Trends in lung cancer incidence and survival: studies based on cancer registries

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Trends in lung cancer incidence and survival: studies based on cancer registries

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Contents

Publications and manuscripts based on the studies described in this thesis

Janssen-Heijnen MLG, Coebergh JWW. Trends in incidence and prognosis of the histological subtypes of lung cancer in North America, Australia, New Zealand and Europe: impact on mortality. (submitted) (chapter 1.2).

Janssen-Heijnen MLG, Nab HW, van Reek J, van der Heijden LH, Schipper RM, Coebergh JWW. Striking changes in smoking behaviour and lung cancer incidence by histological type in south-east Netherlands, 1960-1991. Eur J Cancer 1995; 31A: 949-52 (chapter 3.1).

Janssen-Heijnen MLG, Coebergh JWW, van Reek J. Very high male lung cancer incidence in areas with tobacco industries. Eur J Cancer 1996; 32A: 2373-73 (chapter 3.2).

Janssen-Heijnen MLG, Schipper RM, Klinkhamer PJJM, Crommelin MA, Mooi WJ, Coebergh JWW. Divergent changes in survival for histological types of non-small-cell lung cancer in the southeastern area of the Netherlands since 1975. Br J cancer 1998; 77: 2053-7 (chapter 4.1.1).

Janssen-Heijnen MLG, Coebergh JWW, Klinkhamer PJJM, Schipper RM, Mulder PGH, Mooi WJ. Common factor for the rising incidence and decreasing survival of adenocarcinoma of the lung? (submitted) (chapter 4.1.2).

Janssen-Heijnen MLG, Schipper RM, Klinkhamer PJJM, Crommelin MA, Coebergh JWW. Improvement and plateau in survival of small-cell lung cancer since 1975: a population-based study. Ann Oncol 1998; 9: 543-7 (chapter 4.2).

Janssen-Heijnen MLG, Schipper RM, Razenberg PPA, Crommelin MA, Coebergh JWW. Prevalence of co-morbidity in lung cancer patients and its relationship with treatment: a population-based study. Lung Cancer (in press) (chapter 4.3).

Janssen-Heijnen MLG, Capocaccia R, Gatta G, De Angelis G, Coebergh JWW and the Eurocare study group. Trends in incidence and survival of histological subtypes of lung cancer in European cancer registries, 1978-1992. (submitted) (chapter 5).

Janssen-Heijnen MLG, Damhuis RAM, Klinkhamer PJJM, Schipper RM, Coebergh JWW. Increased but low incidence and poor survival of malignant mesothelioma in the southeastern part of the Netherlands since 1970: a population-based study. (submitted) (chapter 6.1).

Chapter 1. Introduction

1.1 Scope of the thesis

1.2 Review

1.1 Scope of the thesis

In this thesis trends in the incidence and survival of patients with lung cancer since 1960 in the southeastern part of the Netherlands are described and interpreted. These trends may provide an insight into changes in mortality due to lung cancer in a region with the oldest cancer registry in the Netherlands. **Chapter 1.2** contains a review of literature on trends in the incidence and survival of lung cancer. The methods used for the studies of this thesis are described in **chapter 2.**

Only since the beginning of this century has lung cancer become fairly common, the incidence increasing dramatically since the 1940s.[1,2] It has become by far the most frequent type of cancer among Dutch men since the 1960s, causing 35% of all cancer deaths. Among Dutch women it now ranks third, causing 11% of all cancer deaths.[3] Smoking is the most important risk factor for lung cancer,[4,5] now causing about 80% of all lung tumours in men and about 60% of all lung tumours in women. Changes in smoking habits and lung cancer incidence in the southeastern part of the Netherlands and the marked differences between men and women are described in **chapter 3.** An aetiological background for each sex could be obtained from birth cohort analyses and from intraregional differences, especially since this region contained many tobacco-processing industries.

Lung cancer is commonly classified as small-cell carcinoma and non-small-cell carcinoma. The latter includes squamous cell carcinoma, adenocarcinoma, large-cell undifferentiated carcinoma, and some rare subtypes. However, the broad division into small-cell carcinoma and non-small-cell carcinoma may obscure shifts in incidence and prognosis that affect one histological subtype rather than the entire group of non-small-cell lung tumours.[6] Small-cell carcinoma is a highly aggressive neoplasm, which is rarely amenable to surgical treatment but often responds well to chemotherapy and/or palliative radiotherapy, albeit only for a few months. According to clinical trials, the short-term survival rate for patients with small-cell carcinoma seems to have improved since the introduction of chemotherapy. However, little is known about trends in long-term survival for unselected patients. Changes in survival rates, according to the major histological subtypes of lung cancer, are described and interpreted in **chapter 4.** Trends in survival rates may give an indication of variations in detection, aggressiveness of the tumour and treatment over time.

Since the mean age of lung cancer patients is rising as a result of ageing of the general population and declining mortality due to cardiovascular diseases, the proportion with serious co-morbidity is increasing. Co-morbidity is an independent determinant of prognosis (regardless of the chosen therapy) and often necessitates modifications of and/or adversely influences therapy.[7] The prevalence of severe co-morbid conditions among patients with lung cancer and the relationship with therapy for patients with

small-cell carcinoma and non-small-cell carcinoma are described in depth in **chapter 4.3**. This chapter provides an insight into the growing complexity of care for lung cancer patients.

In **chapter 5** changes in incidence and survival rates in the southeastern part of the Netherlands between 1978 and 1992 are compared with those in other European countries. International variations may largely be explained by differences in data collection, smoking behaviour and access to specialized care.

In addition to the two major histological types (small-cell carcinoma and non-small-cell carcinoma) there are also less common tumours of the respiratory tract that clearly differ in aetiology and prognosis:[8] mesotheliomas, carcinoid tumours, carcinosarcomas, sarcomas and malignant melanomas. Since little is known about aetiology, growth rate and sensitivity to therapy, changes in the incidence and survival of these uncommon tumours are described in **chapter 6**.

In the general discussion, **chapter 7**, the quality of our data is considered and the insights gained from this thesis are evaluated.

References

1. Wynder EL, Graham EA. Tobacco smoking as a possible etiologic factor in bronchiogenic carcinoma. J Am Med Assoc 1950; 143: 329-36.
2. Korteweg R. Mortality from lung cancer in the Netherlands during and after the last war. Br J Cancer 1954; 8: 34-9.
3. Visser O, Coebergh JWW, Schouten LJ, van Dijck JAAM (eds.). Incidence of cancer in the Netherlands 1994: sixth report of the Netherlands Cancer Registry. Utrecht: Vereniging van Integrale Kankercentra, 1997.
4. Wassink WF. The aetiology of lung cancer [in Dutch]. Ned Tijdschr Geneeskd 1948; 46: 3732-47.
5. Doll R, Peto R, Wheatly K, Gray R, et al. Mortality in relation to smoking: 40 years' observations on male British doctors. Br Med J 1994; 309: 901-11.
6. Coebergh JWW. Incidence and prognosis of cancer in the Netherlands: studies based on cancer registries. Thesis, Rotterdam, 1991: 131-44.
7. Charlson ME, Pompei P, Ales KL, et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chron Dis 1987; 40: 373-83.
8. Williams CJ, Krikorian JG, Green MR, Raghavan D (eds.). Textbook of uncommon cancer. John Wiley & Sons Ltd, Oxford, 1988: 335-97.

1.2 Review

Trends in incidence and prognosis of the histological subtypes of lung cancer in North America, Australia, New Zealand and Europe: impact on mortality

1.2.1 Introduction

At the beginning of this century lung cancer was a very rare disease. Since the World War II, rates in North America, Australia, New Zealand and Europe have increased dramatically and lung cancer could be called 'one of the epidemics' of the 20th century. The increase was first recognized in autopsy series.[1] Nowadays lung cancer is the first or second most frequent tumour type among men and ranks second or third for women.[2-5] It causes 10-15% of all cancer deaths.[6]
When reporting on trends in mortality one should realize that these trends are influenced by trends in incidence and survival. Studies on trends in incidence of the histological subtypes of lung cancer may help us to recognize aetiologic changes over time, while studies on trends in survival will reveal changes in detection, aggressiveness of the tumour and treatment over time. Since the incidence of the histological subtypes of lung cancer has changed dramatically over the last two decades, we now review time and birth cohort trends in the incidence and prognosis of lung cancer in North America, Australia, New Zealand, and Europe, according to geography and histological subtype, and summarize explanations for the changes in mortality. Trends in incidence are described in the first part of this review, while the second part focuses on trends in prognosis, which so far have received little attention. We focused on North America, Australia, New Zealand and Europe, because the epidemic of smoking and the subsequent temporarily very high incidence of lung cancer in these countries are illustrative for other parts of the world where smoking is on the rise.

1.2.2 Methodological considerations

This review was based on a computerized (Medline database 1966-1997) and a manual search. Included were English-written, peer-reviewed articles on trends in incidence, mortality, risk factors, prognostic factors and survival for the histological subtypes of lung cancer.

Classification
Lung cancer is commonly classified as small-cell carcinoma and a heterogeneous group of non-small-cell carcinomas, which includes squamous cell carcinoma, adenocarcinoma, large-cell carcinoma, and some rare subtypes, such as adenosquamous cell carcinoma, mucoepidermoid carcinoma and adenoid cystic carcinoma. The first histological classification of lung tumours by the World Health

Organization (WHO) was published in 1967 and revised in 1981.[7] The major difference between these two classifications was that a solid carcinoma with mucus formation was classified as 'large-cell carcinoma' in 1967, and as 'adenocarcinoma' in 1981. In some papers undifferentiated carcinomas were included in the group of 'large-cell undifferentiated carcinomas', in others they were not. Large-cell undifferentiated carcinoma has frequently been called a 'wastebasket' or nonentity, because the carcinomas are so poorly differentiated that squamous or glandular differentiation is no longer evident at the light microscopic level. Thus, the incidence of this histological subtype varies with the criteria used to classify the other forms of non-small-cell lung cancer. Primary adenocarcinoma of the lung may be difficult to distinguish from pulmonary metastases of adenocarcinoma of the breast, prostate, colon, rectum or stomach. However, in most population-based or hospital-based registries the diagnosis is corrected when the primary tumour is found. Although bronchioloalveolar carcinoma is a distinct pathological entity,[8,9] it is similar to adenocarcinoma as far as gender, stage, race and age distribution and long-term survival are concerned.[10]

Quality of the data

There are differences in completeness of data between the various countries. This depends not only on the completeness of the registries but also on the degree of ascertainment (access to specialized care and the availability and quality of death certificates). If access to specialized care is good and the cancer registry also collects data from death certificates, then the completeness will be about 100%. In the case of good access to specialized care but a lack of death certificates, completeness will be higher if the registry also collects data on cases with only a clinical diagnosis, but some elderly patients will inevitably be missed. If access to specialized care is poor, completeness may not be very good, even if death certificates are available, because the death certificates are more likely to contain serious errors. Access to specialized care depends on the number of chest physicians and/or internists per one million inhabitants, the distance to hospitals and the extent of health insurance coverage. The completeness of cancer registries also depends on the number of sources of data, such as the pathological laboratory, hospital record offices and radiotherapy institutes. Another indicator of the completeness of the data is the mortality/incidence ratio, which should be almost equal to one in the case of this lethal disease.[2]

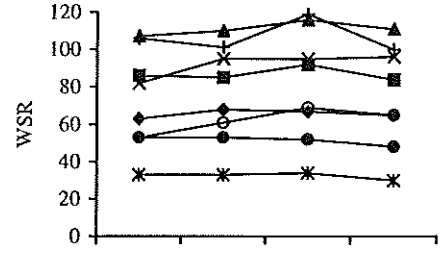
Stage migration

When reporting on trends in stage distribution one should take into account 'stage migration': through improved diagnostic techniques lymph node involvement or distant metastases can be found more easily, thus some tumours that were identified as localized in the past will be considered as metastasized nowadays.[11]

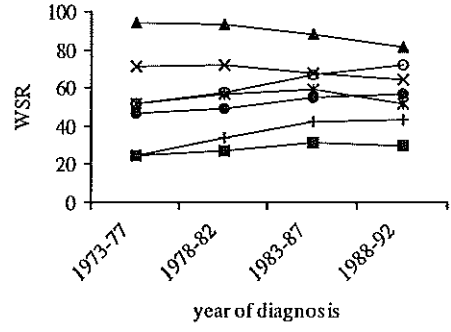
Figure 1 *Trends in age-standardized incidence rates (WSR) per 100,000 person-years. Source: Cancer Incidence in Five Continents, Vol. IV, V, VI, VII*

a) ***Men***

◆ North America white
■ North America black
▲ New Orleans white
X New Orleans black
✳ Utah
● Australia and New Zealand (Non-Maori)
\+ New Zealand (Maori)
O Canada

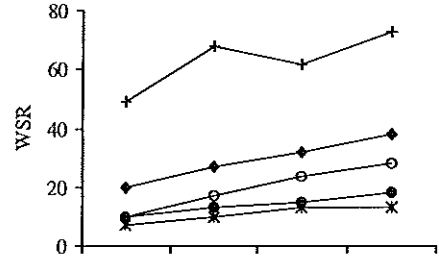


■ Iceland, Norway, Sweden (South)
▲ Scotland, the Netherlands
X Finland, Germany, Italy (North), Switzerland, England
✳ Denmark
● France
\+ Ireland, Italy (South), Spain
O Eastern Europe

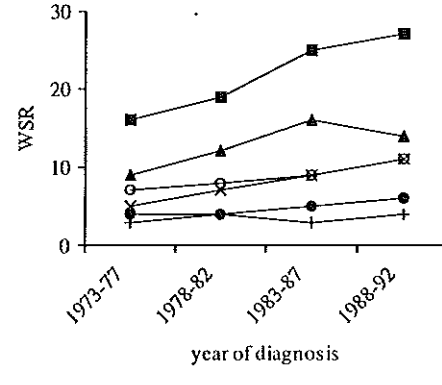


b) ***Women***

◆ North America (white and black), New Orleans (white and black)
✳ Utah
● Australia and New Zealand (Non-Maori)
\+ New Zealand (Maori)
O Canada



■ Denmark, England, Iceland, Scotland
▲ Ireland, Switzerland
X Finland, Germany, Italy (North), the Netherlands, Norway, Sweden (South)
● France
\+ Italy (South), Spain
O Eastern Europe



