be long-term survivors. The SES indicator is suggested to be valid, because it covers a small geographical area, which has been proven to reflect socioeconomic differences well at the individual level.[28]

4.6

Fourth, because we only included supposedly disease-free prostate cancer survivors, results can only be generalized to survivors with the best prognosis. Moreover, inclusion of disease-free survivors could suggest survivorship bias because lower SES is associated with worse self-assessed health.[29] As such, we could have underestimated HRQL inequalities. Recently, a small inequality was observed (low SES 90%, high SES 94%, $P<0.0001$). As far as we know no data on SES inequalities in prostate cancer recurrence are available.

Fifth, since prostate cancer patients can receive multiple treatments during follow-up, it would be better to adjust for combinations of these therapies instead of single therapies. Because only therapies given within 6 months after diagnosis were registered, adjustment was not possible. Finally, the cross-sectional design of our study makes it difficult to draw conclusions about relationships between SES, health care usage, and HRQL.

Despite these limitations, the results of this study form an important contribution to the limited information available on socioeconomic inequalities in HRQL and health care use in the growing group of *long-term* prostate cancer survivors. Moreover, we included an unselected group of cancer patients treated in various general hospitals and not in centers of excellence or tertiary referral centers.

CONCLUSIONS

Even in a country with equal access to care, socioeconomic inequalities exist in mental HRQL of long-term prostate cancer survivors. Physical HRQL and health care use were not or only slightly associated with SES. Although causes of mental health inequalities are still unclear, these data underline the importance the socioeconomic inequalities in HRQL and the role of comorbidities among long-term prostate cancer survivors. Long-term health outcomes of patients with low SES may be maximized by paying extra attention to their comorbidities.

4.6

REFERENCES

1. Quinn, M. & Babb, P. Patterns and trends in prostate cancer incidence, survival, prevalence and mortality. Part I: international comparisons. *BJU Int* 90, 162-73 (2002).

2. Mols, F., van de Poll-Franse, L.V., Vingerhoets, A.J., Hendrikx, A., Aaronson, N.K., Houterman, S., Coebergh, J.W. & Essink-Bot, M.L. Long-term quality of life among Dutch prostate cancer survivors: results of a population-based study. *Cancer* 107, 2186-96 (2006).

3. Siston, A.K., Knight, S.J., Slimack, N.P., Chmiel, J.S., Nadler, R.B., Lyons, T.M., Kuzel, T.M., Moran, E.M., Sharifi, R. & Bennett, C.L. Quality of life after a diagnosis of prostate cancer among men of lower socioeconomic status: results from the Veterans Affairs Cancer of the Prostate Outcomes Study. *Urology* 61, 172-8 (2003).

4. Krupski, T.L., Kwan, L., Afifi, A.A. & Litwin, M.S. Geographic and socioeconomic variation in the treatment of prostate cancer. *J Clin Oncol* 23, 7881-8 (2005).

5. Hall, S.E., Holman, C.D., Wisniewski, Z.S. & Semmens, J. Prostate cancer: socio-economic, geographical and private-health insurance effects on care and survival. *BJU Int* 95, 51-8 (2005).

6. Penson, D.F., Stoddard, M.L., Pasta, D.J., Lubeck, D.P., Flanders, S.C. & Litwin, M.S. The association between socioeconomic status, health insurance coverage, and quality of life in men with prostate cancer. *J Clin Epidemiol* 54, 350-8 (2001).

7. Gore, J.L., Krupski, T., Kwan, L., Fink, A. & Litwin, M.S. Mental health of low income uninsured men with prostate cancer. *J Urol* 173, 1323-6 (2005).

8. Brar, R., Maliski, S.L., Kwan, L., Krupski, T.L. & Litwin, M.S. Changes in quality of life among low-income men treated for prostate cancer. *Urology* 66, 344-9 (2005).

9. Lam, C.L., Fong, D.Y., Lauder, I.J. & Lam, T.P. The effect of health-related quality of life (HRQOL) on health service utilisation of a Chinese population. *Soc Sci Med* 55, 1635-46 (2002).

10. Chan, J.M., Elkin, E.P., Silva, S.J., Broering, J.M., Latini, D.M. & Carroll, P.R. Total and specific complementary and alternative medicine use in a large cohort of men with prostate cancer. *Urology* 66, 1223-8 (2005).

11. Boon, H., Westlake, K., Stewart, M., Gray, R., Fleshner, N., Gavin, A., Brown, J.B. & Goel, V. Use of complementary/alternative medicine by men diagnosed with prostate cancer: prevalence and characteristics. *Urology* 62, 849-53 (2003).

12. Sobin, L.H. & Wittekind, C. (eds.) UICC International Union against Cancer. TNM classification of malignant tumours (Wiley-Liss, Geneva, 2002).

13. Charlson, M.E., Pompei, P., Ales, K.L. & MacKenzie, C.R. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 40, 373-83 (1987).

14. Duin van, C. & Keij, I. Sociaal-economische status indicator op postcodeniveau. *Maandstatistiek van de bevolking* 50, 32-35 (2002).

15. Aaronson, N.K., Muller, M., Cohen, P.D., Essink-Bot, M.L., Fekkes, M., Sanderman, R., Sprangers, M.A., te Velde, A. & Verrips, E. Translation, validation, and norming of the Dutch language version of the SF-36 Health Survey in community and chronic disease populations. *J Clin Epidemiol* 51, 1055-68 (1998).

16. Norman, G.R., Sloan, J.A. & Wyrwich, K.W. Interpretation of changes in health-related quality of life: the remarkable universality of half a standard deviation. *Med Care* 41, 582-92 (2003).

17. Wei, J.T., Dunn, R.L., Litwin, M.S., Sandler, H.M. & Sanda, M.G. Development and validation of the expanded prostate cancer index composite (EPIC) for comprehensive assessment of health-related quality of life in men with prostate cancer. *Urology* 56, 899-905 (2000).

18. Korfage, I.J., Essink-Bot, M.L., Madalinska, J.B., Kirkels, W.J., Litwin, M.S. & de Koning, H.J. Measuring disease specific quality of life in localized prostate cancer: the Dutch experience. *Qual Life Res* 12, 459-64 (2003).

19. Barbareschi, G., Sanderman, R., Tuinstra, J., van Sonderen, E. & Ranchor, A.V. A prospective study on educational level and adaptation to cancer, within one year after the diagnosis, in an older population. *Psychooncology* 17, 373-82 (2008).

4.6

20. Simon, A.E. & Wardle, J. Socioeconomic disparities in psychosocial wellbeing in cancer patients. *Eur J Cancer* 44, 572-8 (2008).

21. Karakiewicz, P.I., Bhojani, N., Neugut, A., Shariat, S.F., Jeldres, C., Graefen, M., Perrotte, P., Peloquin, F. & Kattan, M.W. The effect of comorbidity and socioeconomic status on sexual and urinary function and on general health-related quality of life in men treated with radical prostatectomy for localized prostate cancer. *J Sex Med* 5, 919-27 (2008).

22. Zebrack, B.J., Yi, J., Petersen, L. & Ganz, P.A. The impact of cancer and quality of life for long-term survivors. *Psychooncology* 17, 891-900 (2008).

23. Zeliadt, S.B., Ramsey, S.D., Penson, D.F., Hall, I.J., Ekwueme, D.U., Stroud, L. & Lee, J.W. Why do men choose one treatment over another? A review of patient decision making for localized prostate cancer. *Cancer* 106, 1865-74 (2006).

24. Ramsey, S.D., Zeliadt, S.B., Hall, I.J., Ekwueme, D.U. & Penson, D.F. On the importance of race, socioeconomic status and comorbidity when evaluating quality of life in men with prostate cancer. *J Urol* 177, 1992-9 (2007).

25. Hoeymans, N., van Lindert, H. & Westert, G.P. The health status of the Dutch population as assessed by the EQ-6D. *Qual Life Res* 14, 655-63 (2005).

26. Statistics Netherlands. in Permanent Onderzoek LeefSituatie (POLS). Gezondheidsenquête: Korte onderzoeksbeschrijvingen (2008).

27. Kunst, A.E., Meerding, W.J., Varenik, N., Polder, J.J. & Mackenbach, J.P. Sociale verschillen in zorggebruik en zorgkosten in Nederland 2003 [Dutch] (National Institute of Public Health and Environment (RIVM), Bilthoven, 2007).

28. Bos, V., Kunst, A.E. & Mackenbach, J.P. in Sociaal-economische gezondheidsverschillen: Van verklaren naar verkleinen (ed. Stronks, K.) 8-20 (Zon/MW, Den Haag, 2001).

29. Mackenbach, J.P., Stirbu, I., Roskam, A.J., Schaap, M.M., Menvielle, G., Leinsalu, M. & Kunst, A.E. Socioeconomic inequalities in health in 22 European countries. *N Engl J Med* 358, 2468-81 (2008).

4.6

Chapter 5

Discussion

Our democratic society is characterised by heterogeneity due to unequal distribution of knowledge, intelligence, material and other resources among the inhabitants. Classification of persons into groups based on shared socioeconomic conditions leads to social stratification. This relative position on the social hierarchy is referred to by 'socioeconomic status' (SES). Common indicators of SES are income, education, occupation and race, each referring to a different aspect of social stratification and age. Through SES indicators (trends in) inequalities can be revealed often by age category.

People with lower SES generally have poorer health status and often a lower life expectancy than people in higher socioeconomic groups.[1] This association between SES and health is found for nearly all indicators of SES and nearly all health outcomes.[1] In this thesis the associations of SES and the determinants of cancer risk, detection and outcome were addressed, with the aims to explore:

1. The association of SES and the incidence and (determinants of) detection of cancer in a large population-based setting
2. The association of SES and the outcomes of cancer in terms of (trends in) staging, treatment, survival and long-term health-related quality of life
3. Entry points for interventions to reduce the socioeconomic inequalities as assessed via aforementioned studies.

The associations of (part of) the factors involved in the complex interplay between cancer detection and outcome are shown in Figure 1. Cancer detection is, amongst others, related to lifestyle and its associated cancer risk, health awareness and health literacy, health seeking behaviour, presence of comorbid conditions (comorbidities) and attendance to screening programmes. Most of these factors are also involved in cancer detection. People from different social strata have different exposures to the associations in Figure 1, e.g. levels of physical activity were reduced in low SES, which may result in increased risks of cancer. In this chapter, these diverse associations are discussed in relation to the main findings of this thesis, which are summarised in Table 1. Subsequently, the methodological considerations and implications for further research and practice will be addressed.

CANCER RISK AND DETECTION IN RELATION TO SOCIOECONOMIC STATUS

We have studied cancer detection and its determinants by means of studying the associations of SES and cancer incidence, stage at diagnosis, attendance to screening programmes and the prevalence of comorbidities (see boxed items in figure 1).

Incidence

In the Southern Netherlands, those with low SES had highest incidence rates of most common cancers (Table 1, **chapters 2, 3.1, 3.2**). However, prostate cancer, breast cancer (in age group 25-44 years), basal cell carcinomas (BCCs) and melanomas were more common among the high SES population. Socioeconomic differences in lifestyle are likely to contribute to the increased risks for most cancers (Figure 1), e.g. high smoking rates lead to high incidence of lung cancer in low SES, and higher exposure to sun light due to holidays overseas lead to high incidence of melanomas in high SES. These socioeconomic patterns and associated
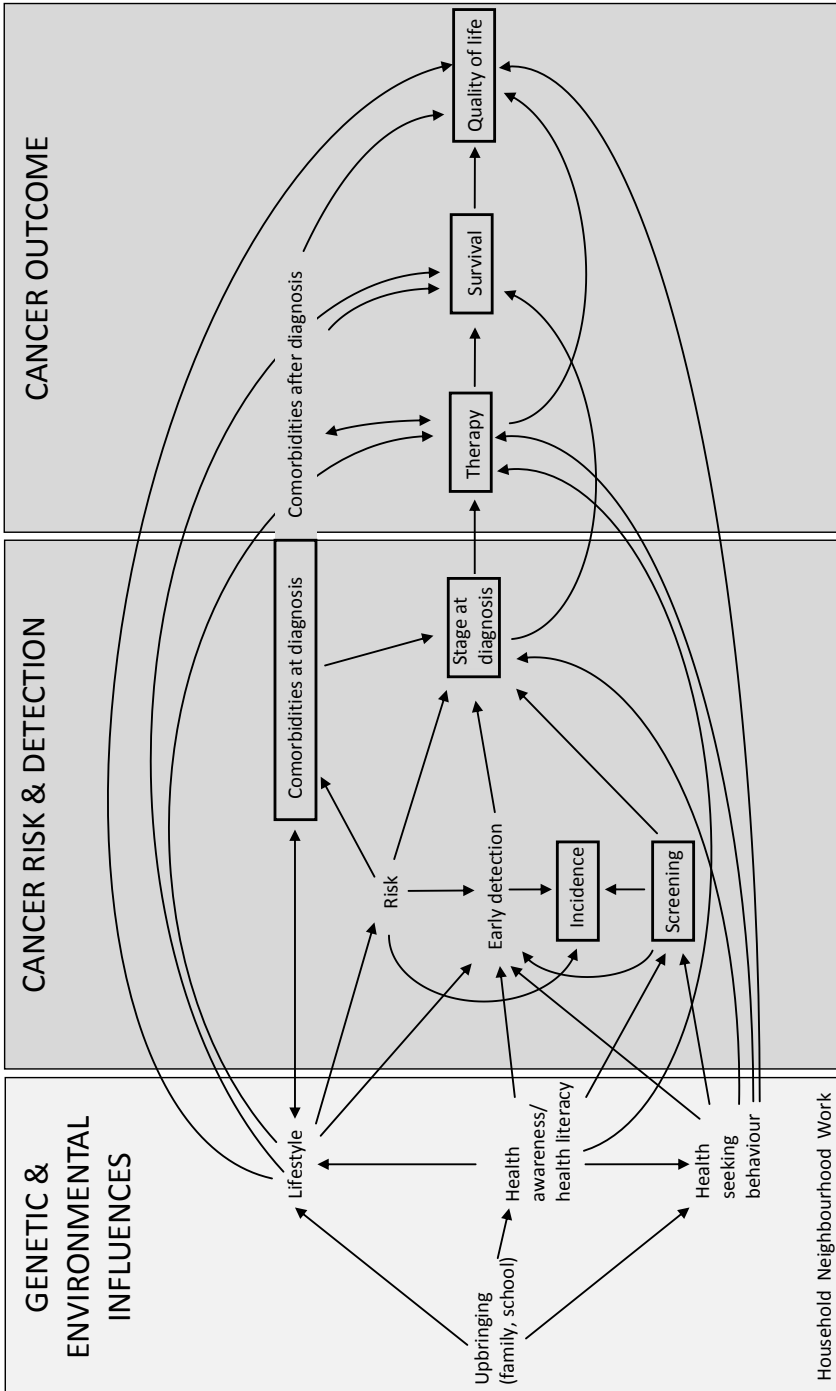
5

Figure 1. *Factors involved in the complex interplay between cancer detection and outcome. The boxed items were investigated in this thesis.*

5

cancer risks may change over time, as smoking rates were highest in high SES groups, and after several decades this association shifted from highest towards lowest in high SES.[2, 3] Subsequently the incidence rates of lung cancer reversed towards highest in low SES.[4] A similar trend was observed for sun tanning, which was first most common in high SES because of more frequent travel for sunny holidays, initially a luxury. It has been postulated that these travels were responsible for increased risk of BCC in high SES.[5] During the last two decades the availability of sunny holidays has also increased for those with a lower SES, and we therefore expect the incidence of BCCs and melanoma to increase in this group.

Height has been reported to be positively associated with cancer incidence. Although those with high SES are on average taller, the association between height and risk of cancer was found to be similar for the SES groups.[6] The underlying mechanism is thought to be related to genetic and environmental influences in the first 20 years of life, or so, or due to the fact that taller people have more cells (including stem cells), which gives higher chances for mutations. Because those with high SES have generally lower incidence rates of most cancers, it seems unlikely that height has played a major role.

Stage at diagnosis

Cancer risk is affected by, among others, health awareness (Figure 1). Health awareness is generally better among high SES groups[7] and will often lead to healthier lifestyle and more health seeking behaviour.[8] This not only reduces risks of most cancers, it also enhances early detection. In case of prostate cancer, it seems likely that PSA testing, which is more common among high SES,[9] is responsible for the strong increase among high SES. We observed that the proportion of opportunistic PSA-detected patients was indeed highest in high SES (**chapter 4.3**). Also the stage of disease was more favourable in high SES patients with prostate, breast and oesophageal cancer (Table 1). Previous studies in the U.S. and U.K. have shown mixed associations, with higher stages at diagnosis in low SES patients with breast, colorectal, upper gastrointestinal or prostate cancer,[10-14] while a U.K. study on 1980s data reported no associations for lung, colorectal, bladder, stomach, pancreatic, ovary, uterus and cervical cancer,[11] and confirmed by a review for colorectal, gynaecological and urological cancers.[14] More recently, an extensive review on the effects of SES and cancer survival reported both null associations as well as more advanced stage in low SES patients.[15] The authors furthermore state that there is no strong evidence that socioeconomic differences in stage at diagnosis result from differential delays in diagnosis.[15] Nevertheless, it seems likely that part of the socioeconomic differences in stage distribution result from more active health seeking behaviour in high SES, and thus earlier detection.

Attendance to screening programmes

Mass cancer screening programmes aim to advance cancer detection and thereby to reduce cancer mortality rates. The introduction of the breast cancer screening programme in the Netherlands indeed improved survival for all women, but women with low SES clearly benefited less from the introduction.[16] Our study showed high participation in the mass screening programme in all SES groups, but slightly less among women from low SES groups (Table 1, 87% in high SES versus 79% in low SES, **chapter 3.3**). However, the group of women with low SES comprised a relatively high proportion of first generation migrants, whose

5

breast cancer risk is usually reduced.[17] Furthermore, more advanced stage in low SES was observed independently of participation in the screening programme. Thus, even in presence of a free, generally well received , mass cancer screening programme with high participation rates, small socioeconomic inequalities in attendance, stage and thereby prognosis still exist.

Comorbidities at diagnosis

Presence of comorbidities is likely to affect cancer detection as well. These concomitant diseases may both hinder (e.g. because of similar complaints) and accelerate (e.g. because of more extensive diagnostic procedures) cancer detection. We found that the prevalence of comorbidities was 50% higher among low SES patients (Table 1, **chapter 4.1**). In addition, we observed more advanced stage at diagnosis for prostate, breast and oesophageal cancer (Table 1, **chapter 3.3, 4.3, 4.4**), although incidence rates of cancers of the prostate and breast are generally lower. Even small stage differences among screen-detected breast cancers were still present. This suggests that the presence of comorbidities may also delay cancer detection, confirming a U.S. study with colorectal, breast and prostate cancer and melanoma.[18] In our study on oesophageal cancer it seemed likely that the comorbidities contributed to the more advanced stage at diagnosis in low SES. In case of prostate and breast cancer, comorbidities and (opportunistic) screening were probably both responsible for socioeconomic differences in stage distribution, with lower stage in high SES patients. Previous studies, however, also reported enhanced early detection due to presence of concomitant diseases for endometrial, prostate, upper gastrointestinal, colorectal and lung cancer.[14, 19-21] Furthermore, not all comorbidities will affect stage at diagnosis. This depends on the anatomic areas, e.g. presence of COPD was only related to early detection in case of lung cancer, not other cancers.[20] Thus, the role of comorbidities in hindering or accelerating cancer detection remains to be explored.

CANCER OUTCOME IN RELATION TO SOCIOECONOMIC STATUS

We have studied the associations of SES and cancer outcome by means of investigating treatment selection and (its effects on) survival (see boxed items in Figure 1). Furthermore, we have studied long-term health-related quality of life in different SES-groups.

Therapy

PROSTATE CANCER THERAPY

In **chapter 4.3** we reported that low SES patients with prostate cancer generally received less invasive therapies independent of stage (Table 1). These results are in line with findings from Australia, England and the SEER database in the U.S.A.; low SES patients receive radical therapies less often and more often hormonal therapy or active surveillance than high SES patients.[22-27] Differences in stage at diagnosis and variation between hospitals did not influence surgery and radiotherapy (both external beam radiotherapy or brachytherapy) use in the U.K.; comorbidities were not taken into account.[25] We expected comorbidity to influence treatment selection as reported recently for Sweden,[28] but in our study it only had a minor effect on treatment selection.

We also observed that the introduction of brachytherapy for patients with localised disease (especially at 70-74 years of age) occurred initially in patients with high SES, becoming more

5

Table 1. Summary of the study results.

Tumour	All	Oesophagus	Colorectal	Lung	Breast	Prostate
DETECTION						
Incidence	Mostly: L, LL Melanoma: H BCC: HH		U.S.&Canada: LL Europe: HH		H	HH
Screening					H	
Higher stage		LL			L independent of screening SNB: L LND: L	L
Axillary staging						
Comorbidity	LL	LL				L
OUTCOME						
Treatment		Palliative: H	Colon: H Rectal: not uniform		BCS: H Chemo: 0 Hormonal: 0	P-ectomy, brachytherapy: H EBRT, HT, WW: L Treatment selection hardly affected by comorbidities. Brachytherapy first introduced in high then to low SES
Survival	H, partly ascribed to lower prevalence of comorbidities in high SES	Curative: H	HH Colon: limited effect of behavioural factors and comorbidity	0, limited effect of behavioural factors and comorbidity	H, due to stage and therapy in non-attenders and interval cancers; in screen-detected cancers partly due to comorbidities. Other study: H, generally limited effect of behavioural factors and comorbidity	H, related to treatment and comorbidity but less to behavioural factors
Mortality			LL			
Quality of life						Mental: H; Physical: 0 Comorbidity stronger effect on QoL than SES

H: little higher in high socioeconomic status compared to low socioeconomic status (SES); HH: much higher in high SES compared to low SES; 0: no (consistent) association; L: little higher in low SES compared to high SES; LL: much higher in low SES compared to high SES. SNB: sentinel node biopsy; LND: lymph node dissection in addition to SNB; BCS: Breast Conserving Surgery; P-ectomy: prostatectomy; EBRT: external beam radiotherapy; HT: hormonal therapy; WW: watchful waiting.

5

common in low SES patients after several years. Presence of comorbidities hardly affected this pattern, suggesting that not performance status but patients' preferences led to these high rates of brachytherapy. Presumably, high SES patients were more eager to explore all treatment options, including the more experimental ones, to overcome their disease, as was suggested for oesophageal cancer before.[29] Furthermore, physicians and high SES patients generally have rather similar educational level, whereby treatment options are more easily discussed. A study performed in the region of the Eindhoven Cancer Registry found that cancer patients with high SES more often searched for information about cancer on the internet.[30] The exact role of SES and patients' search for information on treatment options, information on these treatment options and outcomes provided by the physicians, capacity to understand medical information, and patients' preferences remains to be explored, taking time into account.

Breast cancer therapy
Compared to high SES, early stage breast cancer patients with low SES underwent more often mastectomy than breast conserving surgery (Table 1, **chapter 4.2**). This could not be fully explained by stage, age and year of diagnosis. Our results are in line with previous studies of women with a lower SES and higher mastectomy rates and lower breast conserving surgery rates in certain areas,[31-35] which was explained by more advanced stage in one but not in another study.[31, 33] Because of higher prevalence of concomitant diseases in patients with low SES,[36] type of surgery is expected to be less invasive in low SES patients. Presence of comorbidities might also be indicative for mastectomy, in order to avoid the (harmful) effects of radiotherapy. In fact, we observed higher invasive surgery (mastectomy) rates in low SES women, which may point to a role of comorbidities. No data were available for presence of comorbidities in that nation-wide study, nor were we able to investigate the contributions of ER status or grade. However, previously these factors were reported to be unrelated to SES.[31] More active involvement of the patient in decision making was associated with higher mastectomy rates in the U.S.,[37] but the effects in the Netherlands remain to be studied.

Oesophageal cancer therapy
We observed that, independent of stage and comorbidity, high SES patients with oesophageal cancer more often underwent a curative treatment compared to low SES (Table 1, **chapter 4.4**). In case of palliative treatment, high SES patients more often underwent a combination of chemotherapy and radiotherapy. Our results confirm a previous study of stent placement which was more often applied in low SES patients, while high SES patients more often received chemotherapy or underwent oesophageal resection.[29]

Cancer therapy is related to socioeconomic status
Thus, treatment selection was related to SES as we reported for breast, prostate and oesophageal cancer. We expected both stage at diagnosis and presence of comorbidities to affect treatment selection and although it did, not all of the differences could be explained. On the other hand, we observed suggestions of socioeconomic patterning of the introduction of brachytherapy, which at the time was considered to be more risky. Although speculative, it seems that high SES patients were more eager to explore all treatment options, including experimental, potentially more dangerous, brachytherapy, and that this new therapy became

5

more common among low SES patients several years later. This coincided by widening and subsequently reducing socioeconomic differences in therapies administered. For breast cancer no such patterns were observed since no new therapies were introduced during the study periods (except for the sentinel node biopsy, but this was not associated to SES).

Survival
We observed the highest survival rates for patients with high SES with prostate, oesophageal, colorectal and breast cancer (Table 1, **chapters 2, 4.1, 4.3, 4.4, 4.5**). These socioeconomic differences in cancer survival could not be fully ascribed to treatment selection as we observed in breast and prostate cancer. SES differences in cancer survival were neither completely explained by comorbidities (colorectal, lung, prostate, breast), nor by stage at diagnosis (breast, prostate, oesophageal, lung and colon cancer). Socioeconomic differences in alcohol consumption, physical activity or smoking were not responsible for better survival rates in high educated breast, prostate and colon cancer patients.

The finding that socioeconomic differences in survival can not be fully ascribed to treatment, presence of comorbidities, stage, or lifestyle behaviour, (again) suggests that there might be a role for SES-related patients' preferences and health literacy, to be explored if to be addressed. Health literacy refers to "the degree to which individuals have the capacity to obtain, process and understand basic health information and services needed to make appropriate health decisions."[38] Those with low health literacy may not fully grasp the various treatment options, and therefore some patients may not receive the most appropriate treatment for their medical condition. Also because those with low SES reported higher fear of reporting symptoms to their physician than those with high SES.[39] In contrast, some individuals do not want to be very involved in medical decision making, especially low educated and those with poor health.[40] These preferences should be taken into account in the decision process as well.

Health-related quality of life
Patients' experiences should also be captured in outcome measures. Long-term prostate cancer survivors with high SES reported better mental health than those with low SES 5-10 years after diagnosis (Table 1, **chapter 4.6**). In these patients comorbidity was more important than SES. This suggests that the relatively poor position of patients with low SES may be improved by paying extra attention to their comorbidities.

DATA CONSIDERATIONS
In our studies we have used three measures of SES (Table 2, also described in **chapter 1**).

Area-based measures of socioeconomic status
The first is an area-based measure on self-reported income, employment and education of 1 representative per 6-digit postal code, subsequently aggregated to the 4-position of postal code. The SES proxy captures several aspects. It measures material resources by means of income and employment. Furthermore, by including employment it reflects social standing and social networks, work based stress, specific toxic environmental or work tasks exposures. Finally, education reflects a person's cognitive functioning, making him/her more receptive

5

to health education messages or more able to communicate with and access appropriate health services.[41] The meaning of education varies for the different birth cohorts, and may be less applicable for elderly (those born before 1955). We expect that these effects will be limited, because the SES measure combines educational level with income and employment.