1.2.3 Time and birth cohort trends in incidence

Geographical variations

Worldwide male lung cancer incidence rates between 1988 and 1992 were highest (>50 per 100,000 person-years) in the United States, Canada, New Zealand (Maori) and most European countries, moderate (35-50 per 100,000) in China, Ireland, Malta, Spain, Australia and New Zealand (non-Maori), and low (<35 per 100,000) in Utah (United States), Latin America, most Asian countries, Iceland, Norway and Sweden.[2] For women lung cancer incidence rates were exceptionally high (>50 per 100,000) in New Zealand (Maori), high (20-50 per 100,000) in the United States, Canada, Denmark, Iceland and the United Kingdom, moderate (10-20 per 100,000) in Australia, New Zealand (non-Maori), Utah (United States), Austria, Germany, Ireland, the Netherlands, Norway, Poland, Sweden, Switzerland and Asia, and low (<10 per 100,000) in Latin America, other European countries, India and Africa.[2]

Incidence rates for lung cancer in North America, Australia, New Zealand and Europe have changed markedly over the past two decades. Figure 1 shows the trends in age-standardized incidence rates. In North America, Australia, New Zealand and most countries of northwestern Europe the age-standardized rate for men increased markedly up to the 1970s or 1980s and then started to decline first among middle-aged men and later in the older age groups.[3,12-23] In southern and eastern Europe the peak in incidence was not reached at the beginning of the 1990s.[2,21,24-26] For women lung cancer incidence (being much lower than that for men) started to increase later and is still on the rise, except in southern Ireland and Switzerland (Geneva). In the United States, the Netherlands, Italy and Switzerland the highest rates were found for men born between 1910 and 1930 and women born after 1930.[17,18,20,21,27]

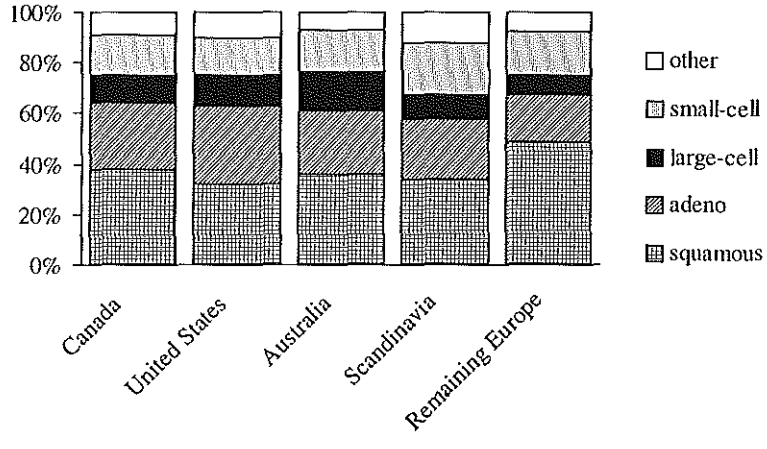
Variations between histological types

The trends in lung cancer incidence were not the same for every histological type. Among men in the United States and western Europe the age-standardized incidence rate for squamous cell carcinoma rose to 25-60 per 100,000 person-years in the early 1980s and then declined to 20-40 in the 1990s. The same trend was found for small-cell carcinoma, the peak (12-18 per 100,000 person-years) also being reached at the beginning of the 1980s. The rates for adenocarcinoma rose from 5-15 per 100,000 person-years in the 1970s to 10-35 in the 1990s;[15,17-20,22,28-31] in the United States (black men) and the southeastern part of the Netherlands the peak was reached at the end of the 1980s; for white American men a plateau was reached in the early 1990s.[18,19] In other countries the peak in the incidence of adenocarcinoma had not been reached at the beginning of the 1990s.

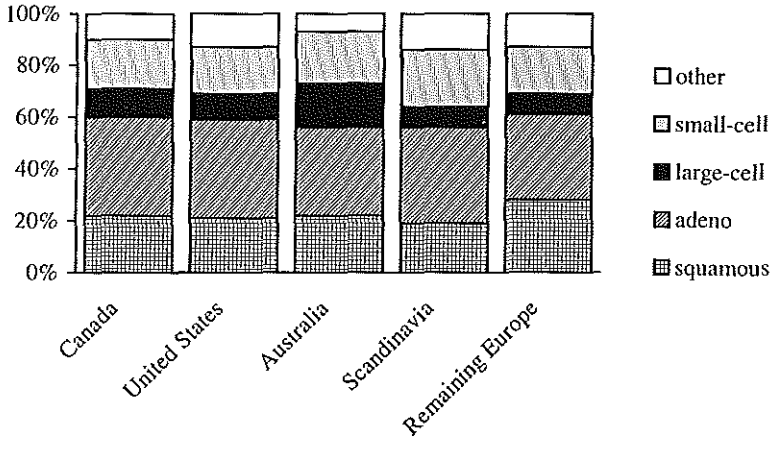
Among European women the incidence rate for every histological type increased from 1-2 per 100,000 in the 1970s to 2-5 in the 1990s.[15,17-20,22,28-31] However, for American women the rise in the incidence of adenocarcinoma from 2-7 per 100,000 to 13-15 was

Figure 2 *Percentage distribution of microscopically verified cases by histological subtype (1988-1992).*
Source: Cancer Incidence in Five Continents, Vol. IV, V, VI, VII

a) Men



b) Women



marked.[17,19,22] In Australia and Europe squamous cell carcinoma is still the most common type of cancer among men, whereas in North America adenocarcinoma is now the leading lung cancer cell type among both men and women (figure 2). Adenocarcinoma is relatively more common in women (representing about one third of all lung carcinomas) than in men (15-25% of all lung carcinomas).
There was also a birth cohort trend apparent for the different histological subtypes of lung cancer: squamous cell carcinoma declined among men born after 1910-25, whereas adenocarcinoma only declined among men born after 1930-35, or even later.[17,20-22] Among women in Connecticut the incidence rates for squamous cell carcinoma and adenocarcinoma have decreased since birth cohort 1930-39,[22] however, in Italy and Switzerland the rates for adenocarcinoma among women increased at least up to the 1950-59 cohort.[20,21] Among Swiss women the rate for squamous cell carcinoma started to decrease with birth cohort 1940-49.[20]

Discussion of incidence
Several studies published since 1948 have indicated that smoking tobacco is the main cause of lung cancer; the latency time is between 15 and 25 years.[32-40] A direct link between a defined cigarette smoke carcinogen and human lung cancer mutations was not found until 1996.[41] The relative risks of smoking are two to four times higher for squamous cell carcinoma and small-cell carcinoma (RR between 10 and 50) than for adenocarcinoma (RR between 2 and 15).[37,42-48] The strength of the association between smoking and lung cancer cell types seems to be related to tumour location: adenocarcinoma is known to occur primarily in the peripheral lung zones, whereas squamous cell carcinoma and small-cell carcinoma occur mainly in central or hilar locations.[37,44,49,50] Higgins and Wynder (1988) showed that when a smoker stopped smoking the decline in risk was more consistent for squamous cell, small-cell and large-cell undifferentiated carcinoma than for adenocarcinoma.[51] The association between smoking and lung cancer cell type is probably related to the inhalation pattern, e.g. a case-control study conducted in the United States between 1977 and 1984 revealed that lung cancer in cigar and pipe smokers was more likely to be a central (squamous cell or small-cell carcinoma) than a peripheral lesion (adenocarcinoma); the authors speculated that cigar and pipe smoke are not inhaled as deeply as cigarette smoke.[52] The risk of smoking also increased with the tar yield.[53]
Other causes of lung cancer have been identified, such as air pollution,[54] occupational exposure to asbestos or radon (however, only a small proportion of the population was exposed),[55-57] vitamin A deficiency,[58-62] indoor radon,[63] possibly bird keeping,[64-69] and previous chronic lung diseases,[70-73] but the effects of smoking are so predominant that trends in other exposures seem unlikely to be largely responsible for the changes in incidence.

The trends in lung cancer incidence for both sexes followed the temporal and geographical variations in smoking behaviour after 15-25 years. The percentage smokers among men was much higher than among women but has dropped since the 1950s/1960s, first among younger men.[50,74-76] While the prevalence of smoking has decreased since the 1950s, the percentage low-tar filter cigarette smokers among smokers has increased markedly.[74,77-79] However, those who continued smoking were the heavily addicted ones.[80] In southwestern Europe the percentage smokers did not start to decrease until the 1980s and in many eastern European countries the prevalence of smoking increased until the 1990s.[76] The very low incidence of lung cancer in Iceland, Norway and Sweden can be explained by the strong anti-smoking campaigns in these countries.[48,76] The low incidence in Utah is probably due to the high proportion (about 70%) of the population that belongs to the Mormon sect, who are forbidden to smoke. The relatively high incidence among women in New Zealand (Maori) can be explained by the high percentage of smokers.

Since squamous cell carcinoma is closely correlated with smoking the decrease in incidence rates was probably due to a decrease in the percentage smokers since the 1950s and to a change to low-tar filter cigarettes. This was not the same for men and women, nor for all age groups. The percentage female smokers was much lower than the percentage male smokers and started to decrease only at the end of the 1970s. This has resulted in an increase in incidence up to the 1990s. Among men both a period effect (decrease in the percentage smokers since the 1950s and a change to more low-tar filter cigarettes) and a birth cohort effect (mainly the elderly – referring to the earlier birth cohorts – continued smoking non-filter, high-tar cigarettes) occurred.

The increase in adenocarcinoma – traditionally with the lowest correlation with smoking – is more difficult to explain. The extent to which changes in diagnostic techniques or classification were responsible for the increase in adenocarcinoma is likely to be small;[22,31,81,82] solid carcinomas with mucus production, only being classified as 'adenocarcinoma' after 1981,[7] cannot be responsible for the increase. Furthermore, the inter-observer reproducibility for adenocarcinoma was good.[83-85]

There are several hypotheses about changes in smoking behaviour which could explain the increase in adenocarcinoma. First, since cigarette filters are less effective in eliminating smaller particles and filter use could also result in taking larger puffs and retaining smoke longer to compensate for the lower nicotine yield, the introduction of filter cigarettes since the mid-1950s may have led to an increase in the incidence of adenocarcinoma, which occurs primarily in the peripheral lung zones.[22,37,49,78,86] Since Thun and colleagues found that the increase in adenocarcinoma only occurred in smokers,[22] the increased use of filter cigarettes seems to be a plausible explanation for the rise. Moreover, a multicentre hospital-based case-control study in the United States revealed that the risk of squamous cell carcinoma for smokers of filter cigarettes was lower than for smokers of non-filter cigarettes, but the risk of adenocarcinoma was not

reduced.[78] A second, complementary hypothesis suggests that smoking low-tar filter cigarettes may increase the risk for adenocarcinoma because these cigarettes have a higher nitrate content. The increased yields of N-nitrosamines, especially NNK, induced adenocarcinoma of the lung in laboratory animals.[87] The higher proportion of Americans with adenocarcinoma can also be explained by the higher proportion of smokers who smoke low-tar filter cigarettes in the United States (almost 100% in 1992) compared to European countries (about 70%).[48,77] The higher proportion of women with adenocarcinoma can also be explained by past smoking behaviour. Prior to the 1950s, cigarettes were predominantly unfiltered, high-tar products smoked largely by men. In the 1950s, when women were just beginning to smoke, filter cigarettes were introduced and thus represented less of a change for women than for men. This has resulted in a higher baseline proportion of women with adenocarcinoma. Furthermore, adenocarcinoma also occurs relatively more often in non-smokers, especially among women.[37,42,48,49,88]
Most of the temporal and geographical variations in lung cancer rates are thus probably related to different patterns of past smoking behaviour.

Conclusions concerning trends in incidence

Although the peak of lung cancer incidence among men in North America, Australia, New Zealand and northwestern Europe was reached in the 1980s, the rate for men in southern and eastern Europe and for women continued to increase, at least until the 1990s. The trends in incidence were closely associated with past smoking behaviour. The decrease in incidence first occurred in younger men, thus the proportion of elderly patients has been increasing.
Despite a decrease since the 1950s, the percentage smokers reached a plateau of 30-50% in the mid-1980s.[76] Furthermore, the average number of cigarettes smoked per day has increased, because the smokers who continued smoking were the heavily addicted ones.
The trend toward smoking more low-tar filter cigarettes, probably caused the increase in the incidence of adenocarcinoma. This tumour type is already the major histological subtype in North America and may also become the major type in Australia, New Zealand and Europe in the near future. It is very likely that adenocarcinoma will give rise to a new epidemic, although it probably will not reach the same magnitude as that of squamous cell carcinoma.

1.2.4 Time trends in prognosis

Geographical variations

Worldwide, the prognosis for patients with lung cancer is very poor, because metastases are often present at the time of diagnosis. Survival is associated with age and tumour stage: one-year relative survival rates decreased from 40% for patients younger than 45 years old to 20% for patients of 75 and older,[89,90] and was better for patients with localized disease (40-65%) than for those with metastasized disease (15-30%).[89,91-93]

In North America the 1- and 5-year survival rates in the 1980s were about 30% and 12%, respectively.[94-97] Between European countries large variations in lung cancer survival rates existed between 1978 and 1985: 1-year rates varied between 21% and 42%, and 5-year rates between 5% and 15%, being highest in Finland, France, the Netherlands and Switzerland, and lowest in Denmark, England, Poland and Scotland.[89-91,98,99]

Between 1975 and 1990 the prognosis for lung cancer patients, regardless of histological type, improved slightly although not significantly over time.[89,90,94,96,97,99-101]

Variations between histological subtypes

Besides being dependent on age and tumour stage, survival for lung cancer patients is closely related to the histology of the tumour. Survival was best for patients with non-small-cell carcinoma and poorest for patients with small-cell carcinoma.[91,93,94,98,102-107] Despite recent advances in treatment the 5-year survival rate for patients with non-small-cell lung cancer is still less than 15% and that for small-cell carcinoma only 5%.[93,95,98,108,109]

Although non-small-cell lung cancer is often considered to be one clinically uniform category, several studies indicate that survival differs according to histological subtype, being better for squamous cell carcinoma and adenocarcinoma (1-year survival rates of 40-50%) than for large-cell undifferentiated carcinoma (1-year survival rates of 25-30%).[91,93,95,98,102,104,110] In Yorkshire, England, UK, the population-based survival for each histological subtype of non-small-cell lung cancer remained largely unchanged between 1976 and 1983;[111] however, the percentage patients with an unknown histology was very high.[112] In contrast, in the southeastern part of the Netherlands the population-based relative 1-year survival rates for adenocarcinoma decreased markedly from 59% in 1975 to 45% in 1992, while that for squamous cell carcinoma remained about 50% and that for large-cell undifferentiated carcinoma remained about 30%.[93]

Small-cell lung cancer can be distinguished from other forms of lung cancer. Its features are: rapid progression, short doubling time, high growth fraction, and sensitivity to multiple chemotherapeutic agents and radiation therapy. Short-term survival seems to have improved since the introduction of chemotherapy in the 1970s.[108,109,113] In Mersey and Yorkshire, England, UK, the population-based 2-year survival rate improved from 2% in the 1970s to 8% in the 1980s and in the southeastern part of the Netherlands the population-based relative 1-year survival rate improved from 15% in the 1970s to 35% in the 1980s, but there was no further improvement in the 1990s and 2-year survival did not exceed 8%.[107,114]

Discussion of prognosis

Despite the improvement in survival for small-cell lung cancer, the overall prognosis for lung cancer remained poor and 5-year survival rates still do not exceed 15%. Until now, the only real chance of cure is surgery for patients with limited disease.[98,105,115,116] About 30% of the patients with non-small-cell carcinoma have undergone surgical treatment since the 1980s compared to only 5% of those with small-cell carcinomas.[104,117] Postoperative mortality, which is higher for the elderly, is related to the type of resection, the risk being highest (6%) after pneumonectomy.[118]

The proportion of patients undergoing surgery decreased slightly between 1974 and 1986; for smaller lesions a trend was apparent toward more lung-sparing resections; the use of radiotherapy has increased since the 1980s.[94,119] Selection for surgery has probably improved as a result of the introduction of flexible bronchoscopy, isotope scanning and computerized tomography as well as mediastinoscopy. Improved diagnostic techniques have probably increased the detection of metastases (stage migration). With the exception of small-cell carcinoma there was almost no change in the proportion of patients receiving chemotherapy in the United States and the United Kingdom.[94,119]

The prognosis for lung cancer varied markedly between countries, probably due to differences in (1) detection of disease, (2) inclusion of patients in studies (selected or unselected cases, patients dead around diagnosis), (3) methods of data collection and completeness (depending on access to medical care and the quality and availability of death certificates), and (4) methods of calculating survival (crude, disease-specific or relative survival). Furthermore, the availability of medical expertise and facilities is dependent on the number of chest physicians and internists per 100,000 inhabitants. It is also influenced by geographical and socio-economic factors, including distance from specialized centres and the extent of health insurance coverage.