The second measure of SES was based on fiscal data of household income and economic value of housing, both objectively collected. As discussed above, both measures mainly capture access to material resources, by means of buying access to better quality material resources and allowing access to services (such as health services or education).[41] Income may change during life, therefore it may be less reliable for relatively young and relatively old adults. Housing, however, is another main marker of material circumstances, as it accounts for a large proportion of the outgoings from income. A disadvantage is that housing may be specific to the temporal and geographical context where it was developed and thus difficult to compare across studies. Since the Netherlands is a relatively small country with a high population density and good access to (health care) facilities, we expect the regional differences in SES to be limited. It should be noted that the Dutch population is heterogeneous in terms of urbanicity, with rural and urban areas. Recently, increasing level of urbanicity was worldwide associated with a social transition of a higher BMI among the more affluent towards a higher BMI among the poorest.[42]

Both SES measures discussed above are available at postal code level, i.e. at the 4-position, with on average 1,765 households, and at the 6-position, average 17 households, respectively.

Table 2. *Description of the proxies of socioeconomic status used in this thesis.*

Source of proxy for socioeconomic status	Area-based or individual level?	Based on	Data collection
The Netherlands Institute for Social Research (governmental organisation)	Area-based, 4-position of postal code (mean number of households=1765)	Income, employment and education	Private organisation performed telephone calls with one person per six-digit postal code area. This person was seen as representative for his/her area. These data were aggregated to four-digital postal code areas. (1995, 1998, 2002, 2006)
Statistics Netherlands (governmental organisation)	Area-based, 6-position of postal code (mean number of households=17)	Household income, economic value of housing	Fiscal data (household income: 1998 and economic value of the house/apartment: 2000)
Dutch GLOBE-study (cohort)	Individual level	Education	Questionnaires including questions on highest attained educational level in 1991

5

Thereby the measures are subject to the ecological fallacy, i.e. problems arise in making a causal inference about individual phenomena on the basis of observations of groups. Although both measures of SES were not available at the individual level, validation studies have found that an area-based measure of SES is a good indicator of SES for individuals.[43-45]

Individual measures of socioeconomic status

The third SES-measure we have used was the individual level of education, which was self- reported by questionnaires in the GLOBE study (**chapter 4.5**). Education is a strong determinant of employment and income, but may not be very reliable for older women, whose occupation or education does not always properly reflect their social class.[46] Besides, in our study selective participation may have led to underestimation of the socioeconomic differences in survival.

Ideally, SES indicators at the individual level should be used. In case these are not available, it is preferred to use a SES proxy available at the lowest aggregate level, i.e. covering the least number of individuals. Furthermore, it would be interesting to take several SES indicators into account, because not all proxies of SES cover all individuals well (e.g. education for older women born before 1950). Moreover, it is preferred to use SES measures which are objectively collected by external clarks or institutions such as by taxes, and thus are unbiased.

Strengths of our studies

We have used population-based data, including *all* cancer patients from Southern Netherlands or from all of the Netherlands (**chapters 3.1, 3.2, 3.3, 4.1, 4.2, 4.3, 4.4, 4.5, 4.6**). We were able to assess the effects of comorbidity, which is strongly related to SES and mostly not available in studies on the effects of SES on cancer. Comorbidities were objectively included in the cancer registry, whereas self-reported comorbidity mostly leads to underestimation in low SES individuals .[47]

THE (IN)EVITABILITY OF SOCIOECONOMIC INEQUALITIES

We observed that both cancer detection and outcome were related to SES in the Netherlands. This may seem unexpected since the Dutch health care system is *supposedly* accessible for everyone and covers (nearly) all costs of oncological health care. However, the SES-differences we observed were relatively small, and rather limited when compared to differences in cancer survival between black and white populations in the U.S.,[48] which are supposedly largely driven by SES-differences.[49] It seems that small socioeconomic inequalities are hard to influence and even inevitable, since socioeconomic inequalities even appeared to exist within the Dutch health care system. General actions or interventions to reduce these differences may even have the adverse effect, since especially those with high SES will benefit. This has been illustrated by the introduction of the mass breast cancer screening program: survival increased for all SES groups, but more for high SES, so inequalities increased.[16]

IMPLICATIONS FOR POLICY

Improving access to care

If socioeconomic differences in cancer detection and outcome are indeed inevitable and sometimes grow as in case of mass screening, what can be done to improve the situation?

5

Further improving access to care is likely to be useful as people always feel barriers te enter the system. The infrastructure of the Dutch health care system is supposedly good for all inhabitants, but in low SES groups cancer is detected in a later stage (or maybe even not detected), due to fear to report symptoms to the physician, unbelief that cancer could be cured, worries about what the physician might find, and ignoring warning signs.[7, 39] The general practitioners (GPs) and their nurse practitioners in principle play an important role in this, since they are gatekeepers to secondary health care in the Netherlands, assuming that there are no barriers to visit a GP.

A French study showed that GPs overestimate the health of low educated individuals compared to self-rated health, although these patients may experience difficulties with estimating their health status.[50] Therefore GPs may need to be extra aware that clients with a lower SES may have difficulties in reporting their problems and that clients with low SES may have poorer health, without clear outward signs and symptoms. However it is important, especially for low SES individuals, to report their problems and medical symptoms to their GP. This could be achieved by improving awareness of cancer by training individuals to recognise cancer warning signs such as provided by Dutch Cancer Society.[51] In addition, there may be socioeconomic differences in timing of referral for specialised (secondary) health care, whereby those with low SES may have longer waiting times for a consult. Since our pilot study (to be discussed later) indicated that the majority of the physicians recognised the problems of individuals with low SES, the symbolic introduction of a 'fast track system' may improve their relatively poor position. In this system, those with low SES would get higher priority for referral than the 'worried well' who might often be unnecessarily vocal and would get lower priority. The effectiveness of such a system has to be investigated.

Improving lifestyle
In the Netherlands, in recent years educational inequalities in life expectancy have increased, especially amongst women.[52] The increase of the differences in life expectancy underlines the importance of prevention, because solidarity becomes more important with increasing health problems, by means of solving problems and the ability to pay for these problems.[53] Just recently, the Dutch Council for Public Health and Health Care presented a report on the prevention of lifestyle diseases, especially prevalent in wealthy countries.[53] The council advised to start a foundation, funded by the health insurance premiums, which stimulates cooperation between health insurance companies and municipalities to prevent lifestyle diseases. The council also mentioned that the health insurance companies and municipalities should provide insight into in which areas extra attention should be paid. Furthermore, the council states that the Minister of Health should play an active role by improving information programmes, by improving health protection e.g. school yards where smoking is forbidden, and by increasing taxes on tobacco, alcohol and unhealthy food.

The success of these interventions to promote healthy lifestyle will strongly depend on the skills to communicate with different SES groups. In addition, the success will depend on the ability of those with poor lifestyle to get loose of the habits from those who surround them. Actual improvement will be difficult to achieve, especially in the low SES group, because these advises will be either too late or the circumstances will be too adverse. However, a

5

review has shown that interventions targeting low income groups to reduce smoking or increase physical activity and/or healthy eating can be effective, but only few studies could be included and there was no evidence for the best design for interventions for disadvantaged groups.[54]

Those with low SES generally have poorer health, as reflected in 50% higher prevalence of overweight, obesity and diabetes compared to high educated Dutch inhabitants.[55] Smoking rate was 32% in low educated Dutch, versus 22% in high educated in 2010.[56] In females the relative inequalities in smoking prevalence have markedly increased from 1985-1988 to 1998-2000, while the relative socio-economic inequalities in smoking prevalence remained unchanged in males.[57] Previous studies have shown that socio-economic differences in smoking and alcohol consumption already develop at very young ages and that smoking initiation at young age predicts educational differences in smoking cessation during adulthood.[58] This suggests that the availability of alcohol and tobacco should be specifically limited in young individuals in the low SES group.

Risk of cancer can be reduced by improving lifestyle, which will hopefully be achieved by the advice of the Dutch Council for Public Health and Health Care. It has been estimated that 24% of all cancers in the U.S. could be prevented by appropriate food, nutrition, physical activity, and body fatness.[59] Smoking still accounts for 30% of cancer deaths in the Netherlands.[60] Thus, improving lifestyle reduces cancer risk, although it may be difficult to reduce the socioeconomic inequalities. In addition, the low SES group will become smaller, since within this group, those with relatively higher SES will adapt their lifestyle and are more likely to migrate to higher SES. For Denmark, trends in lung cancer incidence by education have been modelled under different scenarios for cigarette smoking, and all models will reduce the absolute differences in incidence rates of lung cancer between the SES groups, but none will reduce relative inequalities.[61]

A role for the general practitioner?

GPs may guide their clients with low SES in improving cancer awareness as well as promoting healthier lifestyle, focussing on comorbidities. Furthermore, we underline the importance to reach the vulnerable groups, in view of the upcoming mass screening for colorectal cancer (2013). The GPs may play a role in increasing participation in the screening programme. Better information provision was suggested to improve colorectal cancer uptake in low SES in Spain,[62] but whether this holds true for the Netherlands remains to be explored. However, by providing information on the screening procedure, e.g. by demonstrations or sending letters to clients who will be invited for the mass screening programme, the GPs may underline the importance of participating to the screening programme. As discussed earlier, the introduction of a 'fast track system' for early diagnosis may be useful, in which those with low SES would get higher priority for referral to secondary health care than the 'worried well', who get lower priority.

Experiences and opinions of physicians

We performed a survey to explore experiences and expectations on SES and cancer detection and outcomes among a total of 14 physicians: 4 radiotherapists , 1 surgeon, 3 GPs, 2 medical

5

oncologists and 3 radiotherapists in the region of the Eindhoven Cancer Registry. The main results of this pilot study are summarised in Table 3. The majority of the physicians said to recognise the socio-economic differences in cancer risk; they address them by providing extra information to low SES clients on the risks of their health behaviour, and by consulting a nurse (practitioner). Approximately half of the physicians thinks that these socioeconomic differences in cancer risk need to be reduced, which should be achieved via campaigns/ grants from the government to improve lifestyle specifically in the low SES group, by extra support for healthy lifestyle by the GP, by increasing taxes on unhealthy lifestyle, by coaching, improving addiction care, and by making sports facilities better accessible. Two physicians indicated that nothing should be done on the increased risks of a few cancers in people with high SES, because they consider interventions to be ineffective and because high SES individuals will mostly already be aware of the risks. Besides, there will also be patients who are so addicted that nothing really helps.

Socioeconomic differences in cancer outcome, by means of more advanced stage at diagnosis, treatment selection, survival and health-related quality of life, were also recognised by the majority of the respondents. The physicians indicated that they address these by providing extra information on the therapy and its side effects and consequences, more consultations, especially by nurse (practitioners). Furthermore, half of the physicians indicated that the association between SES and cancer outcomes <u>needs</u> to be attacked, by means of more time for consultations, providing extra information to the patient, by extra consults by nurse (practitioners). It was also indicated that it will be difficult to provide information specifically for each individual patient since this will be too expensive. Furthermore, most of the respondents indicated that the GPs and nurse practitioners play an important role of making health care better accessible for the low SES group. Thus, the majority of the physicians is aware of and recognises the socioeconomic differences in cancer risk, detection and outcome.

5

Table 3. *Summary of a pilot study to explore experiences and expectations on SES and cancer detection and outcomes among 14 physicians in the region of the Eindhoven Cancer Registry.*

CANCER RISK AND DETECTION	N/N
Individuals with low SES have mostly increased risks of cancer. Do you recognise this?	
Yes	12/14
What do you do to reduce the risk of cancer in low SES?	
I give extra information on risk of health behaviour	9/12
I refer for consultations to nurse (practitioner)	3/12
Nothing, patients are often metastasised at diagnosis	2/12
Do you think the risk of cancer in those with low SES should be reduced?	
Yes	8/14
No	2/14
What do you think that should happen to reduce the risk of cancer in low SES?	
Campaigns/funds of government aimed at healthier lifestyle, specifically for low SES	7/12
General practitioner should promote healthy lifestyle	6/12
Taxes on poor lifestyle	3/12
Coaching	3/12
Other, via sports facilities, multidisciplinary collaboration, nothing	4/12
Why do you think nothing should happen to reduce the risk of cancer in low SES?	
Those with low SES will not adhere to the guidelines	1/1
Do you think anything should happen to reduce the increased risks for some cancers in high SES?	
Yes	8/14
No	4/14
What do you think that should happen to reduce the risk of cancer in high SES?	
Campaigns/funds of government aimed at healthier lifestyle, specifically for low SES	7/9
General practitioner should promote healthy lifestyle	6/9
Coaching	3/9
Improving addiction care	1/9
Better information provision in the waiting room	2/9
Why do you think nothing should happen to reduce the risk of cancer in low SES?	
It will not work	2/6
Other	4/6

Table 3 continues on next page.