Non-small-cell lung cancer

Survival of non-small-cell carcinoma is closely associated with tumour stage and treatment. The treatment-of-first-choice for patients with stage I or II non-small-cell lung cancer is surgical resection.[120] Even for elderly lung cancer patients pulmonary resection is justified, however, a careful preoperative assessment ought to be performed and standard resections should be preferred.[121,122] Some patients with stage IIIa disease will qualify for surgical resection, others should be offered combined radiotherapy and chemotherapy. For most patients with stage IIIb disease, the preferred therapeutic modality is thoracic radiotherapy in combination with chemotherapy.[120] For patients with stage IV lung cancer, no curative treatment or 'standard therapy' is available.[120,123] Although radiotherapy was applied sparingly either alone or in combination with chemotherapy for non-small-cell lung cancer, its use has doubled in the last few decades.[101] Adjuvant chemotherapy produces a significant but clinically small advantage for non-small-cell lung cancer patients and should still be considered experimental.[120,124]

Despite an excellent description of the tumour's size and the extent of anatomic spread, the TNM (tumour node metastasis) system does not include important prognostic factors that are manifest in the clinical condition of the patient.[125-128] Since the proportion of elderly patients in most Western countries is growing, co-morbidity or the coexistence of various chronic illnesses in addition to the index disease is of growing importance for the clinical management (especially surgical management) of lung cancer patients. Co-morbidity increases the risk of peroperative and postoperative complications,[129-132] especially those of the cardiorespiratory system.[118,121,122,133,134] Co-morbidity is also an independent prognostic factor.[135-140] Indeed co-morbidity in elderly patients was found to be associated with less surgery and poor survival.[101,141]

In the southeastern part of the Netherlands a marked decrease in survival for patients with adenocarcinoma was found, despite increased application of better diagnostic techniques by more chest physicians.[93] This needs to be confirmed in other countries. The question is whether adenocarcinoma has become a more aggressive tumour. Specific patterns of mutational activation of oncogenes, such as K-ras and erb-B, or disruption of tumour suppressor gene function, such as p53, may play a role in adenocarcinoma with poor survival.[142-144] The continuing expression of cytokeratin 18 in lung tumours and microalbuminuria in lung cancer patients have been recognized as indicators of an aggressive tumour phenotype, regardless of stage and histological type of the tumour.[145-147] Typing of oncogenes or tumour suppressor genes may provide a more accurate diagnosis and therefore facilitate the planning of suitable therapeutic approaches, e.g. adjuvant chemotherapy shortly after undergoing surgery for patients with cytokeratin 18 positive stage I non-small-cell lung cancer.

Small-cell lung cancer

Prior to 1970, irradiation and sometimes surgery were the major modes of treatment of small-cell lung cancer. The overall 5-year survival rate with surgery was <1-3%, even for patients with clinically resectable disease. Neither preoperative nor postoperative radiotherapy improved the poor results of surgery.[148] Nowadays, small-cell lung cancer patients with limited disease generally receive combination chemotherapy and radiotherapy, and approximately 50% experience complete clinical remission. Patients with extensive disease also exhibit an initial response to chemotherapy, but only 20-40% go into complete remission and few survive for 2, let alone 5, years. Although the introduction of intensive combination chemotherapy in the 1970s has resulted in an increase in survival,[111,119] death from recurrent disease occurs within 2 years of diagnosis in 80-98% of the cases.[114,149-152] Furthermore, results of chemotherapy have reached a plateau and further improvement seems impossible with the currently available tools.[107-109,153] The response rates and survival rates after combination chemotherapy with irradiation were moderately higher than after combination chemotherapy alone.[113,154-157]

For elderly patients, whose proportion has been increasing, the survival rate was lower.[114,158-160] This could also be related to the presence of co-morbidity, which may complicate treatment and decrease the prognosis.[130-132,161-163]

Conclusions concerning trends in prognosis

Despite earlier detection through the increased use of flexible bronchoscopy and fine needle aspiration cytology, lymphatic and hematogenous metastases are often present at the time that lung cancer is diagnosed, and prognosis is still very poor. Survival of lung cancer differs markedly, according to histological subtype. The prognosis for non-small-cell lung cancer has remained approximately constant, while the prognosis for adenocarcinoma – one of the subtypes of non-small-cell lung tumours – may even be decreasing over time. In contrast, progress has been made in the short-term survival of small-cell lung cancer – due to the introduction of chemotherapy since the 1970s – but it has stabilized since the mid-1980s and 2-year survival remains very poor. The growing proportion of elderly patients who often present with serious co-morbidity at diagnosis complicates treatment and indicates the need for adapted guidelines for these patients, who usually are not entered in clinical trials.

1.2.5 Summary and conclusions

Since the World War II the incidence of lung cancer has been increasing dramatically in most Western countries; it is now the most frequent or second most frequent tumour

in men and the second or third in women. The peak of the epidemic among men was reached in the 1970s or 1980s in North America, Australia, New Zealand and north-western Europe, first in the younger age groups. The peak among men in southern and eastern Europe and for women has not yet been reached. The trends were not the same for every histological subtype of lung cancer. The incidence of squamous cell carcinoma and small-cell carcinoma, which are supposed to be more closely related to smoking than adenocarcinoma, started to decrease earlier.
These trends followed changes in past smoking behaviour. Among men the proportion of smokers has increased markedly since the beginning of this century but has decreased since the 1950s or 1960s, except in southern and eastern Europe. Younger men were more inclined to quit smoking or to switch to low-tar filter cigarettes than the elderly. Women only started smoking in the 1950s and the percentage female smokers did not decrease before the 1970s. Furthermore, the proportion of smokers of low-tar filter cigarettes has been much higher among women than among men.
The incidence of and proportion with adenocarcinoma have been increasing, possibly because of a shift from high-tar non-filter cigarettes toward low-tar filter cigarettes during the 1960s and 1970s, especially since the increase in adenocarcinoma was found to occur only in smokers. Filter use could result in taking larger puffs and retaining the smoke longer to compensate for the lower nicotine yield and thus may cause adenocarcinoma, which often develops in the peripheral lung zones. Furthermore, cigarettes with a low-tar yield contain higher levels of organ-specific carcinogenic tobacco-specific nitrosamines, which can cause adenocarcinoma.

Despite improvement in both the diagnosis as a result of flexible bronchoscopy and improved treatment, the overall prognosis for patients with non-small-cell lung cancer did not improve significantly over time. In the southeastern part of the Netherlands a decrease was even found in the survival rates for patients with adenocarcinoma. In contrast, the introduction and improvement of chemotherapy since the 1970s gave rise to an improvement in – only short-term (<2 years) – survival for patients with small-cell lung cancer. The increasing proportion of elderly lung cancer patients who present with co-morbidity at the time of diagnosis complicates treatment and probably has a negative effect on survival.
Prognosis can be improved by early detection – although screening was not associated with a decrease in mortality in the United States[164] – and by improvement of the quality of care. Recognition of specific patterns of mutational activation of oncogenes or disruption of tumour suppressor gene function, such as K-ras or cytokeratin 18, may facilitate tailor-made treatment and improve the prognosis for certain subgroups. New (combinations of) chemotherapeutic agents may also improve long-term survival for patients with small-cell lung cancer. Studies on therapy should focus on improvement

of the treatment of adenocarcinoma, because more lung cancer patients will present with this histological subtype.

In this review we have shown that the trends in the incidence of lung cancer were closely associated with past smoking behaviour. Furthermore, except for the improvement in short-term survival of small-cell lung cancer and the possible decrease in survival of adenocarcinoma, the prognosis has not changed significantly over the last two decades. Since mortality is influenced by both incidence and survival, we expect – on the basis of trends in smoking behaviour and survival – the following trends in mortality to develop in the near future.

First, we expect that the decrease in mortality among men in North America, Australia, New Zealand and northwestern Europe will reach a plateau at the beginning of the next century because of the steady percentage smokers since the 1980s and a more or less steady survival. Among women in these regions we expect the mortality to start decreasing soon and also to stabilize at the beginning of the next century; the same trend is expected for men and women in southern Europe. In eastern Europe the percentage smokers increased until the 1990s, thus a decrease in mortality is not expected before the year 2010. In other parts of the world, where smoking is still increasing, mortality due to lung cancer will increase dramatically in the next decades. Smoking can only be countered by decreasing the availability of cigarettes, e.g. by increasing the price, or developing better strategies for handling nicotine addiction, e.g. by offering less harmful nicotine delivery systems.

Second, the mortality of adenocarcinoma will probably increase worldwide, because of the increased incidence and the possibly decreased survival due to the increased use of low-tar filter cigarettes. In contrast, mortality due to squamous cell carcinoma and small-cell carcinoma will probably decrease because of a decrease in incidence and steady or slightly increasing survival rates.

Finally, the mortality of lung cancer may increase, due to the higher proportion of elderly patients who present with co-morbidity at the time of diagnosis.

References

1. De Vries WM. The prevalence of cancer as revealed by mortality returns and at autopsy. Surg Gyn Obst 1927: 217-45.
2. Parkin DM, Whelan SL, Ferlay J, et al. (eds.). Cancer incidence in five continents, vol VII. Lyon: IARC Scientific Publications No. 143, 1992: 992-3.
3. Devesa SS, Silverman DT, Young JL. Cancer incidence and mortality trends among whites in the United States, 1947-84. J Natl Cancer Inst 1987; 79: 701-70.
4. McCredie M, Coates M, Churches T, et al. Cancer incidence in New South Wales, Australia. Eur J Cancer 1991; 27: 928-31.
5. La Vecchia C, Luccini F, Negri E, et al. Trends of cancer mortality in Europe, 1955-1989: II, respiratory tract, bone, connective and soft tissue sarcomas, and skin. Eur J Cancer 1992; 28: 514-99.
6. Sasco AJ. World burden of tobacco-related cancer. Lancet 1991; 338: 123-4.

7. WHO. The World Health Organization histological typing of lung tumours. Am J Clin Path 1982; 77: 123-36.
8. Daly RC, Trastek VF, Pairolero PC, et al. Bronchoalveolar carcinoma: factors affecting survival. Ann Thorac Surg 1991; 51: 368-77.
9. Barsky SH, Cameron R, Osann KE, et al. Rising incidence of bronchioloalveolar lung carcinoma and its unique clinicopathologic features. Cancer 1994; 73: 1163-70.
10. Falk RT, Pickle LW, Fontham ET, et al. Epidemiology of bronchioloalveolar carcinoma. Cancer Epidemiol Biomarkers Prev 1992; 1: 339-44.
11. Feinstein AR, Sosin DM, Walls CE. The Will Rogers' phenomenon: stage migration and new diagnostic techniques as a source of misleading statistics for survival in cancer. New Engl J Med 1985; 312: 1604-6.
12. Horm JW, Kessler LG. Falling rates of lung cancer in men in the United States. Lancet 1986; February 22: 425-6.
13. McCredie M, Coates MS, Ford JM. The changing incidence of cancer in adults in New South Wales. Int J Cancer 1988; 42: 667-71.
14. Dinse GE, Hoel DG. Exploring time trends in cancer incidence. Cancer Causes Control 1992; 3: 409-17.
15. Friis S, Storm HH. Urban-rural variation in cancer incidence in Denmark 1943-1987. Eur J Cancer 1993; 29A: 538-44.
16. La Vecchia, Lucchini F, Negri E, et al. Trends in cancer mortality, 1955-1989: Asia, Africa and Oceania. Eur J Cancer 1993; 29A: 2168-211.
17. Zheng T, Holford T, Boyle P, et al. Time trend and the age-period-cohort effect on the incidence of histologic types of lung cancer in Connecticut, 1960-1989. Cancer 1994; 74: 1556-67.
18. Janssen-Heijnen MLG, Nab HW, van Reek J, et al. Striking changes in smoking behaviour and lung cancer incidence by histological type in the south-east Netherlands, 1960-1991. Eur J Cancer 1995; 31A: 949-52.
19. Travis WD, Lubin J, Ries L, et al. United States lung carcinoma incidence trends: declining for most histologic types among males, increasing among females. Cancer 1996; 77: 2464-70.
20. Levi F, Franceschi S, La Vecchia C, et al. Lung carcinoma trends by histologic type in Vaud and Neuchâtel, Switzerland, 1974-1994. Cancer 1997; 79: 906-14.
21. Russo A, Crosignani P, Franceschi S, et al. Changes in lung cancer histological types in Varese Cancer Registry, Italy 1976-1992. Eur J Cancer 1997; 33: 1643-7.
22. Thun MJ, Lally CA, Flannery JT, et al. Cigarette smoking and changes in the histopathology of lung cancer. J Natl Cancer Inst 1997; 89: 1580-6.
23. McLaughlin JR, Kreiger N, Marrett LD, et al. Cancer incidence registration and trends in Ontario. Eur J Cancer 1991; 27: 1520-4.
24. Waterhouse J, Muir CS, Powell J, Shanmugaratnam K (eds.). Cancer Incidence in Five Continents. Vol. IV. No. 42. Lyon: IARC Scientific Publications, 1982.
25. Muir CS, Waterhouse J, Mack T, Powell J, Whelan S. Cancer incidence in five continents, vol V. No. 88. Lyon: IARC Scientific Publications, 1987.
26. Parkin DM, Muir CS, Whelan SL, Gao YT, Ferlay J, Powell J. Cancer incidence in five continents, vol VI. No. 120. Lyon: IARC Scientific Publications, 1992.
27. Devesa SS, Blot WJ, Fraumeni JF. Declining lung cancer rates among young men and women in the United States: a cohort analysis. J Natl Cancer Inst 1989; 81: 1568-71.
28. Vincent RG, Pickren JW, Lane WW, et al. The changing histopathology of lung cancer: a review of 1682 cases. Cancer 1977; 39: 1647-55.
29. Dodds L, Davis S, Polissar L. A population-based study of lung cancer incidence trends by histologic type, 1974-81. J Natl Cancer Inst 1986; 76: 21-9.
30. Wu AH, Henderson BE, Thomas DC, et al. Secular trends in histologic types of lung cancer. J Natl Cancer Inst 1986; 77: 53-6.
31. El-Torky M, El-Zeky F, Hall JC. Significant changes in the distribution of histologic types of lung cancer: a review of 4928 cases. Cancer 1990; 65: 2361-7.

32. Wassink WF. The aetiology of lung cancer [in Dutch]. Ned Tijdschr Geneeskd 1948; 92: 3732-47.
33. Wynder EL, Graham EA. Tobacco smoking as a possible etiologic factor in bronchiogenic carcinoma. J Am Med Assoc 1950; 143: 329-36.
34. Doll R, Hill AB. Smoking and carcinoma of the lung: preliminary report. Br Med J 1950; September 30: 739-48.
35. Doll R, Peto R. Mortality in relation to smoking: 20 years' observation on male British doctors. Br Med J 1976; 2: 1525-36.
36. Wynder EL. Tobacco as a cause of lung cancer: some reflections. Am J Epidemiol 1997; 146: 687-94.
37. Lubin JH, Blot WJ. Assessment of lung cancer risk factors by histologic category. J Natl Cancer Inst 1984; 73: 383-9.
38. Lubin JH, Blot WJ, Berrino F, et al. Modifying risk of developing lung cancer by changing habits of cigarette smoking. Br Med J 1984; 288: 1953-6.
39. Pathak DR, Samet JM, Humble CG, et al. Determinants of lung cancer risk in cigarette smokers in New Mexico. J Natl Cancer Inst 1986; 76: 597-604.
40. Doll R, Peto R, Wheatly K, et al. Mortality in relation to smoking: 40 years' observations on male British doctors. Br Med J 1994; 309: 901-11.
41. Denissenko MF, Pao A, Tang M, et al. Preferential formation of Benzo[a]pyrene adducts at lung cancer mutational hotspots in P53. Science 1996; 274: 430-2.
42. McDuffie HH, Klaassen DJ, Dosman JA. Determinants of cell type in patients with cancer of the lungs. Chest 1990; 98: 1187-93.
43. Jedrychowski W, Becher H, Wahrendorf J, et al. Effect of tobacco smoking on various histological types of lung cancer. J Cancer Res Clin Oncol 1992; 118: 276-82.
44. Pezzotto SM, Mahuad R, Bay ML, et al. Variation in smoking-related lung cancer risk factors by cell type among men in Argentina: a case-control study. Cancer Causes and Control 1993; 4: 231-7.
45. Ellard GA, de Waard F, Kemmeren JM. Uninary nicotine metabolite excretion and lung cancer risk in a female cohort. Br J Cancer 1995; 72: 788-91.
46. Siemiatycki J, Krewski D, Franco E, et al. Associations between cigarette smoking and each of 21 types of cancer: a multi-site case-control study. Int J Epidemiol 1995; 24: 504-14.
47. De Waard F, Kemmeren JM, van Ginkel LA, et al. Urinary cotinine and lung cancer risk in a female cohort. Br J Cancer 1995; 72: 784-7.
48. Engeland A, Haldorsen T, Andersen A, et al. The impact of smoking habits on lung cancer risk: 28 years' observation of 26,000 Norwegian men and women. Cancer Causes and Control 1996; 7: 336-76.
49. Morabia A, Wynder EL. Cigarette smoking and lung cancer cell types. Cancer 1991; 68: 2074-8.
50. Wynder EL, Hoffmann D. Smoking and lung cancer: scientific challenges and opportunities. Cancer Res 1994; 54: 5284-95.
51. Higgins IT, Wynder EL. Reduction in risk of lung cancer among ex-smokers with particular reference to histologic type. Cancer 1988; 62: 2397-401.
52. Higgins ITT, Mahan CM, Wynder EL. Lung cancer among cigar and pipe smokers. Prev Med 1988; 17: 116-28.
53. Stellman SD, Garfinkel L. Lung cancer risk is proportional to cigarette tar yield: evidence from a prospective study. Prev Med 1989; 18: 518-25.
54. Vena JE. Air pollution as a risk factor in lung cancer. Am J Epidemiol 1982; 116: 42-56.
55. Saracci R. The interactions of tobacco smoking and other agents in cancer etiology. Epid Rev 1987; 9: 175-93.
56. Sankila RJ, Karjalainen ES, Oksanen HM, et al. Relationship between occupation and lung cancer as analyzed by age and histologic type. Cancer 1990; 65: 1651-6.
57. Wilkinson P. Hansell DM, Janssens J, et al. Is lung cancer associated with asbestos exposure when there are no small opacities on the chest radiograph? Lancet 1995; 345: 1074-8.

58. Margetts BM, Jackson AA. Interactions between people's diet and their smoking habits: the dietary and nutritional survey of British adults. Br Med J 1993; 307: 1381-4.
59. Dorant E, van den Brandt PA, Goldbohm RA. A prospective cohort study on Allium vegetable consumption, garlic supplement use and the risk of lung carcinoma in the Netherlands. Cancer Res 1994; 54: 6148-53.
60. Scali J, Astre C, Segala C, et al. Relationship of serum cholesterol, dietary and plasma ß-carotene with lung cancer in male smokers. Eur J Cancer Prev 1995; 4: 169-74.
61. Serdula MK, Byers T, Mokdad AH, et al. The association between fruit and vegetable intake and chronic disease risk factors. Epidemiology 1996; 7: 161-5.
62. Ziegler RG, Colavito EA, Hartge P, et al. Importance of α-Carotene, ß-Carotene, and other phytochemicals in the etiology of lung cancer. J Natl Cancer Inst 1996; 88: 612-5.
63. Lubin JH, Boice JD. Lung cancer risk from residential radon: meta-analysis of eight epidemiologic studies. J Natl Cancer Inst 1997; 89: 49-57.
64. Holst PA, Kromhout D, Brand R. For debate: pet birds as an independent risk factor for lung cancer. Br Med J 1988; 27: 1319-21.
65. Gardiner AJS, Forey BA, Lee PN. Avian exposure and bronchogenic carcinoma. Br Med J 1992; 305: 989-92.
66. Kohlmeier L, Arminger G, Bartolomeycik S, et al. Pet birds as an independent risk factor for lung cancer: case-control study. Br Med J 1992; 305: 986-9.
67. Alavanja MCR, Brownson RC, Berger E, et al. Avian exposure and risk of lung cancer in women in Missouri: population based case control study. Br Med J 1996; 313: 1233-5.
68. Modigh C, Axelsson G, Alavanja M, et al. Pet birds and risk of lung cancer in Sweden: a case-control study. Br Med J 1996; 313: 1236-8.
69. Morabia A, Stellman S, Lumey LH, et al. Parakeets, canaries, finches, parrots and lung cancer: no association. Br J Cancer 1998; 77: 501-4.
70. Samet JM, Humble CG, Pathak DR. Personal and family history of respiratory disease and lung cancer risk. Am Rev Respir Dis 1986; 134: 466-70.
71. Skillrud DM, Offord KP, Miller RD. Higher risk of lung cancer in chronic obstructive pulmonary disease: a prospective, matched, controlled study. Ann Intern Med 1986; 105: 503-7.
72. Tockman MS, Anthonisen NR, Wright EC, et al. Airways obstruction and the risk for lung cancer. Ann Intern Med 1987; 106: 512-8.
73. Alavanja MCR, Brownson RC, Boice JD Jr, et al. Preexisting lung disease and lung cancer among nonsmoking women. Am J Epidemiol 1992; 136: 623-32.
74. Brown CC, Kessler LG. Projections of lung cancer mortality in the United States: 1985-2025. J Natl Cancer Inst 1988; 80: 43-51.
75. Fiore MC, Novotny TE, Pierce JP, et al. Trends in cigarette smoking in the United States: the changing influence of gender and race. JAMA 1989; 261: 49-55.
76. Franceschi S, Naett C. Trends in smoking in Europe. Eur J Cancer Prev 1995; 4: 271-84.
77. Wynder EL, Muscat JE. The changing epidemiology of smoking and lung cancer histology. Environ Health Perspect 1995; 103(suppl 8): 143-8.
78. Stellman SD, Muscat JE, Thompson S, Hoffmann D, Wynder EL. Risk of squamous cell carcinoma and adenocarcinoma of the lung in relation to lifetime filter cigarette smoking. Cancer 1997; 80: 382-8.
79. Giovino GA, Henningfield JE, Tomar SL, et al. Epidemiology of tobacco use and dependence. Epid Rev 1995; 17: 48-65.
80. Wersäll JP, Eklund G. The decline of smoking among Swedish men. Int J Epidemiol 1998; 27: 20-6.
81. Beard CM, Jedd MB, Woolner LB, et al. Fifty-year trend in incidence rates of bronchogenic carcinoma by cell type in Olmsted County, Minnesota. J Natl Cancer Inst 1988; 80: 1404-7.
82. Caldwell CJ, Berry CL. Is the incidence of primary adenocarcinoma of the lung increasing? Virchows Arch 1996; 429: 359-63.
83. Greenberg ER, Korson R, Baker J, et al. Incidence of lung cancer by cell type: a population-based study in New Hampshire and Vermont. J Natl Cancer Inst 1984; 72: 599-603.

84. Campobasso O, Andrion A, Ribotta M, et al. The value of the 1981 WHO histological classification in inter-observer reproducibility and changing pattern of lung cancer. Int J Cancer 1993; 53: 205-8.
85. Brownson RC, Loy TS, Ingram E, et al. Lung cancer in nonsmoking women: histology and survival patterns. Cancer 1995; 75: 29-33.
86. Wynder EL, Covey LS. Epidemiologic patterns in lung cancer by histologic type. Eur J Cancer Clin Oncol 1987; 23: 1491-6.
87. Hecht SS, Hoffmann D. Tobacco-specific nitrosamines, an important group of carcinogens in tobacco and tobacco smoke. Carcinogenesis 1988; 17: 116-28.
88. Kabat GC, Wynder EL. Lung cancer in nonsmokers. Cancer 1984; 53: 1214-21.
89. Carstensen B, Storm HH, Schou G. Survival of Danish cancer patients, 1943-1987. Copenhagen, Danish Cancer Society, Munksgaard 1993.
90. Berrino F, Sant M, Verdecchia A, et al. (eds.). Survival of cancer patients in Europe: the EUROCARE study. IARC Scientific Publications No. 132, Lyon, 1995: 232-44.
91. Sant M, Gatta G, Capocaccia R, et al. Survival for lung cancer in northern Italy. Cancer Causes and Control 1992; 3: 223-30.
92. Vrdoljak E, Mise K, Sapunar D, et al. Survival analysis of untreated patients with non-small-cell lung cancer. Chest 1994; 106: 1797-800.
93. Janssen-Heijnen MLG, Schipper RM, Klinkhamer PJJM, et al. Divergent changes in survival for histological types of non-small-cell lung cancer in southeastern Netherlands since 1975. Br J Cancer 1998; 77: 2053-7.
94. Humphrey EW, Smart CR, Winchester DP, et al. National survey of the pattern of care for carcinoma of the lung. J Thorac Cardiovasc Surg 1990; 100: 837-43.
95. Hilsenbeck SG, Raub WA, Sridhar KS. Prognostic factors in lung cancer based on multivariate analysis. Am J Clin Oncol (CCT) 1993; 16: 301-9.
96. Gilliland FD, Samet JM. Lung cancer. In: Doll R, Fraumeni JF Jr, Muir CS (eds). Cancer Surveys Volume 19: Trends in cancer incidence and mortality. Imperial Cancer Research Fund, New York, United States 1994: 175-95.
97. Ries LAG, Miller BA, Hankey BF, et al. (eds.). SEER cancer statistics review, 1973-1991: tables and graphs. NIH Public. No. 94-2789. Besthesda: National Institutes of Health, 1994.
98. Pastorino U, Berrino F, Valente M, et al. Incident lung cancer survival: long term follow-up of a population-based study in Italy. Tumori 1990; 76: 199-204.
99. Levi F, Randimbison L, Te V-C, et al. Trends in cancer survival in Vaud, Switzerland. Eur J Cancer 1992; 28A: 1490-5.
100. Capocaccia R, Micheli A, Berrino F, et al. Time trends of lung and larynx cancers in Italy. Int J Cancer 1994; 57: 154-61.
101. Clerici M, Panvini D, Torri V, et al. Patterns of care and survival in non-small cell lung cancer: 15 years' experience in a general hospital. Tumori 1994; 80: 106-12.
102. Rossing TH, Rossing RG. Survival in lung cancer: an analysis of the effects of age, sex, resectability, and histopathologic type. Am Rev Respir Dis 1982; 126: 771-7.
103. Nou E. The natural five-year course in bronchial carcinoma: epidemiologic results. Cancer 1984; 53: 2211-6.
104. Capewell S. Patients presenting with lung cancer in South East Scotland. Thorax 1987; 42: 853-7.
105. Foucher P, Coudert B, Arveux P, et al. Age and prognosis of non-small cell lung cancer: usefulness of a relative survival model. Eur J Cancer 1993; 29A: 1809-13.
106. Grosclaude P, Galat JP, Mace-Lesech J, et al. Differences in treatment and survival rates of non-small-cell lung cancer in three regions of France. Br J Cancer 1995; 72: 1278-82.
107. Janssen-Heijnen MLG, Schipper RM, Klinkhamer PJJM, et al. Improvement and plateau in survival of small cell lung cancer since 1975: a population-based study. Ann Oncol 1998; 9: 543-7.
108. Skarin AT. Analysis of long-term survivors with small-cell lung cancer. Chest 1993; 103: 440S-4S.