5

Continuation of table 3

CANCER OUTCOME – stage at diagnosis, therapy, survival, quality of life	
Do you recognise socioeconomic inequalities in cancer outcome?	
Yes	9/14
No	4/14
What do you do to reduce these socioeconomic inequalities?	
I provide extra information on therapy	3/8
I provide extra information on side effects and consequences of therapy	3/8
I provide extra consult with nurse (practitioner)	2/8
More consults	1/8
Other	3/8
Do you think anything should happen to reduce these socioeconomic inequalities?	
Yes	7/13
No	2/13
What do you think that should happen to reduce the risk of cancer in high SES?	
Longer consults	1/11
Providing extra information on therapy	6/11
More emphasis on advanced diagnostics or therapy	1/11
Consulting nurse (practitioner)	4/11
Why do you think nothing should happen to reduce these socioeconomic inequalities?	
It will not work	1/1

DIRECTIONS FOR FURTHER RESEARCH

As we did not observe clear starting points for interventions to reduce socioeconomic inequalities other than the obvious advice to improve diet, quit smoking and increase physical activity levels, it would be interesting to study patient preferences and the effects of health literacy and health awareness in cancer detection and outcome, to see if these further explain the small socioeconomic differences we observed. This could be investigated through PROFILES, a registry for the study of physical and psychosocial impact of cancer and its treatment from a dynamic, growing population-based cohort of cancer survivors.[63] Via the entry points detected, interventions can be developed and by addressing these, health literacy and awareness may be improved, ideally especially in the low SES group. Furthermore, satisfaction with information provision and treatment choice would be interesting to study for each of the SES groups. By measuring patient's preferences and satisfaction this can be surveyed.

Monitoring cancer detection and outcome according to SES provides insight in trends over time and spatial distribution. Since SES is correlated with many causes of diseases, monitoring SES gives valuable information on public health in general. Especially in view of the variability of the associations between SES and health over time, and the transition of overweight/obesity towards low SES,[42, 55] it will be useful to continue monitoring the association of SES and health and comorbidities.

5

CONCLUSION

In the Netherlands, relatively small socioeconomic differences were observed in cancer detection and outcome, conforming to a few Dutch studies that have been done before on this topic. The Netherlands have a health care system which is *supposedly* equally accessible for all inhabitants. In this thesis we describe that low SES groups had the highest risks of most common cancers, except for basal cell carcinoma, melanoma and prostate cancer. Participation in the breast cancer screening programme was however lower in people with low SES, and detection occurred at a more advanced stage. Therapy selection seemed to depend on SES and could be partly ascribed to higher prevalence of comorbidities in low SES patients. Survival rates were higher in high SES, and could not be fully explained by SES-differences in treatment and lower prevalence of comorbidities. In long-term prostate cancer survivors, low SES men had poorer mental health-related quality of life. Thus, both cancer detection and outcome were consistently related to SES in the Netherlands, with generally small absolute differences. These socioeconomic differences seem hard to influence and may even be inevitable. Since SES is related to many causes of diseases, it will be valuable to continue monitoring SES in relation to health. The GPs and their nurse practitioners should play an important role in improving access to care by improving cancer awareness, promoting healthy lifestyle and by patient-specific provision of information.

5

REFERENCES

1. Mackenbach, J.P., Stirbu, I., Roskam, A.J., Schaap, M.M., Menvielle, G., Leinsalu, M. & Kunst, A.E. Socioeconomic inequalities in health in 22 European countries. *N Engl J Med* 358, 2468-81 (2008).

2. STIVORO. in Trendpublicatie percentage rokers (STIVORO, The Hague, 2010).

3. Graham, H. Smoking prevalence among women in the European community 1950-1990. *Soc Sci Med* 43, 243-54 (1996).

4. Aarts, M.J., van der Aa, M.A., Coebergh, J.W. & Louwman, W.J. Reduction of socioeconomic inequality in cancer incidence in the South of the Netherlands during 1996-2008. *Eur J Cancer* 46, 2633-46 (2010).

5. Lear, J.T., Tan, B.B., Smith, A.G., Bowers, W., Jones, P.W., Heagerty, A.H., Strange, R.C. & Fryer, A.A. Risk factors for basal cell carcinoma in the UK: case-control study in 806 patients. *J R Soc Med* 90, 371-4 (1997).

6. Green, J., Cairns, B.J., Casabonne, D., Wright, F.L., Reeves, G. & Beral, V. Height and cancer incidence in the Million Women Study: prospective cohort, and meta-analysis of prospective studies of height and total cancer risk. *Lancet Oncol* 12, 785-94 (2011).

7. Robb, K., Stubbings, S., Ramirez, A., Macleod, U., Austoker, J., Waller, J., Hiom, S. & Wardle, J. Public awareness of cancer in Britain: a population-based survey of adults. *Br J Cancer* 101 Suppl 2, S18-23 (2009).

8. Fitzpatrick, P., Corcoran, N. & Fitzpatrick, J.M. Prostate cancer: how aware is the public? *Br J Urol* 82, 43-8 (1998).

9. Nijs, H.G., Essink-Bot, M.L., DeKoning, H.J., Kirkels, W.J. & Schroder, F.H. Why do men refuse or attend population-based screening for prostate cancer? *J Public Health Med* 22, 312-6 (2000).

10. Dalton, S.O., During, M., Ross, L., Carlsen, K., Mortensen, P.B., Lynch, J. & Johansen, C. The relation between socioeconomic and demographic factors and tumour stage in women diagnosed with breast cancer in Denmark, 1983-1999. *Br J Cancer* 95, 653-9 (2006).

11. Schrijvers, C.T., Mackenbach, J.P., Lutz, J.M., Quinn, M.J. & Coleman, M.P. Deprivation, stage at diagnosis and cancer survival. *Int J Cancer* 63, 324-9 (1995).

12. Parikh-Patel, A., Bates, J.H. & Campleman, S. Colorectal cancer stage at diagnosis by socioeconomic and urban/rural status in California, 1988-2000. *Cancer* 107, 1189-95 (2006).

13. Adams, J., White, M. & Forman, D. Are there socioeconomic gradients in stage and grade of breast cancer at diagnosis? Cross sectional analysis of UK cancer registry data. *Bmj* 329, 142 (2004).

14. Macleod, U., Mitchell, E.D., Burgess, C., Macdonald, S. & Ramirez, A.J. Risk factors for delayed presentation and referral of symptomatic cancer: evidence for common cancers. *Br J Cancer* 101 Suppl 2, S92-S101 (2009).

15. Woods, L.M., Rachet, B. & Coleman, M.P. Origins of socio-economic inequalities in cancer survival: a review. *Ann Oncol* 17, 5-19 (2006).

16. Louwman, W.J., van de Poll-Franse, L.V., Fracheboud, J., Roukema, J.A. & Coebergh, J.W. Impact of a programme of mass mammography screening for breast cancer on socio-economic variation in survival: a population-based study. *Breast Cancer Res Treat* 105, 369-75 (2007).

17. Visser, O. & van Leeuwen, F.E. Cancer risk in first generation migrants in North-Holland/Flevoland, The Netherlands, 1995-2004. *Eur J Cancer* 43, 901-8 (2007).

18. Gonzalez, E.C., Ferrante, J.M., Van Durme, D.J., Pal, N. & Roetzheim, R.G. Comorbid illness and the early detection of cancer. *South Med J* 94, 913-20 (2001).

19. De Marco, M.F., Janssen-Heijnen, M.L., van der Heijden, L.H. & Coebergh, J.W. Comorbidity and colorectal cancer according to subsite and stage: a population-based study. *Eur J Cancer* 36, 95-9 (2000).

20. van de Schans, S.A., Janssen-Heijnen, M.L., Biesma, B., Smeenk, F.W., van de Poll-Franse, L.V., Seynaeve, C. & Coebergh, J.W. COPD in cancer patients: higher prevalence in the elderly, a different treatment strategy in case of primary tumours above the diaphragm, and a worse overall survival in the elderly patient. *Eur J Cancer* 43, 2194-202 (2007).

5

21. Zanders, M.M.J., Boll, D., Van Steenbergen, L.N., Van de Poll-Franse, L.V. & Haak, H.R. Endometrial Cancer and Diabetes Mellitus: Mutual Influence on Treatment and Outcome. (submitted).

22. Fairley, L., Baker, M., Whiteway, J., Cross, W. & Forman, D. Trends in non-metastatic prostate cancer management in the Northern and Yorkshire region of England, 2000-2006. *Br J Cancer* 101, 1839-45 (2009).

23. Hall, S.E., Holman, C.D., Wisniewski, Z.S. & Semmens, J. Prostate cancer: socio-economic, geographical and private-health insurance effects on care and survival. *BJU Int* 95, 51-8 (2005).

24. Krupski, T.L., Kwan, L., Afifi, A.A. & Litwin, M.S. Geographic and socioeconomic variation in the treatment of prostate cancer. *J Clin Oncol* 23, 7881-8 (2005).

25. Lyratzopoulos, G., Barbiere, J.M., Greenberg, D.C., Wright, K.A. & Neal, D.E. Population based time trends and socioeconomic variation in use of radiotherapy and radical surgery for prostate cancer in a UK region: continuous survey. *Bmj* 340, c1928 (2010).

26. Byers, T.E., Wolf, H.J., Bauer, K.R., Bolick-Aldrich, S., Chen, V.W., Finch, J.L., Fulton, J.P., Schymura, M.J., Shen, T., Van Heest, S. & Yin, X. The impact of socioeconomic status on survival after cancer in the United States : findings from the National Program of Cancer Registries Patterns of Care Study. *Cancer* 113, 582-91 (2008).

27. Berglund, A., Garmo, H., Robinson, D., Tishelman, C., Holmberg, L., Bratt, O., Adolfsson, J., Stattin, P. & Lambe, M. Differences according to socioeconomic status in the management and mortality in men with high risk prostate cancer. *Eur J Cancer* (2011).

28. Berglund, A., Garmo, H., Tishelman, C., Holmberg, L., Stattin, P. & Lambe, M. Comorbidity, treatment and mortality: a population based cohort study of prostate cancer in PCBaSe Sweden. *J Urol* 185, 833-9 (2011).

29. van Vliet, E.P., Eijkemans, M.J., Steyerberg, E.W., Kuipers, E.J., Tilanus, H.W., van der Gaast, A. & Siersema, P.D. The role of socio-economic status in the decision making on diagnosis and treatment of oesophageal cancer in The Netherlands. *Br J Cancer* 95, 1180-5 (2006).

30. van de Poll-Franse, L.V. & van Eenbergen, M.C. Internet use by cancer survivors: current use and future wishes. *Support Care Cancer* 16, 1189-95 (2008).

31. Henley, N.C., Hole, D.J., Kesson, E., Burns, H.J., George, W.D. & Cooke, T.G. Does deprivation affect breast cancer management? *Br J Cancer* 92, 631-3 (2005).

32. Norredam, M., Groenvold, M., Petersen, J.H. & Krasnik, A. Effect of social class on tumour size at diagnosis and surgical treatment in Danish women with breast cancer. *Soc Sci Med* 47, 1659-63 (1998).

33. Taylor, A. & Cheng, K.K. Social deprivation and breast cancer. *J Public Health Med* 25, 228-33 (2003).

34. Raine, R., Wong, W., Scholes, S., Ashton, C., Obichere, A. & Ambler, G. Social variations in access to hospital care for patients with colorectal, breast, and lung cancer between 1999 and 2006: retrospective analysis of hospital episode statistics. *Bmj* 340, b5479 (2010).

35. Downing, A., Prakash, K., Gilthorpe, M.S., Mikeljevic, J.S. & Forman, D. Socioeconomic background in relation to stage at diagnosis, treatment and survival in women with breast cancer. *Br J Cancer* 96, 836-40 (2007).

36. Louwman, W.J., Aarts, M.J., Houterman, S., van Lenthe, F.J., Coebergh, J.W. & Janssen-Heijnen, M.L. A 50% higher prevalence of life-shortening chronic conditions among cancer patients with low socioeconomic status. *Br J Cancer* 103, 1742-1748 (2010).

37. Katz, S.J., Lantz, P.M., Janz, N.K., Fagerlin, A., Schwartz, K., Liu, L., Deapen, D., Salem, B., Lakhani, I. & Morrow, M. Patient involvement in surgery treatment decisions for breast cancer. *J Clin Oncol* 23, 5526-33 (2005).

38. National Network of Libraries of Medicine. in Health Literacy (ed. Glasman, P.) (Bethesda, 2010).

39. Beeken, R.J., Simon, A.E., von Wagner, C., Whitaker, K.L. & Wardle, J. Cancer fatalism: deterring early presentation and increasing social inequalities? *Cancer Epidemiol Biomarkers Prev* 20, 2127-31 (2011).

40. Levinson, W., Kao, A., Kuby, A. & Thisted, R.A. Not all patients want to participate in decision making. A national study of public preferences. *J Gen Intern Med* 20, 531-5 (2005).

41. Galobardes, B., Shaw, M., Lawlor, D.A., Lynch, J.W. & Davey Smith, G. Indicators of socioeconomic position (part 1). *J Epidemiol Community Health* 60, 7-12 (2006).

5

42. Fleischer, N.L., Diez Roux, A.V. & Hubbard, A.E. Inequalities in body mass index and smoking behavior in 70 countries: evidence for a social transition in chronic disease risk. *Am J Epidemiol* 175, 167-76 (2012).

43. Bos, V., Kunst, A.E. & Mackenbach, J. in Verslag aan de Programmacommissie Sociaal-economische gezondheidsverschillen II (Instituut Maatschappelijke Gezondheidszorg, Erasmus Universiteit, Rotterdam, 2000).

44. Bos, V., Kunst, A.E. & Mackenbach, J.P. in Sociaal-economische gezondheidsverschillen: Van verklaren naar verkleinen (ed. Stronks, K.) 8-20 (Zon/MW, Den Haag, 2001).

45. Smits, J., Keij, I. & Westert, G.P. Effecten van sociaal-economische status van kleine, middelgrote en grote geografische eenheden op de sterfte [in Dutch]. *Maandstatistiek van de bevolking* 11, 4-10 (2001).

46. Berkman, L.F. & Macintyre, S. The measurement of social class in health studies: old measures and new formulations. *IARC Sci Publ*, 51-64 (1997).

47. Mackenbach, J.P., Looman, C.W. & van der Meer, J.B. Differences in the misreporting of chronic conditions, by level of education: the effect on inequalities in prevalence rates. *Am J Public Health* 86, 706-11 (1996).

48. Coleman, M.P., Quaresma, M., Berrino, F., Lutz, J.M., De Angelis, R., Capocaccia, R., Baili, P., Rachet, B., Gatta, G., Hakulinen, T., Micheli, A., Sant, M., Weir, H.K., Elwood, J.M., Tsukuma, H., Koifman, S., GA, E.S., Francisci, S., Santaquilani, M., Verdecchia, A., Storm, H.H. & Young, J.L. Cancer survival in five continents: a worldwide population-based study (CONCORD). *Lancet Oncol* 9, 730-56 (2008).

49. Siegel, R., Ward, E., Brawley, O. & Jemal, A. Cancer statistics, 2011: the impact of eliminating socioeconomic and racial disparities on premature cancer deaths. *CA Cancer J Clin* 61, 212-36 (2011).

50. Kelly-Irving, M., Delpierre, C., Schieber, A.C., Lepage, B., Rolland, C., Afrite, A., Pascal, J., Cases, C., Lombrail, P. & Lang, T. Do general practitioners overestimate the health of their patients with lower education? *Soc Sci Med* 73, 1416-21 (2011).

51. Dutch Cancer Society. in Zou het kanker zijn? [in Dutch] (2011).

52. Statistics Netherlands. in Socioeconomic health inequalities in the Netherlands (2005/2008): differences in life expectancies (2012).

53. Council for Public Health and Health Care. in Preventie van welvaartsziekten - effectief en efficiënt georganiseerd. [in Dutch] (2011).

54. Michie, S., Jochelson, K., Markham, W.A. & Bridle, C. Low-income groups and behaviour change interventions: a review of intervention content, effectiveness and theoretical frameworks. *J Epidemiol Community Health* 63, 610-22 (2009).

55. Blokstra, A., Vissink, P., Venmans, L.M.A.J., Holleman, P., Van der Schouw, Y.T., Smit, H.A. & Verschuren, W.M.M. in [Nederland de Maat Genomen, 2009-2010. Monitoring van risicofactoren in de algemene bevolking] (Rijksinstituut voor Volksgezondheid en Milieu (RIVM), 2011).

56. Nagelhout, G., De Korte, D., Van der Meer, R., Zeegers, T., Van Gelder, B. & Willemsen, M.C. in Sociaaleconomische verschillen in roken in Nederland 1988-2010 [in Dutch] (STIVORO, 2011).

57. Kunst, A. Socioeconomic inequalities in mortality and health in the Netherlands [in Dutch]. *Bevolkingstrends* 1e kwartaal, 34-44 (2007).

58. Droomers, M. in Socioeconomic Differences in Health Related Behaviour (Erasmus University Rotterdam, Rotterdam, 2001).

59. World Cancer Research Fund. in Cancer preventability estimates for food, nutrition, body fatness, and physical activity (2012).

60. Dutch Cancer Society.

61. Menvielle, G., Soerjomataram, I., de Vries, E., Engholm, G., Barendregt, J.J., Coebergh, J.W. & Kunst, A.E. Scenarios of future lung cancer incidence by educational level: modelling study in Denmark. *European Journal of Cancer* 46, 2625-32 (2010).

62. Molina-Barcelo, A., Salas Trejo, D., Peiro-Perez, R. & Malaga Lopez, A. To participate or not? Giving voice to gender and socio-economic differences in colorectal cancer screening programmes. *Eur J Cancer Care (Engl)* 20, 669-78 (2011).

5

63. van de Poll-Franse, L.V., Horevoorts, N., van Eenbergen, M., Denollet, J., Roukema, J.A., Aaronson, N.K., Vingerhoets, A., Coebergh, J.W., de Vries, J., Essink-Bot, M.L. & Mols, F. The Patient Reported Outcomes Following Initial treatment and Long term Evaluation of Survivorship registry: scope, rationale and design of an infrastructure for the study of physical and psychosocial outcomes in cancer survivorship cohorts. *Eur J Cancer* 47, 2188-94 (2011).

5

DECISION
ROLE
CURATIVE
SINCE 1990
data
RECOGNISING
OUTCOME
BRACHYTHERAPY
DETERMINANTS
CATEGORY
material resources
HOUSING
health seeking behaviour
METASTASIS
CONTRIBUTION
RADIOTHERAPY
COVERAGE
INTERVAL CANCER
CHARLSON
socioeconomic position
estimated
annual
percent
change
axillary
staging
EAPC
SMOKING
statistical
STUDIES
GP
central nervous system
HOSPITAL
staging
socioeconomic status
DISCUSS
lifestyle
dementia
intelligence
education
hazard
ratio
RISK FACTORS
DIAGNOSIS
SEP
Eindhoven Cancer Registry
Comprehensive Cancer Centre South
stage
HORMONAL THERAPY
VISITS
ATTENDANCE
EXPLANATION
SOCIAL SUPPORT
HYPERTENSION
diagnostics
mastectomy
distribution
CARDIOVASCULAR DISEASE
therapy
HIGH
MENTAL
ADVANCED
FEAR
colorectal
UPBRINGING
ENVIRONMENT
MAMMOGRAPHY
incidence
prostatectomy
p-value
QUESTIONNAIRE
HEALTH BEHAVIOUR
SF-36
GLOBE
NEIGHBOURHOOD
EXPOSURE
LOW
value of housing
PHYSICAL
socioeconomic
SOCIOEC
occupation
ALCOHOL CONSUMPTION
INTERMEDIATE
TUBERCULOSIS
physical activity
REVIEW
colorectal
cancer
screening
VARIATION
comorbidities
CHEMORADIATION
INVITATION
INVASIVE
numbers
CONTACTS
gap
concomitant disease
LOCALISED
logistic
regression
ACCESS TO CARE
CONSULTATION
ASSETS
PSA
income
WORK
percentages
SCREEN-DETECTED TUMOUR
THE NETHERLANDS
HEALTH INSURANCE
health awareness
HOUSEHOLD
search
DETECTIO

Summary

survival
opportunistic screening
sentinel node biopsy
understanding
GENETICS
mortality
selection
OESOPHAGUS
CHARACTERISTICS
option
HEALTH LITERACY
KNOWLEDGE
PREFERENCES
rates
screening
watchful waiting
LUNG
HR
BREAST CONSERVING SURGERY
INEQUALITIES
SOCIAL STRATIFICATIONS
INFORMATION
lymph node dissection
SEX
TUMOURS
postal code
PATIENTS
CONOMIC
CANCER
NETHERLANDS CANCER REGISTRY
BCC
DEPRIVATION
PROGNOSIS
CHEMOTHERAPY
COPD
TNM
MELANOMA
quality of life
opportunities
95%CI
IKZ
breast conserving surgery
RISK
CCCS
studies
SUNNY
WARNING SIGNS
MONITOR
HETEROGENEITY
analyses
referral
PROSTATE
tumour size
TRENDS
chances
social class
chi-square test
BREAST
(IN)EVITABILITY
odds ratio
OR
palliative
Cox regression
REPORTING SYMPTOMS
AGE
N
population-based
disparities

Our democratic society is characterised by heterogeneity due to unequal distribution of knowledge, intelligence, material and other resources among the inhabitants. Classification of persons into groups based on shared socioeconomic conditions leads to social stratification. This relative position on the social hierarchy is referred to by 'socioeconomic status' (SES) or socioeconomic position.

People with a lower SES generally have poorer health status and higher mortality than people from higher socioeconomic groups. The inverse association between SES and health is found for nearly all measures of SES and nearly all health outcomes. In this thesis the associations of SES and the determinants of cancer risk, detection and outcome were addressed, with the aims to explore:
1. The association of SES and the incidence and (determinants of) <u>detection</u> of cancer in a large population-based setting
2. The association of SES and the <u>outcomes</u> of cancer in terms of (trends in) staging, treatment, survival, and long-term health-related quality of life
3. Entry points for interventions to reduce the socioeconomic inequalities as assessed via aforementioned studies.

Cancer detection and outcome and the associated factors have a complex interplay (see Figure 1 in Chapter 5). Cancer detection is, amongst others, related to lifestyle and its associated cancer risk, health awareness and health literacy, health seeking behaviour, presence of comorbidities and attendance to screening programmes. Most of these factors are also involved in cancer detection. People from different social strata have different exposures to these associations, e.g. levels of physical activity were reduced in low SES, which may result in increased risks of cancer. The Eindhoven Cancer Registry and the Netherlands Cancer Registry were used as the main data sources.

Cancer detection in relation to socioeconomic status
Incidence
In the Southern Netherlands, those with low SES had highest incidence rates of most common cancers (**chapters 2, 3.1, 3.2**), probably due to socioeconomic differences in lifestyle, with generally higher prevalence of smoking, lower levels of physical activity and poorer diet in low SES. However, prostate cancer was more common among high SES. PSA testing, which is more frequently used among high SES, is probably responsible for the strong increase among high SES. This was confirmed by the highest proportion of opportunistic PSA-detected patients among high SES (**chapter 4.3**). Also basal cell carcinomas (BCCs) and melanomas were more common in high SES. These high incidence rates likely result from sunny holidays, which were first only affordable for those with high SES. These socioeconomic patterns and associated cancer risks may change over time.

Stage at diagnosis
Cancer risk is affected by, among others, health awareness. Health awareness is generally better among high SES groups and will often lead to healthier lifestyle and more health seeking behaviour. This not only reduces risks of most cancers, it also enhances early detection. In case of prostate cancer, it seems likely that PSA testing is responsible for the

strong increase among high SES, because the proportion of opportunistic PSA-detected patients was indeed highest in high SES (**chapter 4.3**). Also the stage of disease was more favourable in high SES patients with prostate, breast and oesophageal cancer (**chapters 3.3, 4.2, 4.3, 4.4**). It seems likely that part of the socioeconomic differences in stage distribution result from more active health seeking behaviour in high SES, and thus earlier detection.

Attendance to screening programmes

Mass cancer screening programmes aim to advance cancer detection and thereby to reduce cancer mortality rates. In the Netherlands, women aged 50-75 are biennially invited for mammography screening. Despite the absence of financial barriers for participation in this mass-screening programme for breast cancer, attendance rates were slightly higher in high SES (87% compared to 79% in low SES) between 1998 and 2005 (**chapter 3.3**). Furthermore, more advanced stage in low SES was observed independently of participation in the screening programme. Thus, even in presence of a free cancer screening programme with high participation rates, small socioeconomic inequalities in attendance, stage and thereby prognosis still to exist.

Comorbidities at diagnosis

Presence of comorbidities is likely to affect cancer detection as well. These concomitant diseases may both hinder (e.g. because of similar complaints) and accelerate (e.g. because of more extensive diagnostic procedures) cancer detection. We found that the prevalence of comorbidities was 50% higher among low SES patients (**chapter 4.1**). In addition, we observed more advanced stage at diagnosis for prostate, oesophageal and breast cancer (**chapter 3.3, 4.2, 4.3, 4.4**). Even small stage differences among screen-detected breast cancers were present. This suggests that the presence of comorbidities may also delay cancer detection. In our study on oesophageal cancer it seemed likely that the comorbidities contributed to the more advanced stage at diagnosis in low SES. In case of prostate and breast cancer, comorbidities and (opportunistic) screening were probably both responsible for socioeconomic differences in stage distribution. Thus, the role of comorbidities in hindering or accelerating cancer detection remains to be explored.

Cancer outcome in relation to socioeconomic status

Therapy

Treatment selection according to SES was found in colorectal, prostate, oesophageal and breast cancer patients (**chapters 2, 4.2, 4.3, 4.4**). In general, high SES patients were more likely to receive curative treatment and more often underwent invasive therapies. In early stage breast cancer, women with low SES had higher rates of mastectomy, while higher rates of breast conserving surgery were reported in high SES women. Based on higher prevalence of comorbidities in low SES patients, breast conserving surgery rates were expected to be higher among low SES patients. No data were available for presence of comorbidities. More active involvement of the patient in decision making has led to higher mastectomy rates in a foreign study, but the effects in the Netherlands remain to be investigated. Furthermore, high SES breast cancer patients were less likely to receive sentinel node biopsy or lymph node dissection. This could not be fully explained by age, stage and year of diagnosis (**chapter 4.2**).

In prostate cancer we observed that the introduction of new therapies was related to SES. Brachytherapy for patients with localised disease (especially at 70-74 years of age) occurred first in patients with high SES and after several years it became more common in low SES patients. Presence of comorbidities hardly affected this pattern, suggesting that not performance status but patients' preferences led to these high rates of brachytherapy. Thus, treatment selection was related to SES as we reported for colorectal, breast, prostate and oesophageal cancer. We expected both stage at diagnosis and comorbidities to affect treatment selection and although it did for some tumours, not all of the differences could be explained. The exact role of SES and patients' search for information, information provided by the doctors, capacity to understand medical information, patients' active involvement in decision making and patients' preferences remains to be explored.

Survival

We observed highest survival rates for patients with high SES with prostate, oesophageal, colorectal, and breast cancer (Table 1, c**hapters 2, 4.1, 4.3, 4.4, 4.5**). These socioeconomic differences in survival from cancer could not be fully ascribed to differences in treatment selection, comorbidities, alcohol consumption, physical activity or smoking, and stage at diagnosis.

This suggests that the role of SES-related patients' preferences and an individuals' capacity to obtain, process and understand basic health information and services needed to make appropriate health decisions ("Health literacy") also plays a role. Low health literacy may lead to treatment options that are not fully understood, and therefore some patients may not receive the most appropriate treatment for their medical condition. Therefore more clear and adapted communication by health care providers will be useful in reducing these survival inequalities, also because low SES previously reported higher fear of reporting symptoms to their doctor than high SES. In contrast, some patients do not want to be very involved in decision making and these preferences should be taken into account in the decision making process as well.