109. Lassen U, Osterlind K, Hansen M, et al. Long-term survival in small-cell lung cancer: posttreatment characteristics in patients surviving 5 to 18+ years: an analysis of 1,714 consecutive patients. J Clin Oncol 1995; 13: 1215-20.
110. Travis WD, Travis LB, Devesa SS. Lung cancer. Cancer Suppl 1995; 75: 191-202.
111. Connolly CK, Jones WG, Thorogood J, et al. Investigation, treatment and prognosis of bronchial carcinoma in the Yorkshire Region of England 1976-1983. Br J Cancer 1990; 61: 579-83.
112. Crawford SM, Atherton F. Lung cancer: histological aspects of diagnosis in England and the south east Netherlands. J Epidemiol Community Health 1994; 48: 420-1.
113. Choi NC, Carey RW, Kaufman D, et al. Small cell carcinoma of the lung: a progress report of 15 years' experience. Cancer 1987; 59: 6-14.
114. Davis S, Wright PW, Schulman SF, et al. Long-term survival in small-cell carcinoma of the lung: a population experience. J Clin Oncol 1985; 3: 80-91.
115. Flehinger BJ, Kimmel M, Melamed MR. The effect of surgical treatment on survival from early lung cancer: implications for screening. Chest 1992; 101: 1013-8.
116. Pearson FG. Current status of surgical resection for lung cancer. Chest 1994; 106(suppl): 337S-9S.
117. De Rijke JM, Schouten LJ, Schouten HC, et al. Age-specific differences in the diagnostics and treatment of cancer patients aged 50 years and older in the province of Limburg, the Netherlands. Ann Oncol 1996; 7: 677-85.
118. Damhuis RAM, Schütte PR. Resection rates and postoperative mortality in 7,899 patients with lung cancer. Eur Respir J 1996; 9: 7-10.
119. Watkin SW, Hayhurst GK, Green JA. Time trends in the outcome of lung cancer management: a study of 9,090 cases diagnosed in the Mersey Region, 1974-1986. Br J Cancer 1990; 61: 590-6.
120. Bunn PA, van Zandwijk N, Pastorino U, et al. European school of oncology first Euro-American forum on lung cancer treatment. Eur J Cancer 1994; 30A: 710-3.
121. Thomas P, Sielezneff I, Ragni J, et al. Is lung cancer resection justified in patients aged over 70 years? Eur J Cardiothorac Surg 1993; 7: 246-51.
122. Osaki T, Shirakusa T, Kodate M, et al. Surgical treatment of lung cancer in the octogenarian. Ann Thorac Surg 1994; 57: 188-93.
123. Jett JR. Current treatment of unresectable lung cancer. Mayo Clin Proc 1993; 68: 603-11.
124. Brodin O, Nou E, Mercke C, et al. Comparison of induction chemotherapy before radiotherapy with radiotherapy only in patients with locally advanced squamous cell carcinoma of the lung. Eur J Cancer 1996; 32A: 1893-1900.
125. Feinstein AR. On classifying cancers while treating patients. Arch Intern Med 1985; 145: 1789-91.
126. Greenberg ER, Baron JA, Dain BJ, et al. Cancer staging may have different meanings in academic and community hospitals. J Clin Epidemiol 1991; 44: 505-12.
127. Satariano WA. Comorbidity and functional status in older women with breast cancer: implications for screening, treatment, and prognosis. J Gerontol 1992; 47: 24-31.
128. Picirrilo JF, Feinstein AR. Clinical symptoms and comorbidity: significance for the prognostic classification of cancer. Cancer 1996; 77: 8334-42.
129. DeMaria LC, Cohen HJ. Characteristics of lung cancer in elderly patients. J Gerontol 1987; 42: 540-5.
130. Guadagnoli E, Weitberg A, Mor V, et al. The influence of patient age on the diagnosis and treatment of lung and colorectal cancer. Arch Intern Med 1990; 150: 1485-90.
131. Monfardini S, Yancik R. Cancer in the elderly: meeting the challenge of an aging population. J Natl Cancer Inst 1993; 85: 532-8.
132. Wei JY. Cardiovascular comorbidity in the older cancer patient. Semin Oncol 1995; 22: 9-10.
133. Ginsberg RJ, Hill LD, Eagan RT, et al. Modern thirty day operative mortality for surgical resections in lung cancer. J Thorac Cardiovasc Surg 1983; 86: 654-8.
134. Nagasaki F, Flehinger BJ, Martini N. Complications of surgery in the treatment of carcinoma of the lung. Chest 1982; 82: 25-9.

135. Burrows B, Earle RH. Course and prognosis of chronic obstructive lung disease: a prospective study of 200 patients. N Engl J Med 1969; 280: 379-404.
136. Postma DS, Burema J, Gimeno F, et al. Prognosis in severe chronic obstructive pulmonary disease. Am Rev Resp Dis 1979; 119: 357-67.
137. Merrilees MA, Scott PJ, Norris RM. Prognosis after myocardial infarction: results of 15 year follow up. Br Med J 1984; 288: 356-9.
138. Feinstein AR, Wells CK. A clinical-severity staging system for patients with lung cancer. Medicine 1990; 69: 1-33.
139. Satariano WA, Ragland DR. The effect of comorbidity on 3-year survival of women with primary breast cancer. Ann Intern Med 1994; 120: 104-10.
140. Wong DH, Weber EC, Schell MJ, et al. Factors associated with postoperative pulmonary complications in patients with severe chronic obstructive pulmonary disease. Anesth Analg 1995; 80: 276-84.
141. Goodwin JS, Samet JM, Hunt WC. Determinants of survival in older cancer patients. J Natl Cancer Inst 1996; 88: 1031-8.
142. Van de Wetering ML, Mooi WJ, Wagenaar SjSc, et al. K-ras oncogene activation in adenocarcinoma of the lung: incidence and relation to smoking. Cancer Res 1988; 48: 5738-41.
143. Kern JA, Slebos RJC, Top B, et al. C-erbB-2 expression and codon 12 K-ras mutations both predict shortened survival for patients with pulmonary adenocarcinomas. J Clin Invest 1994; 93: 516-20.
144. Rodenhuis S, Boerrigter L, Top B, et al. Mutational activation of the K-ras oncogene and the effect of chemotherapy in advanced adenocarcinoma of the lung: a prospective study. J Clin Oncol 1997; 15: 285-91.
145. Pantel K, Izbicki J, Passlick B, et al. Frequency and prognostic significance of isolated tumour cells in bone marrow of patients with non-small-cell lung cancer without overt metastases. Lancet 1996; 347: 649-53.
146. Cohen R, Guber A, Siegal A, et al. The prognostic application of cytokeratin typing of nonsmall cell lung carcinoma: a retrospective study. Cancer 1997; 79: 468-73.
147. Pedersen LM, Milman N. Microalbuminuria in patients with lung cancer. Eur J Cancer 1998; 34: 76-80.
148. Morstyn G, Ihde DC, Lichter AS, et al. Small cell lung cancer 1973-1983: early progress and recent obstacles. Int J Radiation Oncology 1984; 10: 515-39.
149. Osterlind K, Hansen HH, Hansen M, et al. Mortality and morbidity in long-term surviving patients treated with chemotherapy with or without irradiation for small-cell lung cancer. J Clin Oncol 1986; 4: 1044-52.
150. Findley MPN, Griffin AM, Raghaven D, et al. Retrospective review of chemotherapy for small cell lung cancer in the elderly: does the end justify the means? Eur J Cancer 1991; 27: 1597-1601.
151. Schiller JH, Ettinger DS, Larson MM, et al. Phase II trial of oral etoposide plus cisplatin in extensive stage small cell carcinoma of the lung: an Eastern Cooperative Oncology Group Study. Eur J Cancer 1994; 30A: 158-61.
152. Van der Gaast A, Postmus PE, Burghouts J, et al. Long term survival of small cell lung cancer patients after chemotherapy. Br J Cancer 1993; 67: 822-4.
153. Souhami RL, Law K. Longevity in small cell lung cancer: a report to the Lung Cancer Subcommittee of the United Kingdom Coordinating Committee for Cancer Research. Br J Cancer 1990; 61: 584-9.
154. Arriagada R, Pignon JP, Ihde DC, et al. Effect of thoracic radiotherapy on mortality in limited small cell lung cancer: a meta-analysis of 13 randomized trials among 2,140 patients. Anticancer Res 1994; 14: 333-5.
155. Johnson BE, Ihde DC, Bunn PA, et al. Patients with small-cell lung cancer treated with combination chemotherapy with or without irradiation: data on potential cures, chronic toxicities, and late relapses after a five- to eleven year follow-up. Ann Intern Med 1985; 103: 430-8.

156. Perry MC, Eaton WL, Propert KJ, et al. Chemotherapy with or without radiation therapy in limited small-cell carcinoma of the lung. N Engl J Med 1987; 316: 912-8.
157. Pignon J-P, Arriagada R, Ihde DC, et al. A meta-analysis of thoracic radiotherapy for small-cell lung cancer. N Engl J Med 1992; 327: 1618-24.
158. Crown JPA, Phillippe Chahinian A, Jaffrey IS, et al. Predictors of 5-year survival and curability in small cell lung cancer. Cancer 1990; 66: 382-6.
159. Osterlind K, Andersen PK. Prognostic factors in small cell lung cancer: multivariate model based on 778 patients treated with chemotherapy with or without irradiation. Cancer Res 1986; 46: 4189-94.
160. Allan SG, Stewart ME, Love S, et al. Prognosis at presentation of small cell carcinoma of the lung. Eur J Cancer 1990; 26: 703-5.
161. Clamon GH, Audeh MW, Pinnick S. Small cell lung carcinoma in the elderly. Am Geriatr Soc 1982; 30: 299-302.
162. Shepherd FA, Amdemichael E, Evans WK, et al. Treatment of small cell lung cancer in the elderly. J Am Geriatr Soc 1994; 42: 64-70.
163. Siu LL, Shepherd FA, Murray N, et al. Influence of age on the treatment of limited-stage small-cell lung cancer. J Clin Oncol 1996; 14: 821-8.
164. McNaughton Collins M, Barry MJ. Controversies in prostate cancer screening: analogies to the early lung cancer screening debate. JAMA 1996; 276: 1976-9.

Chapter 2. Methods

2.1 Cancer registry, medical care system and region

2.2 Histological classification: codes and changes

2.3 Staging: classification of partially unknown data

2.4 Co-morbidity: list of conditions and validity of recording

2.5 Data analysis

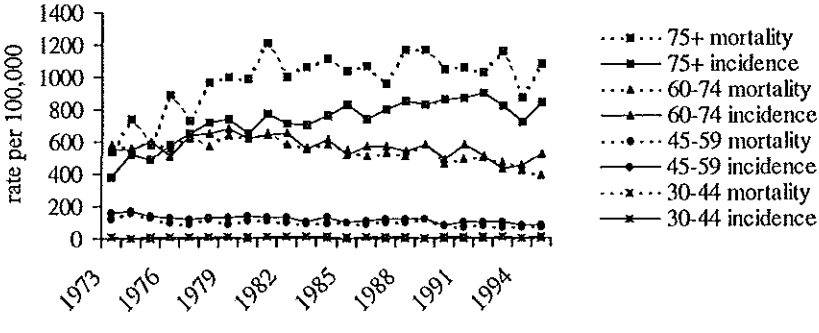
2.6 European data: EUROCIM and EUROCARE

2.1 Cancer registry, medical care system and region

Figure 1

The Eindhoven Cancer Registry (ECR) was started in 1955 as part of a programme for nationwide cancer registration in the area of southeastern North Brabant. Data on all new cancer patients were collected directly from pathology reports and patient records. The registry was started in three hospitals in Eindhoven and gradually expanded to include the southeastern part of the Dutch province of North-Brabant, the northern part of the province of Limburg (since 1970) and the southwestern part of North-Brabant (since 1986) (figure 1). Completeness could be assessed on the basis of referral patterns and registration procedures. Despite the absence of death-certificate-only cases and the increase in the proportion of cases with only a cytological diagnosis, analyses of incidence and comparison with cancer mortality suggested reasonable completeness, except for the very elderly (figure 2). Incidence rates could thus be determined for a core area, comprising 85% of the population covered by the registry.

Figure 2 *Incidence and mortality rates of lung cancer in the southeastern part of the Netherlands, according to age (years).*



The basis for diagnosis of most tumours was histological or cytological verification which was obtained for at least 85% of all lung cancer patients. The proportion of patients diagnosed by means of cytology increased over time to 20% of those younger than 70 years and almost 30% of those 70 and older. The percentage based on clinical diagnosis was higher for the elderly (10%) than for younger patients (4%). Diagnoses

established at autopsy decreased during the study period to less than 2% of all diagnoses (table 1). Access to medical care was easy as a result of the relatively short distances to a hospital (<30 km), ample supply of health services and a sickness insurance system without major financial obstacles. Between 1960 and 1985 the number of chest physicians increased from about 5 to almost 20 per one million inhabitants.

Table 1 *Basis for diagnosis of lung cancer in the Eindhoven Cancer Registry, according to period of diagnosis and age.*

		1972-77 (%)	1978-82 (%)	1983-87 (%)	1988-92 (%)
age <70 years	histology	85	90	78	76
	cytology	3	3	17	19
	clinical	3	4	3	4
	autopsy	3	3	2	1
	unknown	7	0	0	0
age ≥70 years	histology	78	81	61	59
	cytology	5	5	27	28
	clinical	7	8	9	10
	autopsy	4	5	3	3
	unknown	6	0	0	0

Between 1965 and 1975 the (high) fertility rate dropped from 3 to 1.5, illustrating secularization of the largely Roman-Catholic population. As a consequence, there is a pronounced ageing of the population, which is further enhanced by an annual increase in the number of people over 55 years of age of about 2%. The tobacco processing industry, traditionally important in the Eindhoven area, has been in decline since the 1960s. The prevalence of smoking among male adults decreased from more than 90% in the 1950s and 1960s to about 40% in the 1990s. In contrast, the percentage women who smoked was very low in the 1950s but increased to about 40% between the end of the 1960s and the end of the 1970s, later it declined.

2.2 Histological classification: codes and changes

Lung tumours were classified as small-cell carcinoma, non-small-cell carcinoma and some rare subtypes, according to the WHO classification.[1] Non-small-cell carcinomas consisted of squamous cell carcinoma, adenocarcinoma, large-cell undifferentiated carcinoma and some rare subtypes, such as adenosquamous cell carcinoma, adenoid cystic carcinoma and mucoepidermoid carcinoma. Uncommon tumours were mesotheliomas, carcinoid tumours, carcinosarcomas and sarcomas. Malignant mesotheliomas were located in the pleura, peritoneum and tunica vaginalis testis.