Health-related quality of life

Long-term prostate cancer survivors with high SES reported better mental health than those with low SES 5-10 years after diagnosis (**chapter 4.6**). In these patients comorbidity was more important than SES, suggesting that long-term health outcomes of patients with low SES may be improved by paying extra attention to their comorbidities. Thus, extra attention towards adapted communication and presence of concomitant conditions may improve the relatively poor position in terms of cancer detection and outcome of low SES patients.

Conclusion

To conclude, cancer risk, detection and outcome were differently related to SES in the Netherlands, a country with *supposedly* equally accessible health care for all inhabitants. These SES-differences were consistent, with generally small absolute differences which seem hard to influence and which may even seem inevitable. Therefore one should strive for an optimal situation, in which the GPs and their nurse practitioners could play an important

role in improving access to care by improving cancer awareness, promoting healthy lifestyle and by patient-specific provision of information.

Samenvatting

opportunistic screening
survival
sentinel node biopsy
understanding
GENETICS
mortality
INEQUALITIES
HEALTH LITERACY
selection OESOPHAGUS CHARACTERISTICS
option
KNOWLEDGE
PREFERENCES
rates
screening
watchful waiting
LUNG HR BREAST CONSERVING SURGERY
SOCIAL STRATIFICATIONS
INFORMATION
CANCER
ECONOMIC
lymph node dissection
SEX
TUMOURS
PATIENTS
NETHERLANDS CANCER REGISTRY
postal code
MELANOMA
BCC
quality of life
DEPRIVATION
PROGNOSIS
CHEMOTHERAPY
COPD
TNM
CCCS
studies
SUNNY
opportunities
95%CI
IKZ
breast conserving surgery
RISK
HETEROGENEITY
analyses
referral
PROSTATE
WARNING SIGNS
chances
social class
chi-square test
BREAST
tumour size
TRENDS
MONITOR
palliative
Cox regression
AGE
(IN)EVITABILITY
odds ratio
OR
REPORTING SYMPTOMS
N
population-based
disparities

Iedereen is uniek, wordt gezegd. En dat heeft ook zijn keerzijde. Kennis, intelligentie en vermogen zijn in onze samenleving ongelijk verdeeld. Mensen met veel kennis, intelligentie en geld staan hoog op de sociale ladder, zij hebben een hoge sociaaleconomische status. De mensen die lager op de sociale ladder staan, hebben over het algemeen een slechtere gezondheid en een hogere sterfte vergeleken met mensen met een hogere sociaaleconomische status. Dit omgekeerd verband tussen sociaaleconomische status en gezondheid is in eerder onderzoek gevonden voor veel ziekten, zoals suikerziekte en hart- en vaatziekten. In dit proefschrift wordt de relatie tussen sociaaleconomische status en het risico, de ontdekking, behandeling en prognose van kanker onderzocht. Daarbij wilden we inzicht krijgen in:

1. Het verband tussen enerzijds sociaaleconomische status en de incidentie (het vóórkomen) van kanker en anderzijds de factoren die een rol spelen bij de ontdekking van kanker.
2. Het verband tussen sociaaleconomische status en de behandeling, overleving en kwaliteit van leven van kankerpatiënten.
3. Mogelijke aangrijpingspunten om de situatie voor mensen met een lage sociaaleconomische status te verbeteren.

De detectie van kanker (1) en de uitkomsten van kankerbehandelingen (2) zijn afhankelijk van veel factoren met daartussen een ingewikkelde wisselwerking. Zo zijn kankerdetectie en kankeruitkomst allebei gerelateerd aan de aanwezigheid van andere ziekten (comorbiditeit). Voor mensen uit diverse sociaaleconomische groepen hangen deze factoren bovendien anders met elkaar samen. Mensen met een lage sociaaleconomische status hebben bijvoorbeeld vaker te maken met comorbiditeit die ook invloed heeft op de overlevingskansen.

Om deze effecten te bestuderen, hebben we gebruik gemaakt van gegevens van de Nederlandse Kankerregistratie en de Eindhovense Kankerregistratie, uit de periode 1990 – 2008. De resultaten van de onderzoeken hebben we opgesplitst naar 1. risico en opsporing en 2. behandeling, overleving en kwaliteit van leven.

1. Het risico op kanker en de opsporing er van in relatie tot sociaaleconomische status
Vóórkomen van kanker

Uit dit onderdeel van de studie komt naar voren dat in Zuid-Nederland in de periode tussen 1996 en 2008 diverse vormen van kanker het vaakste voorkwamen bij mensen met een lage sociaaleconomische status. Zij hadden dus de hoogste incidentie. De oorzaak hiervoor ligt waarschijnlijk bij verschillen in de leefstijl, mensen met een lage sociaaleconomische status roken vaker, bewegen minder en eten vaak ongezond. Bij prostaatkanker vonden we juist het omgekeerde: deze ziekte kwam frequenter voor bij mensen met een hoge sociaaleconomische status. Dit lijkt te worden veroorzaakt door het feit dat mannen met een hoge sociaaleconomische status vaker een PSA-test laten uitvoeren; een test waarmee prostaatkanker kan worden opgespoord. Ook bepaalde vormen van huidkanker, de basaalcelcarcinomen en melanomen, kwamen juist vaker voor bij mensen met een hoge sociaaleconomische status. Bekend is dat overmatig zonnen (zonvakanties) de kans op huidkanker vergroot. Aangezien deze vakanties in eerste instantie alleen betaald

konden worden door mensen met een hoge sociaaleconomische status, kwam huidkanker aanvankelijk vooral voor bij mensen met een hoge sociaaleconomische status. Verwacht kan worden dat de incidentie van deze vormen van huidkanker bij mensen met een lage sociaaleconomische status de komende jaren zal toenemen. Met andere woorden: de invloed van sociaaleconomische verschillen op het krijgen van kanker zijn onderhevig aan veranderingen in de tijd.

Tumorstadium bij diagnose

Iemand met een hoge sociaaleconomische status is zich doorgaans beter bewust van het belang van een goede gezondheid, leeft gezonder en bezoekt vaker en eerder de huisarts bij klachten of symptomen. Hierdoor neemt de kans op het krijgen van kanker af en worden tumoren in een eerder stadium opgespoord. Een voorbeeld hiervan is de introductie van de PSA-test, die leidde tot een sterke stijging van prostaatkanker onder mannen met een hoge sociaaleconomische status. Ook waren bij borstkanker en slokdarmkanker de tumoren veelal kleiner bij patiënten met een hoge sociaaleconomische status op het moment van diagnose in vergelijking met mensen met een lage sociaaleconomische status.

Deelname bij bevolkingsonderzoek borstkanker

Bevolkingsonderzoeken voor kanker zijn opgezet om tumoren in een eerder stadium op te sporen en om zo de sterfte door kanker te verminderen. In Nederland worden vrouwen in de leeftijdsgroep 50-75 jaar elke twee jaar uitgenodigd voor een mammogram. Hoewel deelname aan de borstkankerscreening gratis is, zagen we dat tussen 1998 en 2005 vrouwen met een hoge SES vaker deelnamen aan het bevolkingsonderzoek dan vrouwen met een lage SES (87% ten opzichte van 79%). Verder zagen we dat patiënten met een lage sociaaleconomische status frequenter een grotere tumor hadden, ongeacht of zij wel of niet hadden deelgenomen aan het bevolkingsonderzoek voor borstkanker.

Comorbiditeit bij diagnose

Ook de aanwezigheid van comorbiditeit beïnvloedt de opsporing van kanker. Het kan zowel de opsporing vertragen door bijvoorbeeld vergelijkbare klachten, als versnellen door bijvoorbeeld uitgebreidere diagnostische onderzoeken al is die rol nog niet helemaal duidelijk. We vonden dat kankerpatiënten met een lage sociaaleconomische status 50% meer comorbiditeiten hadden. Uit onze studies blijkt overigens dat comorbiditeiten bijdroegen aan de verschillen in overleving tussen de sociaaleconomische groepen.

2. Behandeling, overleving en kwaliteit van leven bij kanker in relatie tot sociaaleconomische status

Therapie

Wat betreft de uitkomsten van behandeling werden tussen mensen met een lage en hoge sociaaleconomische status verschillen gevonden voor dikke darm-, prostaat-, slokdarm- en borstkanker. Over het algemeen kregen patiënten met een hoge sociaaleconomische status vaker een ingrijpende behandeling en was de behandeling vaker gericht op genezing. We hadden verwacht dat tumorgrootte en comorbiditeiten de behandelingskeuzes zouden beïnvloeden. Dat deden ze inderdaad voor een aantal tumoren, maar niet

alle behandelverschillen konden hiermee worden verklaard. Zo moet de rol van de sociaaleconomische status van de patiënt, zijn betrokkenheid bij de keuze voor een therapie en zijn voorkeuren, maar ook de zoektocht van de patiënt naar informatie, de informatie die artsen verstrekken en de mate waarin een patiënt deze medische informatie kan begrijpen, nog worden onderzocht.

Bij prostaatkanker zagen we dat de introductie van een nieuwe behandeling samenhing met de sociaaleconomische status van de patiënt. Brachytherapie (inwendige radiotherapie) voor patiënten met een relatief kleine tumor werd namelijk in eerste instantie vooral toegepast bij patiënten met een hoge sociaaleconomische status, pas een paar jaar later ook bij patiënten met een lage sociaaleconomische status. Het maakte hierbij nauwelijks verschil of iemand daarnaast ook comorbiditeiten had. Het lijkt er op dat niet de gezondheid van de patiënt, maar de persoonlijke voorkeuren van de patiënt geleid hebben tot het hoge gebruik van brachytherapie in de groep patiënten met een hoge sociaaleconomische status.

Overleving
De overleving was het hoogste voor patiënten met een hoge sociaaleconomische status met prostaat-, slokdarm-, dikkedarm-, long- en borstkanker. Dit kon niet volledig worden verklaard door verschillen in behandeling, comorbiditeiten, alcoholconsumptie, lichaamsbeweging, roken of tumorstadium bij diagnose. Mogelijk is er een rol weggelegd voor onder andere sociaaleconomische verschillen in het omgaan met gezondheidsvaardigheden. Hieronder verstaan we de mate waarin een patiënt in staat is om te gaan met informatie over gezondheid, ziekte en zorg (health literacy).

Kwaliteit van leven
Vijf tot tien jaar na diagnose hadden prostaatkankerpatiënten met een hoge sociaaleconomische status een betere mentale kwaliteit van leven dan patiënten met een lage sociaaleconomische status. De kwaliteit van leven bij de prostaatkankerpatiënten werd meer bepaald door comorbiditeit dan door de sociaaleconomische status. Daaruit kan worden afgeleid dat de gezondheid van prostaatkankerpatiënten met een lage sociaaleconomische status op langere termijn kan worden verbeterd door extra aandacht te schenken aan comorbiditeiten.

Conclusie
Concluderend kunnen we stellen dat het risico op kanker, de opsporing en de uitkomst van kankerbehandeling gedurende de onderzochte periode op verschillende wijze samenhingen met de sociaaleconomische status van patiënten in Nederland. Deze sociaaleconomische verschillen waren consistent met over het algemeen kleine, absolute verschillen die lastig te veranderen lijken te zijn. Een optimale situatie zou moeten worden nagestreefd, waarbij huisartsen en praktijkondersteuners een belangrijke rol kunnen spelen in het verbeteren van de toegankelijkheid van zorg. Zij kunnen mensen bewuster te maken van kanker, de behandelmogelijkheden, een gezonde leefstijl te stimuleren en informatie op maat aan de patiënt.

DZIĘKUJĘ

DÍKY

OBRIGADO

esker

DANKON

GRACIAS

PALDIES

MULŢUMIRI

BEDANKT

tack ska du ha

THANKS

SHUKRANI

FALËNDERIM

KÖSZÖNÖM

teşekkürler

GRATIAS

DANKON

DZIĘKUJĘ

go raibh maith agat

go raibh maith agat

terima kasih

takk

KIITOS

shukrani

OBRIGADO

VD'AKA

tänan

HVALA

tack ska du ha

DIOLCH

salamat

go raibh maith agat

dzięki

tak

obrigado

kiitos

gracias

FALËNDERIM

SHUKRANI

merci

GRAZZI

DANKE

danke

gracias

köszönöm

ESKER

TERIMA KASIH

TERIMA KASIH

TACK

TEŞEKKÜRLER

DANKON

KÖSZÖNÖM

Díky

shukrani

OBRIGADO

paldies

KIITOS

DIOLCH

gratias

diolch

VD'AKA

mèsi

MULŢUMIRI

TEŞEKKÜRLER

MÈSI

TACK

THANKS

DIOLCH

BEDANKT

mulţumiri

DZIĘKUJĘ

dziękuję

danke

tack ska du ha

KÖSZÖNÖM

FALËNDERIM

mèsi

grazas

GRAZZI

SHUKRANI

PALDIES

THANKS

TACK

díky

OBRIGADO

KÖSZÖNÖM

tack ska du ha

MULŢUMIRI

FALËNDERIM

GRAZI

DZIĘKUJĘ

grazas

GO RAIBH MAITH AGAT

TACK

vd'aka

GO RAIBH MAITH AGAT

TERIMA KASIH

KÖSZÖNÖM

tack ska du ha

MULŢUMIRI

TEŞEKKÜRLE

Dankwoord

terima kasih

merci

tack ska du ha

falënderim

TÄNAN

köszönöm

FALËNDERIM

OBRIGADO

dankon

SALAMAT

DIOLCH

vd'aka

díky

SHUKRANI

mulţumiri

GRATIAS

paldies

TAK

TERIMA KASIH

FALËNDERIM

vd'aka

gratias

SHUKRANI

TAKK

HVALA

dankon

BEDANKT

THANKS

GO RAIBH MAITH AGAT

DÍKY

SALAMAT

GRAZAS

TACK

KIITOS

DANKIE

grazas

mulţumiri

MÈSI

TACK

takk

danke

GRAZI

hvala

hvala

mèsi

ESKER

DIOLCH

go raibh maith agat

DZIĘKUJĘ

gracias

bedankt

tänan

gracias

DZIĘKUJĘ

thanks

PALDIES

köszönöm

KIITOS

terima

obrigado

TACK SKA DU HA

TAK

GRAZZI

kasih

teşekkürler

dzięki

ER

DANKWOORD

En dan nu waarschijnlijk het meest gelezen hoofdstuk van mijn proefschrift. Er zijn veel mensen die ik heel graag wil bedanken en ik ben blij dat ik dat hier kan doen.