About sixty percent of histological specimens of (suspected) mesotheliomas have been reviewed by two or three experts of the Netherlands Mesothelioma Panel since 1969. The histological classification of tumours of the respiratory tract is shown in table 2. During the period 1970-96 data on 13,501 lung cancer patients (9605 non-small-cell lung tumours, 2395 small-cell lung tumours, 99 uncommon lung tumours, 57 other lung tumours such as small-cell carcinomas with other components, 510 malignancies of unknown morphology and 835 tumours diagnosed clinically), and 176 patients with pleural mesothelioma were registered.

Table 2 *Histological classification of tumours of the respiratory tract.*

	ICD-codes
non-small-cell	
squamous cell carcinoma	8070-8080
adenocarcinoma	8140, 8230, 8250, 8260, 8480, 8481, 8550
large-cell undifferentiated carcinoma	8012, 8020, 8021, 8030, 8031, 8310
rare subtypes:	
adenosquamous cell carcinoma	8560
adenoid cystic carcinoma	8200
mucoepidermoid carcinoma	8430
small-cell	8040-8043
uncommon lung tumours	
carcinoid tumour	8240
carcinosarcoma	8980
sarcoma	8800-8900
malignant mesothelioma	9050-9053

2.3 Staging: classification of partially unknown data

In the 1950s and 1960s the Extent of Disease (EoD) system was used, since the 1970s the Tumour Node Metastasis (TNM) system is preferred.[2] Stage assessment has improved due to a combination of modern visual diagnostics, extensive lymph node sampling by surgeons, more extensive searches by pathologists, better documentation by clinicians and better ascertainment by the registrars. When postoperative TNM was not available, the corresponding clinical TNM data were considered. One problem was the high percentage of patients with tumours of unknown stage due to the strict rules for staging. Most physicians in the Eindhoven area were no full-time oncologists and were therefore reluctant to document 'negative' results of staging, especially for elderly patients; fortunately this problem has decreased over time. When analysing the data according to stage, algorithms were developed to make maximum use of data of patients who had not been fully staged according to the strict guidelines. For example,

according to the strict rules for staging, the percentage patients with a non-small-cell lung tumour of unknown stage decreased from 58% in 1975-79 to 39% in 1980-84 and 32% in 1985-94, whereas the percentage patients with localized disease increased from the very low level of 5% in 1975-79 to 19% in 1980-84 and 25% in 1985-94. In order to lower the proportion of tumours of unknown stage patients with Mx were considered as M0, Nx as N0 or N1 and Tx as T1 or T2, but only if the other two variables (T, N or M) were known. Furthermore, the total group of non-small-cell lung cancer patients was divided into two categories (localized and non-localized) in order to include as much information about stage as possible (table 3). The group 'localized' consisted of stages I and II, the group 'non-localized' of stages III (A & B) and IV.

Table 3 *Simplified stage classification.*

Localized	Non-localized
T1/2 N0/1 M0	all T N2/3 all M
T1/2 N0/1 Mx	T3/4 all N all M
T1/2 Nx M0	all T all N M1
Tx N0/1 M0	

The percentage patients with a tumour of unknown stage who underwent resection was rather high in the 1970s, but subsequently decreased. This can be explained by the fact that in 1984 the registry team had to record the TNM-code for patients diagnosed between 1975 and 1983 retrospectively from the data that they had already recorded at the time of diagnosis of the tumour, without going back to the medical records in the hospitals. A review of clinical records of patients diagnosed between 1975 and 1983 showed that most patients with a tumour of unknown stage, who underwent surgical resection, could be reclassified as having 'localized' disease. Furthermore, the prognosis for this group was almost similar to that for the group of patients with localized lung cancer. Thus, in the next step, patients with a tumour of unknown stage who underwent surgical resection were classified as 'localized'. Since the percentage tumours of unknown stage in 1975-79 was very high before the conversion (58%), only data on patients diagnosed since 1980 were used in the analysis of treatment and prognosis. After the conversion the percentage patients with disease of an unknown stage since 1980 was about 5% for patients younger than 70 and 15% for the elderly (table 4).

The stage of small-cell lung tumours is separated into two categories, according to a system of classification of the Veterans Administration Lung Cancer Study Group (VALG):[3] limited disease (confined to one hemithorax including hilar, ipsilateral and contralateral mediastinal and ipsilateral and contralateral supraclavicular lymph nodes) and extensive disease (any disease at sites beyond the definition of limited disease). Data on tumour stage collected since 1990 could be used for analysis of treatment and

prognosis of small-cell carcinoma. Since the proportion of surgical resections among these patients was very low, only the clinical stage was used.

Table 4 *Stage distribution of non-small-cell lung cancer after conversion.*

	1975-79	1980-84	1985-89	1990-92
age <70 years				
localized (%)	31	34	37	33
non-localized (%)	58	60	58	63
unknown (%)	11	6	5	4
age ≥70 years				
localized (%)	18	28	37	40
non-localized (%)	58	55	48	48
unknown (%)	24	18	15	12

2.4 Co-morbidity: list of conditions and validity of recording

With the rising mean age, care for cancer patients with serious concomitant diseases is becoming increasingly complex because of interactive effects of the various therapies and complications. The prognosis for patients with co-morbidity is likely to be worse, independent of age, disease stage, and type of treatment. The Eindhoven Cancer Registry, in close consultation with clinicians, has been collecting data on clinically relevant concomitant diseases in all new cancer patients since 1993. An adapted version of the list of Charlson and colleagues (1987) is used (table 5).[4] The cancer registry collects data from records of the Department of Pulmonary Diseases but also from the medical records of other specialists, especially the Departments of Radiotherapy and Surgery.

To validate data on co-morbidity recorded by registry personnel, 127 consecutive patients with lung cancer diagnosed in 1995 in three hospitals in the registration area were studied. A comparison was made between data recorded by chest physicians and those recorded by the registry team. An epidemiologist studied the clinical records of patients when disagreement occurred between the chest physician and the registry team. In total 103 of 132 diseases were correctly registered by the registry personnel and 32 patients were correctly registered as having no co-morbidity (table 6). Thus 82% of all co-morbidity was scored correctly by the cancer registry (correct registration/total = (103+32)/(132+32) = 82%). There was an underestimation of the total number of diseases by the registry of 8% (11/132). The number of cardiovascular diseases was underestimated by 27%, while the occurrence of COPD was overestimated by 6%.

Table 5 *Classification of co-morbidity, according to an adapted version of the list of Charlson et al. (1987).*

Chronic Obstructive Pulmonary Disease (COPD) (medically treated)
Cardiovascular diseases:
myocardial infarction, cardiac decompensation, angina pectoris, peripheral arterial disease, intermittent claudication, abdominal aneurysm
Cerebrovascular diseases (cerebrovascular accident, hemiplegia)
Other malignancies (except basal cell skin carcinoma)
Hypertension (medically treated)
Diabetes Mellitus (medically treated)
Other:
connective tissue diseases (Besnier Boeck disease (sarcoidosis), Wegener's granulomatosis, systemic lupus erythematodes)
rheumatoid arthritis (only severe)
kidney diseases (chronic glomerulonephritis, chronic pyelonephritis)
bowel diseases (Crohn's disease, ulcerative colitis)
liver diseases (cirrhosis, hepatitis)
dementia
tuberculosis

The main causes for disagreement were: (1) unfamiliarity with names of diseases or treatment that were not included in the list used by the cancer registry for recording co-morbidity (mainly cardiovascular diseases), (2) vague description of the disease in the medical records (mainly COPD), and (3) data not reported in the clinical records of the Department of Pulmonary Diseases. The discrepancies can in part be explained by the fact that the registry team used not only the clinical records of the Department of Pulmonary Diseases but also those of Radiotherapy and Surgery.

Table 6 *Percentages underestimation and overestimation by the cancer registry.*

	Correct*		Overestimation		Underestimation		Total
co-morbidity	N	(%)	N	(%)	N	(%)	N(=100%)
COPD	23	(74)	5	(16)	3	(10)	31
cardiovascular	28	(64)	2	(5)	14	(32)	44
hypertension	18	(95)	1	(5)	0	(0)	19
other malignancy	16	(100)	0	(0)	0	(0)	16
metabolic disorder	8	(89)	1	(11)	0	(0)	9
other diseases	10	(77)	0	(0)	3	(23)	13
total	**103**		**9**		**20**		**132**

* correct registration by the cancer registry (opinion of the epidemiologist was the golden standard)

Improvement in the registration of cardiovascular diseases was achieved by adding names of diseases to the list of co-morbid conditions used since 1996. However, improvement in the registration of COPD remains difficult, because the description in the medical records is sometimes vague.

2.5 Data analysis

Incidence

For the analyses of incidence only data from the eastern part of the region were used. The population-at-risk for each year was derived from data provided by Statistics Netherlands. For each 5-year period age-specific (15 years) incidence rates were calculated per 100,000 person-years. Incidence rates for uncommon tumours were given per one million person-years and for longer periods (10 years). For time-trend analysis of incidence 3-year moving means were computed from annual rates. Since age is an important risk factor for lung cancer and the age structure of populations differs over time and between countries, adjustment for age was performed with the 'World Standard Population' or the 'European Standard Population' as reference.[5] Since trends in incidence may reflect changes in exposure of birth cohorts rather than period-related exposure, trends according to birth cohort were also calculated.

Survival

There was a combination of passive and active follow-up of the patients, with the latest check on vital status on 1 April 1994, using municipal population records. Only 0.3% of patients was lost to follow-up, mainly due to repeated migration. For survival analyses data on patients diagnosed since 1975 in the eastern part of the registration area were used. To enhance comparability with clinical studies, patients diagnosed around the day of death and those who died within the first month of diagnosis were excluded from survival analyses (14% of patients younger than 70 years and 8% of the elderly).

Usually the main interest is disease-specific survival. Since some patients die of causes other than the underlying cancer, particularly in older age groups, the observed survival (irrespective of the cause of death) does not reflect the disease-specific survival. Since causes of death are not listed in the cancer registry, it is not possible to calculate disease-specific survival. In order to estimate the latter, the relative survival rate was calculated as the ratio of the observed to the expected actuarial rates. Expected survival rates were calculated from life tables for regional male and female populations with the same 5-year age distribution (supplied by Statistics Netherlands). The risk of death due to lung cancer was modelled using a program of the Finnish Cancer Registry.[6] The standard error of the survival rates was calculated according to Greenwood's formula.[7] For multivariate relative survival analysis a program based on Cox regression analysis was used (Relsurv).[8,9]

For patients younger than 70 years of age diagnosed between 1975 and 1989 and alive one, three, five or eight years after diagnosis, the conditional relative 5-year survival rates were also computed. The aim was to assist physicians and patients in assessing prognosis for patients who are still alive at or after these intervals.

2.6 European data: EUROCIM and EUROCARE

For comparison of incidence data within Europe the EUROCIM (EUROpean Cancer Incidence and Mortality) database was used (1978-92). EUROCIM consists of cancer incidence and mortality data from many European cancer registries.
For comparison of survival figures within Europe the EUROCARE (European cancer registry-based study of survival and care of cancer patients) database was used (1978-92).[10] EUROCARE is a concerted action of initially 30, now 50, European cancer registries to estimate and compare the survival of cancer patients in different European populations. Included are cancer registries with a substantial proportion (>75%) of diagnoses, verified histologically.

References

1. WHO. The World Health Organization histological typing of lung tumours. Am J Clin Path 1982; 77: 123-36.
2. Mountain CF. A new international staging system for lung cancer. Chest 1986; 89 (suppl): 225-33.
3. Stahel RA, Ginsberg R, Havemann K, et al. Staging and prognostic factors in small-cell lung cancer: a consensus report. Lung Cancer 1989; 5: 119-26.
4. Charlson ME, Pompei P, Ales KL, et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chron Dis 1987; 40: 373-83.
5. Parkin DM, Whelan SL, Ferlay J, et al. Cancer Incidence in Five Continents Vol. VII. IARC Scientific Publications No. 143. Lyon, 1997.
6. Hakulinen T, Abeywickrama KH. A computer package for relative survival analysis. Computer Programmes in Biomedicine 1985; 19: 197-207.
7. Greenwood M. Reports on Public Health and Medical Subjects No. 33, appendix 1: the "errors of sampling" of the survivorship tables. London: Her Majesty's Stationary Office, 1926.
8. Estève J, Benhamou E, Croasdale M, et al. Relative survival and the estimation of net survival: elements for further study. Stat Medicine 1990; 9: 529-38.
9. Hedelin G. RELSURV 2.0: a program for relative survival. Technical report Department of epidemiology and public health. Strasbourg: Louis Pasteur University, 1997.
10. Berrino F, Sant M, Verdecchia A, et al. (eds.). Survival of cancer patients in Europe: the EUROCARE study. IARC Scientific Publications No. 132, Lyon, 1995, 232-44.

Chapter 3. Trends in incidence

3.1 Striking changes in smoking behaviour and lung cancer incidence by histological type in south-east Netherlands, 1960-1991

3.2 Very high male lung cancer incidence rates in areas with tobacco industries

3.1 Striking changes in smoking behaviour and lung cancer incidence by histological type in south-east Netherlands, 1960-1991*

Abstract

Changes in lung cancer incidence in the southeastern part of the Netherlands between 1960 and 1991 were analysed, using data from the Eindhoven Cancer Registry, and related to previous changes in smoking habits. Male lung cancer incidence rates increased markedly from birth cohorts 1890-1899 to 1910-1919, followed by a decline. The peak incidences for both squamous cell carcinoma and small-cell carcinoma were reached in 1978, while for adenocarcinoma it was 1985. A rising trend in female lung cancer incidence up to 1988 was found for each successive birth cohort and for every histological type. These changes in lung cancer incidence rates are most likely related to the pattern of past smoking habits: the percentage of male adult smokers in the southern part of the Netherlands decreased from 95% in 1960 to 40% in 1981 and the percentage of female adult smokers increased from 27% in 1960 to 40% in 1967, slightly decreasing only after 1979. In view of the trends in smoking behaviour, the incidence rates for male lung cancer will decline further, whereas female lung cancer incidence may decrease after the year 2000.

* Reprinted from Eur J Cancer, 31A. Janssen-Heijnen MLG, Nab HW, van Reek J, van der Heijden LH, Schipper RM, Coebergh JWW. Striking changes in smoking behaviour and lung cancer incidence by histological type in south-east Netherlands, 1960-1991, pp. 949-52, Copyright (1995), with permission from Elsevier Science.