Allereerst noem ik mijn promotor prof. dr. Jan Willem Coebergh, dankzij hem kon ik dit promotieonderzoek doen. Jan Willem, overleg met jou leverde altijd weer nieuwe inzichten op. Je zei regelmatig 'kijk nog even naar dit of dat' en vaak had je gelijk met je onderbuikgevoel. Ik heb veel van je geleerd, niet alleen over kankeronderzoek maar ook over de meest uiteenlopende andere zaken. Wat was nu ook alweer het nut van op één been staan tijdens het tandenpoetsen? Bedankt!

Ook mijn copromotor dr. ir. Marieke Louwman verdient een plaatsje in dit dankwoord. Marieke, jouw hulp bij mijn onderzoek was onmisbaar. Je hebt me vaak geholpen om de rode draad weer te zien. Jouw pragmatische blik zorgde dat ik weer met frisse blik kon focussen. Maar ook onze gedeelde liefde voor het buitenleven en in het bijzonder de schapen waren vaak onderwerp van gesprek. Dank voor je copromotorschap.

De leden van de leescommissie, dr. Frank van Lenthe, prof. dr. Victor Pop, en prof. dr. Karin van der Rijt, wil ik hartelijk danken voor het beoordelen van mijn proefschrift. Uiteraard ben ik ook de andere leden van de promotiecommissie dank verschuldigd voor de tijd en energie die ze in mijn proefschrift hebben gestoken. Special thanks to Dr. Sanne Dalton for her visit to the Netherlands to take place in my defence commission.

Ook kunnen de namen van de coauteurs niet ontbreken. Zij hebben mij voorzien van kritisch commentaar op de artikelen die in dit proefschrift opgenomen zijn. Ik kijk terug op een prettige samenwerking, Maaike van der Aa, Jantine van Baal, Esther Bastiaannet, Pauline Bus, Geert-Jan Creemers, Lucien Duijm, Victoria Hamelinck, Simone van Hattem, Maryska Janssen-Heijnen, Carlijn Kamphuis, Evert Koldewijn, Anton Kunst, Valery Lemmens, Frank van Lenthe, Gerrit Jan Liefers, Caspar Looman, Johan Mackenbach, Floor Mols, Martino Neumann, Grard Nieuwenhuijzen, Tamar Nijsten, Martijn van Ooijen, Lonneke van de Poll-Franse, Philip Poortmans, Peter Siersema, Melissa Thong en Adri Voogd, Esther de Vries. Dankzij jullie zijn mijn artikelen beter geworden.

Marlies van Hoof, erg bedankt dat je de cover en het binnenwerk voor dit boekje hebt ontworpen. Ik ben er erg blij mee.

Mevrouw Bieger en Nicole Horevoorts hebben mijn manuscripten gecorrigeerd, veel dank daarvoor.

Zonder de bijzonder waardevolle gegevens uit de kankerregistratie waren mijn en vele andere studies onmogelijk. Ik ben dan ook de registratiemedewerkers heel dankbaar voor de precisie en accuraatheid waarmee zij de gegevens verzamelen.

Erica en Gitty, jullie weten zo enorm veel over de kankerregistratie, ik ben blij dat ik jullie zo vaak heb mogen storen met al mijn vragen. Maar gelukkig ook voor een gezellig praatje. Bedankt!

IKZ-directeur dr. Janny van den Eijnden-van Raaij ben ik dankbaar voor de mogelijkheden die zij mij heeft geboden voor het doen van dit onderzoek. Het is erg fijn om een directeur te hebben die onderzoek zo'n warm hart toedraagt!

Mede dankzij mijn (vroegere) collega's ga ik met veel plezier naar mijn werk. Adri, Bregje, Corina, Erna, Esther, Felice, Floor, Liza, Kim, Lonneke, Marieke, Marinka, Marjolein, Maryska, Melissa, Mijke, Nicole E, Nicole H, Nienke, Olga, Pauline, Rob, Sandra, Saskia, Simone, Valery en Yvette, dank voor alle gezelligheid, potten thee en het snoep (!). Jullie zijn stuk voor stuk fijne collega's! Jan bedankt voor je commentaar op de Nederlandse samenvatting en Liza bedankt voor je tips voor dit dankwoord.

Rob, ik vind het fijn dat je vandaag naast me wilt staan. Bedankt voor alle fijne en leuke gesprekken over werk, maar zeker ook over allerlei andere zaken. We houden allebei van honden, misschien moeten we Neo en Fons maar eens kennis laten maken? Bedankt ook dat ik je zo vaak heb mogen lastigvallen met allerlei vragen over promoveren. Ik hoop dat mijn verdediging net zo goed zal gaan als die van jou!

Lieve familie en vrienden, nu zijn jullie aan de beurt. Hoewel jullie je er misschien niet echt bewust van waren, hebben jullie een belangrijke bijdrage geleverd aan dit proefschrift. Want naast werk is er nog zo veel meer! Ik heb de momenten van ontspanning en voor de interesse in mijn onderzoek erg gewaardeerd. Mijn voormalige "collega's" Christ, Anita en Tonny, de zaterdagen in de winkel waren een fijne afwisseling op mijn onderzoek. Bedankt voor alle gezelligheid en kopjes koffie (met gebak!). Mijn studievriendinnen Antje, Ellen en Willeke, ik vind het erg leuk dat we nog steeds regelmatig daten. Ik kijk al uit naar de volgende date! Antje, je wilt het eigenlijk niet, maar toch ga ik je nog een keer noemen om je te bedanken voor je waardevolle commentaar op dit dankwoord en de samenvatting. Noortje, jij snapt precies welke frustraties en stress bij promoveren horen. Bedankt voor al je support. Nog even en jij bent aan de beurt, succes! Sanne bedankt voor de wekelijkse gezelligheid, ik hoop dat we nog veel kilometers samen mogen wandelen. Het Lónse clubje, Anke, Lotte, Marjolijn, Marlies, Sandra, Sofie, Dirk, Mario, Martijn, Pierre, René en Robert, bedankt voor onze fijne vriendschap, die is erg waardevol voor mij.

Lieve Patricia, lief Patje, ik ben blij dat je vandaag mijn paranimf wilt zijn. We zijn vriendinnen sinds de brugklas en ik hoop dat dat nog lang zo zal blijven. Lieve Juul, Roos, John, Anouk, Pauline, Stefan, ik ben blij met jullie als schoonfamilie. Fijn dat ik op jullie interesse en steun kan rekenen.

Mijn lieve broertjes, Toon en Thijs, zusje Els, de "aanhang" Eva, Annet, Jos, en nichtje Emmy wil ik danken voor alle warmte en het fijne contact dat we hebben. Toon, Eva en Emmy, wat jammer dat we niet meer zomaar even op de koffie kunnen komen. We komen jullie snel weer opzoeken, want ook Fons mist jullie (of eigenlijk vooral zijn speelmaatje Patrick). Pap en mam, lieve pap en mam, bedankt dat voor alle goede zorgen en steun. Jullie hebben me

de vrijheid en mogelijkheid gegeven om te gaan doen wat ik graag wilde doen. Jullie staan altijd voor Frank en mij klaar en dat geeft een heel warm gevoel.

Ik kan hier niet alle familieleden, vrienden en kennissen noemen die mijn leven zo prettig maken. Maar ik ben vooral blij dat het er zoveel zijn die me omringen.

En dan ben jij Frank. Als laatste, juist omdat je de belangrijkste bent. Bedankt voor alle keren dat je me zei: "Maak je toch niet zo druk". We hebben het mooi samen. Je bent mijn maatje, wat ben ik blij met jou!

DECISION
CURATIVE
ROLE
SINCE 1990
data
BRACHYTHERAPY
DETERMINANTS
CATEGORY
HOUSING
RECOGNISING
OUTCOME
INTERVAL CANCER
material resources
CHARLSON
health seeking behaviour
METASTASIS
CONTRIBUTION
COVERAGE
estimated annual percent change
staging
axillary
EAPC
socioeconomic position
RADIOTHERAPY
GP
SMOKING
statistical
STUDIES
staging
socioeconomic status
lifestyle
central nervous system
HOSPITAL
DISCUSS
Eindhoven Cancer Registry
dementia
intelligence
education
hazard ratio
RISK FACTORS
DIAGNOSIS
SEP
VISITS
ATTENDANCE
EXPLANATION
SOCIAL SUPPORT
HYPERTENSION
mastectomy
diagnostics
distribution
CARDIOVASCULAR DISEASE
Comprehensive Cancer Centre South
stage
HORMONAL THERAPY
ADVANCED
FEAR
colorectal
therapy
HIGH
MENTAL
MAMMOGRAPHY
UPBRINGING
ENVIRONMENT
incidence
prostatectomy
p-value
QUESTIONNAIRE
HEALTH BEHAVIOUR
SF-36
GLOBE
PHYSICAL
SOCIOEC
NEIGHBOURHOOD
EXPOSURE
LOW
value of housing
socioeconomic
occupation
INTERMEDIATE
physical activity
colorectal cancer screening
comorbidities
INVITATION
TUBERCULOSIS
REVIEW
VARIATION
CHEMORADIATION
INVASIVE
numbers
CONTACTS
gap
concomitant disease
logistic regression
ACCESS TO CARE
ASSETS
PSA
LOCALISED
CONSULTATION
income
WORK
percentages
SCREEN-DETECTED TUMOUR
THE NETHERLANDS
HEALTH INSURANCE
health awareness
HOUSEHOLD
search
DETECTIO
ALCOHOL CONSUMPTION

Curriculum Vitae

opportunistic screening
survival
sentinel node biopsy
understanding
GENETICS
mortality
HEALTH LITERACY
selection
OESOPHAGUS
CHARACTERISTICS
KNOWLEDGE
option
INEQUALITIES
rates
screening
PREFERENCES
watchful waiting
LUNG
HR
BREAST CONSERVING SURGERY
SOCIAL STRATIFICATIONS
INFORMATION
lymph node dissection
SEX
TUMOURS
CANCER
PATIENTS
NETHERLANDS CANCER REGISTRY
ECONOMIC
postal code
MELANOMA
BCC
quality of life
DEPRIVATION
opportunities
PROGNOSIS
CHEMOTHERAPY
COPD
breast conserving surgery
TNM
RISK
CCCS
studies
HETEROGENEITY
analyses
referral
SUNNY
95%CI
IKZ
WARNING SIGNS
MONITOR
chances
social class
chi-square test
PROSTATE
tumour size
TRENDS
odds
palliative
Cox regression
BREAST
(IN)EVITABILITY
ratio
OR
REPORTING SYMPTOMS
AGE
N
population-based
disparities

Mieke Aarts werd geboren in Oploo op 30 januari 1984. In 2002 behaalde zij haar VWO-diploma aan Scholengemeenschap Stevensbeek te Stevensbeek. In datzelfde jaar begon zij aan de studie 'Voeding en Gezondheid' aan Wageningen Universiteit. Tijdens haar bachelor-afstudeeropdracht deed zij een literatuurstudie naar de potentiële rol van voeding in de preventie van metabool syndroom via hormonen afgescheiden door de darmen. Voor haar eerste master-afstudeeropdracht onderzocht zij de efficiëntie van metabole routes en de gevolgen voor gewichtshandhaving. Tijdens haar tweede master-afstudeeropdracht ontwikkelde zij een *in vitro* model voor vaatcalcificatie, en onderzocht de effecten op vitamine K_2 en warfarine op osteoblast differentiatie en vaatcalcificatie. Haar stage doorliep ze bij Numico Research (tegenwoordig Danone) en deed ze onderzoek naar het effect van voedingsinterventies op kankercachexie bij dieren. In september 2007 studeerde ze af in de Humane Voeding aan Wageningen Universiteit, richtingen Voedingsfysiologie en Moleculaire Voeding. Sinds december 2007 is Mieke als epidemiologisch onderzoeker in dienst van het Integraal Kankercentrum Zuid (IKZ) te Eindhoven. Middels diverse cursussen heeft zij haar epidemiologische kennis vergroot. Bij het IKZ houdt zij zich naast de studies voor dit proefschrift onder andere ook bezig met studies naar de consumptie van radiotherapie, ethniciteit en kanker, en kwaliteit van zorg bij longkanker. Zij werkte mee aan het rapport dat verscheen ter gelegenheid van het 55-jarig bestaan van de Eindhovense Kankerregistratie en schreef mee aan een hoofdstuk in het Handboek Kanker bij Ouderen. Tevens was zij projectleider van de vernieuwde cijferapplicatie van de Nederlandse Kankerregistratie (www.cijfersoverkanker.nl).