Introduction

In the southeastern part of the Netherlands male lung cancer incidence and mortality were among the highest in Europe from 1969 up to 1990, whereas female lung cancer incidence and mortality were among the lowest until 1980.[1-4] Previous reports have suggested that the mortality rate for lung cancer among Dutch men has changed markedly: a decline is now apparent after a marked increase since the World War II. In contrast, female lung cancer mortality has increased steadily.[5,6] In this survey, temporal trends in the incidence of lung cancer in the southeastern part of the Netherlands during the period 1960-1991 were investigated, using data from the Eindhoven Cancer Registry. To assess completeness, regional mortality data were also considered. We analysed the changing trends according to period of diagnosis and 10-year birth cohort. Since smoking is by far the most prominent risk factor for lung cancer,[7] and relative risks of smoking are higher for squamous cell carcinoma and small-cell carcinoma than for adenocarcinoma,[8-10] the trend in incidence was also analysed according to histological type. Regional patterns in smoking habits, obtained from national surveys held since 1958, were considered.

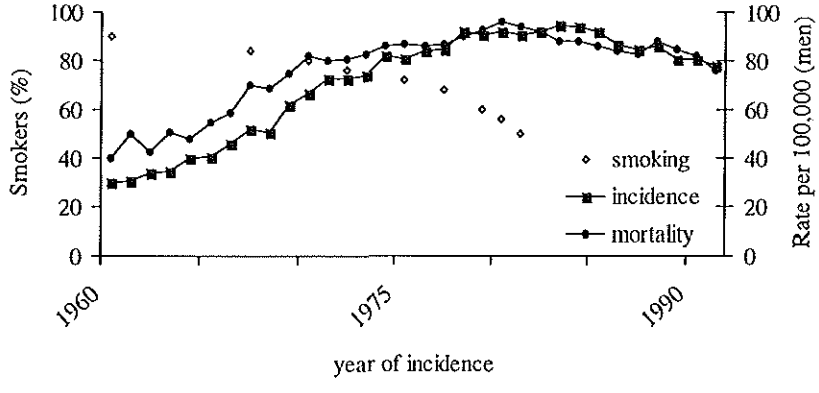
Patients and methods

Data were obtained from the Eindhoven Cancer Registry, which contains data on patients with cancer newly diagnosed since 1955 in community hospitals (data collected from clinical records after notification by pathologists, radiotherapists, and medical record administrations). This registry covers a large part of the southeastern area of the Dutch province of North Brabant since 1960, and this complete area together with the northern part of the adjacent province of Limburg since 1970. The ICD code for lung cancer was 162. We distinguished between squamous cell carcinoma, adenocarcinoma, small-cell carcinoma and 'other plus not otherwise specified (NOS)', according to the WHO classification.[11] Because of the poor reproducibility for large-cell and undifferentiated carcinoma we classified these tumours into the group of 'other and not otherwise specified'.[12] Analyses according to histological type were only applied to patients diagnosed since 1971, because then the percentage 'not otherwise specified' became small enough (10%). The composition of the population was determined annually from data of the Department of Population Statistics of the Central Bureau of Statistics (CBS). Because the registry does not receive data from death certificates, the incidence data were compared with mortality data to assess completeness. Regional mortality data were derived from the CBS.

Incidence rates were computed per 100,000 person-years for each sex and displayed as 3-year moving means. Age-adjustment was performed by direct standardization according to the World Standard Population (WSR: World Standardized Rate).[3] Age-specific incidence rates were calculated per 10-year birth cohort since 1890. Smoking habits of the Dutch population were derived from periodic surveys, conducted in every region of the Netherlands from 1958 to 1981.[13]

Figure 1 *Age-standardized incidence and mortality rates for lung cancer, 1960-1991, and percentage of male smokers in southern Netherlands between 1960 and 1981.*

a) male



b) female

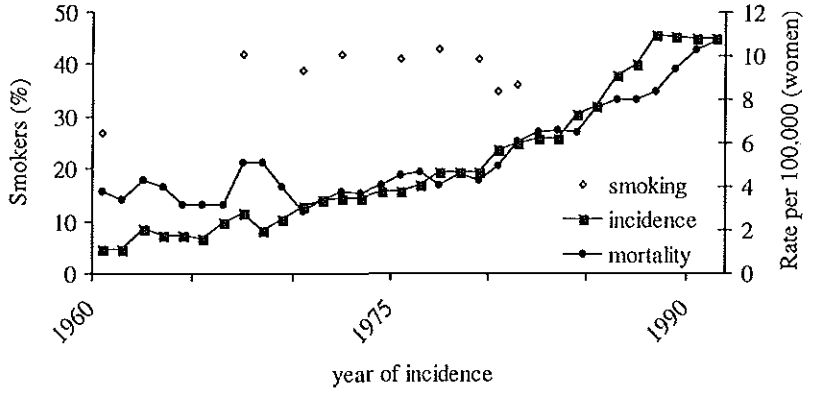
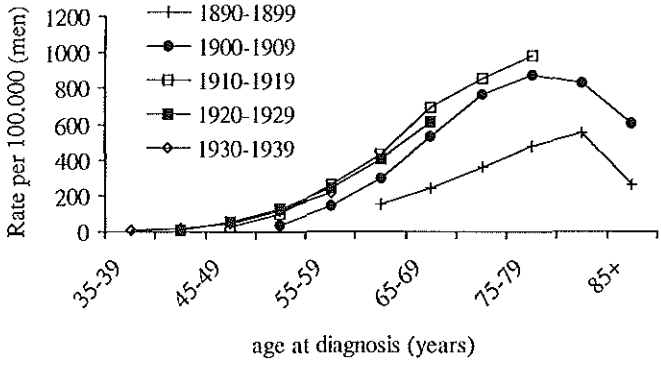
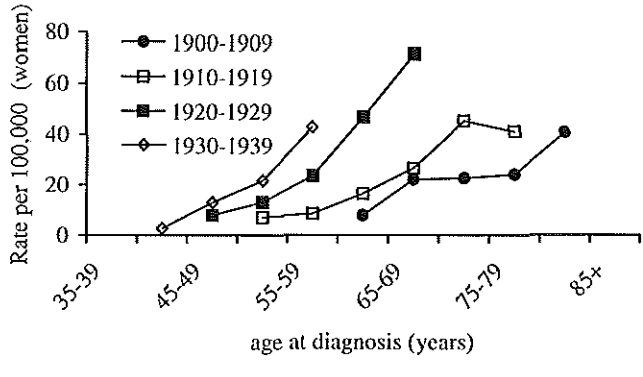


Figure 2 *Age-specific incidence rates for lung cancer in the southeastern part of the Netherlands, according to 10-year birth cohort.*

a) male



b) female



Results

Between 1960 and 1991, 10,223 lung cancer patients (9412 men and 811 women) were registered in the southeastern part of the Netherlands. The age-adjusted male lung cancer incidence rate increased from 30 per 100,000 person-years in 1960 to 95 in 1983 and then decreased to 78 in 1991. The percentage male adult smokers in the southern Netherlands decreased remarkably, from the very high 95% in 1960 to 50% in 1981 (figure 1a). Between 1960 and 1981, the number of cigarettes smoked per day among males rose from 18 to 23. Age-adjusted incidence rates for females increased

from 1 per 100,000 person-years in 1960 to 11 in 1988 and then stabilised (figure 1b). In contrast to men, the percentage of female adult smokers in the southern Netherlands increased strongly from 27% in 1960 to 40% in 1967. After 1979, it decreased to 36% in 1981 (figure 1b). Between 1960 and 1981, the number of cigarettes smoked per day among females rose from 8 to 19.
The trends of lung cancer mortality rates were similar to the incidence rates, but until 1977 lung cancer mortality was higher than incidence. Lung cancer incidence and mortality rates for males were markedly higher than for females. However, the male/female ratio declined from 20 between 1960 and 1976 to 8 in 1991 (figure 1a and b). The incidence rate increased for men born between 1890 and 1919 and then decreased (figure 2a), while for females it has increased continuously for every successive birth cohort between 1900 and 1939 (figure 2b).
Among men the age-standardized incidence rate for squamous cell carcinoma, being the most common histologic type of lung cancer, and small-cell carcinoma increased until 1978, whereas that for adenocarcinoma increased until 1985 (figure 3a). The proportion of adenocarcinoma varied between 4 and 7% until 1980, thereafter rising steadily to 15%. Among women, the incidence of all histological types increased between 1971 and 1988 (figure 3b).

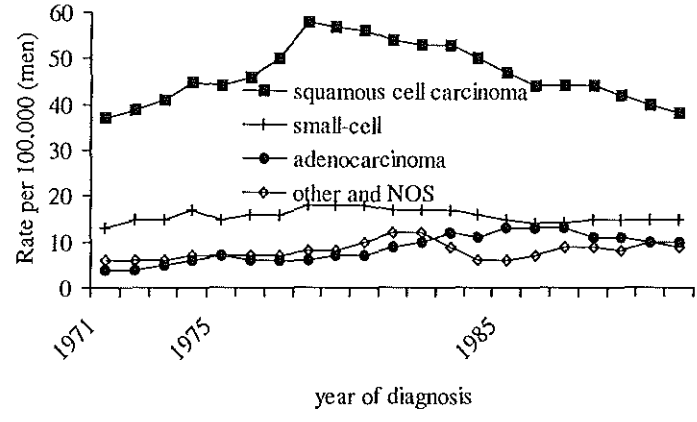
Discussion

Dramatic changes have occurred in the male lung cancer incidence rates in the southeastern part of the Netherlands, increasing markedly until 1983, for birth cohorts from 1890-1899 to 1910-1919 and then declining. For squamous cell carcinoma and small-cell carcinoma, the peak incidence rates were reached in 1978 and for adenocarcinoma in 1985. Female lung cancer incidence rates, initially at a very low level, increased continuously to a plateau in 1988. This rising trend was found for every successive birth cohort and for every histological type.

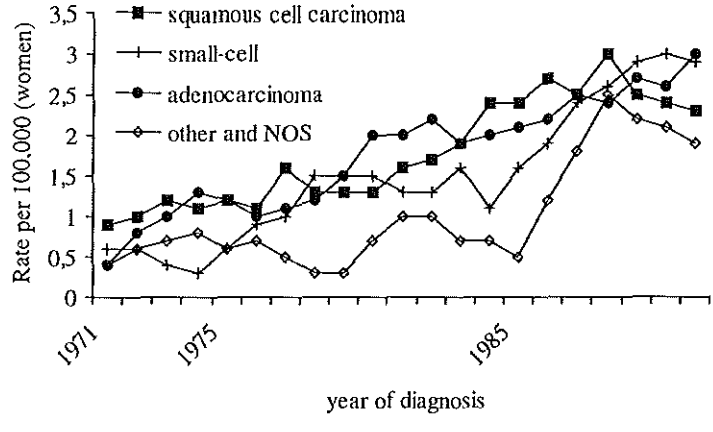
From trends in lung cancer mortality, it also appears that a small part of the increase (especially among the elderly) can be explained by better detection and verification of the diagnosis through flexible bronchoscopy and cytology.[14] The percentage of cytological verification increased from 0% in 1960 to 11% in 1977 and to 22% in 1991. The presumably more rapid decrease in mortality due to cardiovascular diseases since 1970 may also play a role.[15,16]
The trends in lung cancer incidence are most likely related to the changing habits in cigarette smoking, the greatest single cause of lung cancer.[7] The decline of male smokers since 1958 was followed by a reduction in male lung cancer incidence after

Figure 3 *Age-standardized incidence rates in the southeastern part of the Netherlands, according to histological type.*

a) male



b) female



20-25 years. In the earlier male birth cohorts, the average duration of exposure to cigarettes was longer than in later birth cohorts. Whereas the number of cigarettes smoked per day by those who continued to smoke rose from 18 to 23 for males and from 8 to 19 for females, more low tar and/or filter cigarettes were smoked.[13,17]
Whereas previous studies, covering the Netherlands as a whole, have shown similar trends in lung cancer mortality, our study seems to show a more extreme situation.[4,5,18] Firstly, the male lung cancer incidence in the southeastern part of the Netherlands was

one of the highest in Europe and between 1969 and 1990 regional mortality was also higher than in other parts of the Netherlands.[1,2,4,19] Between 1958 and 1981, the percentage of male smokers was 5% higher in the southern part of the Netherlands than in the rest of the country, which was possibly related to high social acceptance due to the presence of many tobacco processing industries. Secondly, female lung cancer incidence and mortality in the southeastern part of the Netherlands were among the lowest in the Netherlands and in Europe up to 1980,[1,2,4,19] due to the very low initial percentage of female smokers in this part of the Netherlands, which may be explained by the traditional life-style of largely Catholic women.
Another argument for the role of smoking habits is the fact that the peak incidences for males of squamous cell carcinoma and small-cell carcinoma, both of which are related to smoking more than adenocarcinoma,[8-10] were reached in 1978, while that of adenocarcinoma was not reached until 1985. The changing histopathology of lung cancer, which was also seen in other surveys,[20,21] is not likely to be related to the use of the new WHO-classification since 1981,[22] because solid carcinomas with mucus formation were classified in the group of adenocarcinoma during the whole period. It is uncertain whether the increased incidence of adenocarcinoma for males points to a more delayed effect of tobacco on adenocarcinoma and/or (combined) exposure to other risk factors relevant to this area, such as occupational exposure (heavy metals).[8,19]

In view of the trends in known risk factors and latency time, the incidence rates for male lung cancer will probably decline further in the near future. A decrease in female lung cancer incidence is not expected before the beginning of the next century.

References

1. Netherlands Central Bureau of Statistics. Atlas of the cancer mortality in the Netherlands 1969-1978. The Hague: Staatsuitgeverij, 1980.
2. Netherlands Central Bureau of Statistics. Atlas of the cancer mortality in the Netherlands 1979-1990. The Hague: SDU/publishers/CBS publications, 1992.
3. Parkin DM, Muir CS, Whelan SL, et al. (eds.) Cancer incidence in five continents, vol VI. Lyon: IARC Scientific Publications No.120, 1992: 865-70.
4. Kunst AE, Mackenbach JP. Regional lung cancer death rates unrelated to smoking? The case of the Netherlands. Eur J Cancer 1993; 29A: 270-3.
5. Verbeek ALM, Peeters PHM, Sturmans F. Is the peak of the lung cancer epidemic in the Netherlands visible already? [in Dutch] Ned Tijdschr Geneeskd 1985; 129: 2365-9.
6. Van der Hoff NM. Cohort analysis of lung cancer in the Netherlands. Int J Epidemiol 1979; 8: 41-6.
7. Doll R, Peto R. Mortality in relation to smoking: 20 years' observation on male British doctors. Br Med J 1976; 2: 1525-36.
8. Lubin JH, Blot WJ. Assessment of lung cancer risk factors by histologic category. J Natl Cancer Inst 1984; 73: 383-9.