DECISION

CURATIVE

ROLE

SINCE 1990

data

DETERMINANTS

BRACHYTHERAPY

CATEGORY

INTERVAL CANCER

HOUSING

health seeking behaviour

RECOGNISING

METASTASIS

CONTRIBUTION

socioeconomic position

RADIOTHERAPY

COVERAGE

OUTCOME

GP

estimated annual percent change

axillary staging

EAPC

material resources

CHARLSON

DISCUSS

statistical

STUDIES

central nervous system

Comprehensive Cancer Centre South

SMOKING

staging

socioeconomic status

lifestyle

dementia

HOSPITAL

intelligence

education

hazard ratio

Eindhoven Cancer Registry

RISK FACTORS

diagnostics

DIAGNOSIS

SEP

stage

HORMONAL THERAPY

VISITS

ATTENDANCE

EXPLANATION

SOCIAL SUPPORT

HYPERTENSION

mastectomy

distribution

CARDIOVASCULAR DISEASE

therapy

HIGH

MENTAL

ADVANCED

MAMMOGRAPHY

FEAR

colorectal

UPBRINGING

ENVIRONMENT

incidence

prostatectomy

p-value

QUESTIONNAIRE

HEALTH BEHAVIOUR

SF-36

GLOBE

NEIGHBOURHOOD

EXPOSURE

LOW

value of housing

PHYSICAL

socioeconomic

SOCIOEC

occupation

ALCOHOL CONSUMPTION

INTERMEDIATE

TUBERCULOSIS

INVASIVE

physical activity

REVIEW

colorectal cancer screening

VARIATION

comorbidities

CHEMORADIATION

INVITATION

ASSETS

numbers

CONTACTS

gap

PSA

concomitant disease

LOCALISED

WORK

logistic regression

ACCESS TO CARE

CONSULTATION

income

percentages

SCREEN-DETECTED TUMOUR

THE NETHERLANDS

HEALTH INSURANCE

health awareness

HOUSEHOLD

search

DETECTIO

List of publications

PUBLICATIONS IN THIS THESIS

1. **Aarts, M.J**., Koldewijn, E.L., Poortmans, P.M.P., Coebergh, J.W.W. & Louwman, W.J. The impact of socioeconomic status on prostate cancer treatment and survival in the Southern Netherlands. (submitted).

2. **Aarts, M.J.**, Kamphuis, C.B.M., Louwman, M., Coebergh, J.W.W., Mackenbach, J.P. & van Lenthe, F.J. Educational inequalities in cancer survival: a role for comorbidities and health behaviours? (submitted).

3. **Aarts, M.J.**, Hamelinck, V.C., Bastiaannet, E., Coebergh, J.W.W., Liefers, G.J., Voogd, A.C., Van der Sangen, M. & Louwman, M.W.J. Small but significant socioeconomic inequalities in axillary staging and treatment of breast cancer in the Netherlands. *Br J Cancer* (in press).

4. Bus, P., **Aarts, M.J.**, Lemmens, V.E., van Oijen, M.G., Creemers, G.J., Nieuwenhuijzen, G.A., van Baal, J.W. & Siersema, P.D. The Effect of Socioeconomic Status on Staging and Treatment Decisions in Esophageal Cancer. *J Clin Gastroenterol* (in press).

5. **Aarts, M.J.**, Voogd, A.C., Duijm, L.E., Coebergh, J.W. & Louwman, W.J. Socioeconomic inequalities in attending the mass screening for breast cancer in the south of the Netherlands--associations with stage at diagnosis and survival. *Breast Cancer Res Treat* 128, 517-25 (2011).

6. **Aarts, M.J.**, Lemmens, V.E., Louwman, M.W., Kunst, A.E. & Coebergh, J.W. Socioeconomic status and changing inequalities in colorectal cancer? A review of the associations with risk, treatment and outcome. *Eur J Cancer* 46, 2681-95 (2010).

7. **Aarts, M.J.**, Mols, F., Thong, M.S., Louwman, M.W., Coebergh, J.W. & van de Poll-Franse, L.V. Long-term prostate cancer survivors with low socioeconomic status reported worse mental health-related quality of life in a population-based study. *Urology* 76, 1224-30 (2010).

8. Louwman, W.J., **Aarts, M.J.**, Houterman, S., van Lenthe, F.J., Coebergh, J.W. & Janssen-Heijnen, M.L. A 50% higher prevalence of life-shortening chronic conditions among cancer patients with low socioeconomic status. *Br J Cancer* 103, 1742-8 (2010).

9. **Aarts, M.J.**, van der Aa, M.A., Coebergh, J.W. & Louwman, W.J. Reduction of socioeconomic inequality in cancer incidence in the South of the Netherlands during 1996-2008. *Eur J Cancer* 46, 2633-46 (2010).

10. van Hattem, S., **Aarts, M.J.**, Louwman, W.J., Neumann, H.A., Coebergh, J.W., Looman, C.W., Nijsten, T. & de Vries, E. Increase in basal cell carcinoma incidence steepest in individuals with high socioeconomic status: results of a cancer registry study in The Netherlands. *Br J Dermatol* 161, 840-5 (2009).

RADIOTHERAPY

11. Struikmans, H., **Aarts, M.J.**, Jobsen, J.J., Koning, C.C., Poortmans, P.M., Louwman, M.W. & Coebergh, J.W. [Trends in the use of primary radiotherapy for cancer in the Netherlands in patients with breast, prostate, rectal and lung tumours]. *Ned Tijdschr Geneeskd* 156, A4426 (2012).

12. Koning, C.C., **Aarts, M.J.**, Struikmans, H., Poortmans, P.M., Lybeert, M.L., Jobsen, J.J., Coebergh, J.W., Janssen-Heijnen, M.L., Visser, O., Louwman, W.J. & Burgers, J.A. Mapping Use of Radiotherapy for Patients with Non-small Cell Lung Cancer in the Netherlands between 1997 and 2008. *Clin Oncol (R Coll Radiol)* 24, e46-53 (2012).

13. Jobsen, J.J., **Aarts, M.J.**, Siesling, S., Klaase, J., Louwman, W.J., Poortmans, P.M., Lybeert, M.L., Koning, C.C., Struikmans, H. & Coebergh, J.W. Use of Primary Radiotherapy for Rectal Cancer in the Netherlands between 1997 and 2008: A Population-based Study. *Clin Oncol (R Coll Radiol)* 24, e1-8 (2012).

14. Poortmans, P.M., **Aarts, M.J.**, Jobsen, J.J., Koning, C.C., Lybeert, M.L., Struikmans, H., Vulto, J.C., Louwman, W.J., Coebergh, J.W. & Koldewijn, E.L. A population-based study on the utilisation rate of primary radiotherapy for prostate cancer in 4 regions in the Netherlands, 1997-2008. *Radiother Oncol* 99, 207-13 (2011).

15. Struikmans, H., **Aarts, M.J.**, Jobsen, J.J., Koning, C.C., Merkus, J.W., Lybeert, M.L., Immerzeel, J., Poortmans, P.M., Veerbeek, L., Louwman, M.W. & Coebergh, J.W. An increased utilisation rate and better compliance to guidelines for primary radiotherapy for breast cancer from 1997 till 2008: a population-based study in the Netherlands. *Radiother Oncol* 100, 320-5 (2011).

OTHER

16. Holster, I.L., **Aarts, M.J.**, Lemmens, V.E.P.P. & Kuipers, E.J. Gastric cancer incidence trends in the Southeastern Netherlands: analysis by age-group and anatomical subsite. (in preparation).

17. Factsheet Longkanker in onze IKZ-regio, 2010. (in preparation).

18. Andrykowski, M.A., Thong, M.S. & **Aarts, M.J.** Disparities in Psychosocial Outcomes in Colorectal Cancer Survivors Associated with Socioeconomic Status: A Report From the Population-Based PROFILES Registry. (in preparation).

19. Arnold, M., **Aarts, M.J.**, Van der Aa, M.A., Visser, O. & Coebergh, J.W. Investigating the risk and survival of cervical, oesophageal and colon cancer among migrants in the Netherlands. (submitted).

20. Arnold, M., **Aarts, M.J.**, Siesling, S., van der Aa, M., Visser, O. & Coebergh, J.W. Breast and stomach cancer incidence and survival in migrants in the Netherlands, 1996-2006. *Eur J Cancer Prev* 20, 150-6 (2011).

21. Bastiaannet, E., de Craen, A.J., Kuppen, P.J., **Aarts, M.J.**, van der Geest, L.G., van de Velde, C.J., Westendorp, R.G. & Liefers, G.J. Socioeconomic differences in survival among breast cancer patients in the Netherlands not explained by tumor size. *Breast Cancer Res Treat* 127, 721-7 (2011).

22. Coebergh, J.W.W., **Aarts, M.J.** & Aben, K.K.H. in Handboek Kanker bij Ouderen (eds. Wymenga, A.N.M., Coebergh, J.W.W., Maas, H.A.A.M. & Schouten, H.C.) (De Tijdstroom, Utrecht, 2011).

23. Lemmens, V.E.P.P., Voogd, A.C., **Aarts, M.J.** & Coebergh, J.W.W. in Leren door registreren - 55 jaar kankerregistratie IKZ (ed. Coebergh, J.W.W.) (Eindhoven, 2010).

PhD Portfolio

Name PhD student:　　　　Mieke Aarts
Erasmus MC Department:　Public Health / Comprehensive Cancer Centre South (Eindhoven)
PhD period:　　　　　　　December 2007 – June 2012
Promotor:　　　　　　　　Prof.dr. Coebergh
Supervisor:　　　　　　　Dr. W.J. Louwman

	Year	Workload Hours (ECTS)
Courses		
'Principles of epidemiologic data analysis', Netherlands Institute for Health Sciences	2008	40 hours (1.4 ECTS)
'Cancer epidemiology', Netherlands Institute for Health Sciences	2008	40 hours (1.4 ECTS)
'Methods of public health research', Netherlands Institute for Health Sciences	2008	20 hours (0.7 ECTS)
'Case control studies', Netherlands Institute for Health Sciences	2008	20 hours (0.7 ECTS)
'Public health research', Netherlands Institute for Health Sciences	2008	96 hours (3.4 ECTS)
'Basiscursus Oncologie', Nederlandse Vereniging voor Oncologie	2010	40 hours (1.4 ECTS)
Seminars and workshops		
Netherlands Cancer Registry seminar series	2007-2010	12 hours (0.4 ECTS)
Tumour specific IKZ seminar series	2007-2011	24 hours (0.9 ECTS)
Other IKZ seminar series	2007-2011	50 hours (1.8 ECTS)
'Career development', Federatie van medisch wetenschappelijke verenigingen (FEDERA)	2008	4 hours (0.1 ECTS)
'How to print your thesis?' + 'Fear & loathing dissertation desert', Erasmus Medical Centre	2008	8 hours (0.3 ECTS)
PhD day, Erasmus Medical Centre	2009	8 hours (0.3 ECTS)
'Subsidie aanvragen' + 'Netwerken doe je zo', Nederlandse Organisatie voor Wetenschappelijk Onderzoek	2009	8 hours (0.3 ECTS)
'Methodologie van Patiëntgebonden Onderzoek en Voorbereiding van Subsidieaanvragen', Erasmus Medical Centre	2009	8 hours (0.3 ECTS)
Preconference WEON Colorectal cancer screening	2010	4 hours (0.1 ECTS)
Preconference WEON Health and Ethnicity	2011	4 hours (0.1 ECTS)
'Hands on Grants', Dutch Cancer Society	2011	8 hours (0.3 ECTS)
'Cancer in the Elderly', Gerionne	2011	8 hours (0.3 ECTS)
Pharmo-IKZ symposium	2011	8 hours (0.3 ECTS)

	Year	Workload Hours (ECTS)
Presentations		
2 Poster presentations WEON	2009	64 hours (2.3 ECTS)
2 Oral presentations IKZ – cancer screening organisation	2009	32 hours (1.1 ECTS)
2 Oral presentations WEON	2010	64 hours (2.3 ECTS)
2 Oral presentations Eurocourse	2010	64 hours (2.3 ECTS)
1 Oral presentation IKZ Urology seminar	2010	32 hours (1.1 ECTS)
1 Poster presentation WEON	2011	32 hours (1.1 ECTS)
1 Oral presentation Erasmus MC, department of Public Health	2012	32 hours (1.1 ECTS)
1 Oral presentation Dutch Conference on Public Health	2012	32 hours (1.1 ECTS)
Conferences		
Werkgroep Epidemiologisch Onderzoek Nederland (WEON) congress	2008-2011	64 hours (2.3 ECTS)
Federatie van medisch wetenschappelijke verenigingen (FEDERA) day	2008-2009	16 hours (0.6 ECTS)
CoRPS symposium 'Leven met kanker'	2009	8 hours (0.3 ECTS)
'Cancer Screening: trials and modelling to guide public health policies', Erasmus Medical Centre	2009	8 hours (0.3 ECTS)
Vereniging van Integrale Kanker Centra (VIKC) research day	2009	8 hours (0.3 ECTS)
Dutch Conference on Public Health	2012	8 hours (0.3 ECTS)
Supervising Master's thesis		
Melina Arnold, 'Breast and stomach cancer incidence and survival in migrants in the Netherlands, 1996-2006'	2010	80 hours (3 ECTS)
Other		
TG External communication	2009-2011	100 hours (3.6 ECTS)
Project leader developing www.cijfersoverkanker.nl	2010-2011	300 hours (10.7 ECTS)
Variation RT consumption study	2009-2011	240 hours (8.6 ECTS)
Lung cancer study Europe	2010	40 hours (1.4 ECTS)
Other studies	2007-2012	40 hours (1.4 ECTS)
Research group cancer screening organisation (BOZ)	2009-2012	32 hours (1.1 ECTS)
Total		**1706 hours (60.9 ECTS)**