9. Pezotto SM, Mahuad R, Bay ML, et al. Variation in smoking-related lung cancer risk factors by cell type among men in Argentina: a case-control study. Cancer Causes and Control 1993; 4: 231-7.
10. Risch HA, Howe GR, Jain M, et al. Are female smokers at higher risk for lung cancer than male smokers?. Am J Epidemiol 1993; 138: 281-93.
11. Anonymous. The World Health Organization histological typing of lung tumours. Am J Clin Path 1982; 77: 123-36.
12. Watkin SW. Temporal demographic and epidemiologic variation in histologic subtypes of lung cancer: a literature review. Lung cancer 1989; 5: 69-81.
13. Van Reek J. Smoking behaviour in the Netherlands: a striking decrease between 1958-1982. Hygie 1985; 4: 19-23.
14. Coebergh JWW. Epidemiology of lung cancer in the Netherlands: trends in incidence, patterns of care and survival in southeastern Netherlands in the period 1975-87. In: Incidence and prognosis of cancer in the Netherlands: studies based on cancer registries. Rotterdam: Erasmus University. Thesis, 1991: 131-44.
15. US DHHS (Department of Health and Human Services). The health benefits of smoking cessation. A report of the Surgeon General 1990. Bethesda: US Department of Health and Human Services, Public Health Service, Office on Smoking and Health, 1990.
16. LaCroix AZ, Lang J, Scherr P, et al. Smoking and mortality among older men and women in three communities. N Engl J Med 1991; 324: 1619-25.
17. Wynder EL, Goodman MT, Hoffmann D. Demographic aspects of the low-yield cigarette: considerations in the evaluation of health risk. J Natl Cancer Inst 1984; 72: 817-22.
18. La Vecchia C, Luccini F, Negri E, et al. Trends of cancer mortality in Europe, 1955-1989: II, respiratory tract, bone, connective and soft tissue sarcomas, and skin. Eur J Cancer 1992; 28: 514-99.
19. La Vecchia C, Boyle P, Franceschi S, et al. Smoking and cancer with emphasis on Europe. Eur J Cancer 1991; 27: 94-104.
20. Dodds L, Davis S, Polissar L. A population-based study of lung cancer incidence trends by histologic type, 1974-81. J Natl Cancer Inst 1986; 76: 21-9.
21. Wu AH, Henderson BE, Thomas DC, et al. Changing patterns of lung cancer incidence by histological type. J Natl Cancer Inst 1986; 77: 53-6.
22. Campobasso O, Andrion A, Ribotta M, et al. The value of the 1981 WHO histological classification in inter-observer reproducibility and changing pattern of lung cancer. Int J Cancer 1993; 53: 205-8.

3.2 Very high male lung cancer incidence in areas with tobacco industries*

In the 1970s in the southeastern part of the Netherlands, the male lung cancer incidence rate was among the highest in Europe, whereas that for females was among the lowest.[1] However, the rates for men have been decreasing since 1983; those for women are still increasing. In a previous report (Eur J Cancer 1995; 31A: 949-52), it was shown that the changes in lung cancer incidence reflect changes in smoking behaviour, considered to be the major risk factor,[2] which occurred 20-25 years ago.[3] The traditional presence of tobacco-processing industries in the southeastern part of the Netherlands, concentrated mainly in a few rural communities (Valkenswaard, Bladel, Eersel and Tegelen), very likely influenced smoking behaviour. Between 1900 and 1935 approximately 20% of the inhabitants of Valkenswaard (just south of Eindhoven) were employed in the tobacco-processing industries and had an ample supply of tobacco. Since the southeastern part of the Netherlands was mainly Catholic, smoking was acceptable for men, but not for women (until the 1960s), especially in rural areas. In 1991, the proportion of male smokers in Valkenswaard was still 50% higher than in other rural municipalities. According to Dutch national surveys performed since 1958,[4] the percentage of male smokers in urban and rural areas in the southeastern part of the Netherlands was approximately the same between 1958 and 1981; however, the percentage of female smokers was much higher in urban than in rural areas (figure 1).

Using data from the Eindhoven Cancer Registry, we calculated incidence rates for lung cancer in municipalities with tobacco-processing industries and, because of the different smoking behaviour, in urban and rural municipalities.[5]

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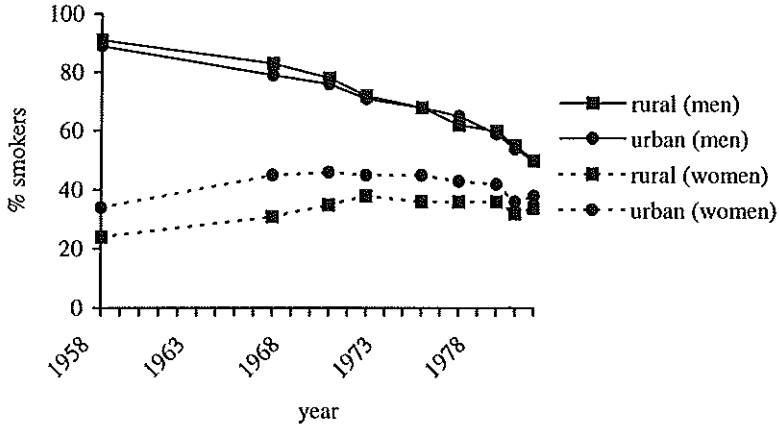
Figure 1 Trends in geographical distribution of smoking behaviour, according to sex.



In municipalities with tobacco-processing industries, lung cancer incidence for men was clearly higher than in other municipalities (figure 2a). In contrast, lung cancer incidence among women was much higher in urban than in rural areas, and the presence of tobacco industries did not make any notable difference (figure 2b).

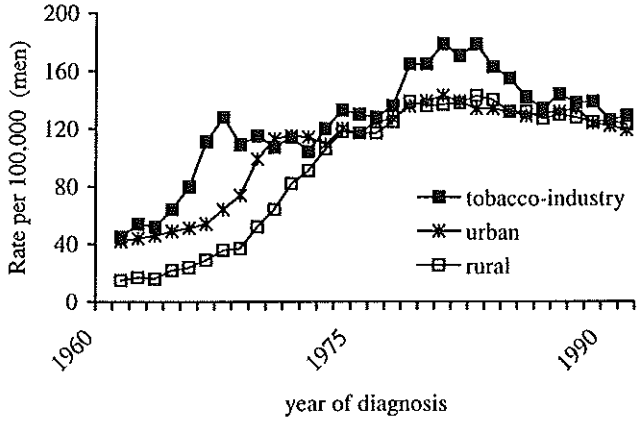
We are not aware of any other explanation for these divergent male and female rates than their past smoking behaviour. This study shows that the presence of tobacco-processing industries in the southeastern part of the Netherlands very likely has increased the percentage of male smokers and the amount smoked per day among employees and their acquaintances, which subsequently has given rise to a very high lung cancer incidence rate after a lag time of 20-25 years. In short, the tobacco industry may be good for jobs, but bad for health in its environment.

References

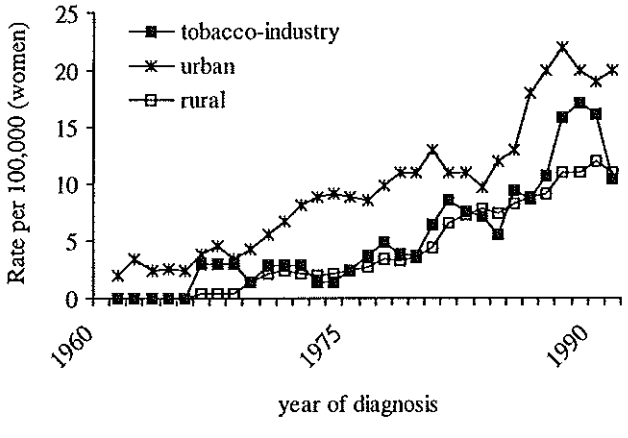
1. Parkin DM, Muir CS, Whelan SL, et al.. (eds.) Cancer incidence in five continents, vol VI. Lyon: IARC Scientific Publications No.120, 1992: 865-70.
2. Doll R, Peto R, Wheatly K, et al. Mortality in relation to smoking: 40 years' observations on male British doctors. Br Med J 1994; 309: 901-11.
3. Janssen-Heijnen MLG, Nab HW, van Reek J, et al. Striking changes in smoking behaviour and lung cancer incidence by histological type in the south-east Netherlands, 1960-1991. Eur J Cancer 1995; 31A: 949-52.
4. Van Reek J. Smoking behaviour in the Netherlands; a striking decrease between 1958-1982. Hygie 1985; 4: 19-23.
5. Heijnen MLG, Coebergh JWW, Nab HW, et al.. Lung cancer incidence and tobacco use in South-east Netherlands since 1960: trends and geographical distribution. [in Dutch]. Tijdschr Soc Gezondheidsz 1994; 72: 194-7.

Figure 2 *Trends in geographical distribution of lung cancer incidence (World Standardized Rate).*

a) male



b) female



Chapter 4. Trends in survival

4.1 Trends in survival of non-small-cell lung cancer.

4.1.1 Divergent changes in survival for histological types of non-small-cell lung cancer in the southeastern area of the Netherlands since 1975.

4.1.2 Common factor for the rising incidence and decreasing survival of adenocarcinoma of the lung?

4.2 Improvement and plateau in survival of small-cell lung cancer since 1975: a population-based study.

4.3 Prevalence of co-morbidity in lung cancer patients and its relationship with treatment: a population-based study.

4.1 Trends in survival of non-small-cell lung cancer.

4.1.1 Divergent changes in survival for histological types of non-small-cell lung cancer in the southeastern area of the Netherlands since 1975*

Abstract

We studied the changes in incidence and survival rates for the histological subtypes of non-small-cell lung cancer, using data of the Eindhoven Cancer Registry over the period 1975-1994.

The proportions with adenocarcinoma and large-cell undifferentiated carcinoma increased from 11% to 21% and from 11% to 15%, respectively, while that with squamous cell carcinoma decreased from 78% to 62%. The increase in the proportion with adenocarcinoma was only found among men. Although the overall prognosis for patients with non-small-cell lung cancer has remained unchanged, there have been divergent changes between morphological subtypes. Relative 1- and 5-year survival rates for squamous cell carcinoma have improved slightly from 48% to 51% and from 14% to 16%, respectively, because of an increase in the proportion with localized tumours, while relative 1- and 5-year survival rates for adenocarcinoma have decreased from 59% to 45% and from 28% to 18%, respectively, because of a decrease in localized tumours. The proportion with localized tumours and the relative 1-year survival for large-cell undifferentiated carcinoma (about 18% and 30%, respectively) were markedly lower.

The divergent trends could partly be explained by changes in the histological classification of tumours, but changes in patterns of risk and biological behaviour of adenocarcinoma cannot be excluded.

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Introduction

Overall survival of patients with lung cancer is poor, but it is better for non-small-cell than small-cell tumours. Although non-small-cell lung cancer is often considered to be one clinically uniform category, several studies indicate that survival may differ according to histological subtype, being better for squamous cell carcinoma and adenocarcinoma than for large-cell undifferentiated carcinoma.[1-4] The morphological distribution of non-small-cell lung cancers has been changing in many countries, including the southeastern part of the Netherlands: the incidence rates for adenocarcinoma and large-cell undifferentiated carcinoma have increased, whereas that for squamous cell carcinoma has decreased.[4-8] The overall survival rates for non-small-cell lung cancer, however, have not changed over time.[9] We studied the changes in incidence and survival rates for unselected patients with non-small-cell lung cancer in the southeastern part of the Netherlands since 1975, separately for each histological subtype.

Patients and methods

The patient data were obtained from the Eindhoven Cancer Registry, which serves the Dutch province of North Brabant and the northern part of the adjacent province of Limburg, an area characterized by a high incidence of lung cancer and by good access to specialized care (medically, financially and geographically). The data were derived directly from clinical records of community hospitals and the Department of Radiotherapy, upon notification by three regional pathological laboratories and hospital record offices. Despite the lack of access to death certificates, the infrastructure of and good access to Dutch health care facilities and the notification procedures used have made it possible to establish cancer registries with a completeness exceeding 95%.[10] The percentage of clinical diagnoses without histological confirmation remained steady at 5% for patients aged younger than 70 and 11% for those over 70 years. Between 1975 and 1994 10,149 lung cancer patients were diagnosed: 7273 non-small-cell lung cancer, 1796 small-cell lung cancer, 471 other lung tumours and 609 clinically diagnosed lung tumours. There was a combination of passive and active follow-up of all patients diagnosed up to 31 December 1992. The latest follow-up to determine vital status by the municipal population administrations occurred on 1 April 1994: 538 patients (8.5%) were still alive, 5738 patients (91.1%) were dead and 22 patients (0.4%) were lost to follow-up.

Non-small-cell lung tumours were classified as squamous cell carcinoma, adenocarcinoma, large-cell undifferentiated carcinoma, and some rare subtypes (adenosquamous cell carcinoma, adenoid cystic carcinoma, mucoepidermoid

carcinoma and others) according to the WHO classification.[11] Stage of disease was recorded on the basis of clinical and/or pathological examination: if available, the postoperative TNM was used, otherwise the clinical TNM. Two categories were considered: localized (stages I and II) and non-localized (stages III (A&B) and IV), according to the Tumour-Node-Metastasis (TNM) system of the Union Internationale Contre le Cancer, version 4.[12] Data on tumour stage collected since 1980 can be considered to be reliable. For analysis of treatment policy, the clinical TNM was used.

Table 1 *Characteristics of patients with non-small-cell lung cancer diagnosed between 1975 and 1994, according to period.*

	1975-79		1980-84		1985-89		1990-94	
	No.	(%)	No.	(%)	No.	(%)	No.	(%)
Sex								
Male	1423	(95)	1695	(94)	1761	(90)	1737	(%)
Female	67	(5)	117	(6)	205	(10)	268	(13)
Age (years)								
<70	979	(66)	1130	(62)	1188	(60)	1186	(59)
≥70	511	(34)	682	(38)	778	(40)	819	(41)
Histology								
Squamous cell	1163	(78)	1324	(73)	1300	(66)	1243	(62)
Adenocarcinoma	170	(11)	295	(16)	397	(20)	425	(21)
Large-cell undiff.	157	(11)	189	(11)	239	(12)	298	(15)
Other	0	(0)	4	(0)	30	(2)	39	(2)
Stage of disease								
Age <70 years								
Localized	*		368	(33)	424	(36)	395	(33)
Non-localized	*		694	(61)	694	(58)	726	(61)
Unknown	*		68	(6)	70	(6)	65	(6)
Age ≥70 years								
Localized	*		170	(25)	252	(33)	292	(36)
Non-localized	*		378	(55)	382	(49)	378	(46)
Unknown	*		134	(20)	144	(18)	149	(18)
Therapy								
Age <70 years								
Surgery	321	(33)	317	(28)	338	(28)	327	(28)
Surgery+radiotherapy	58	(6)	98	(9)	115	(10)	112	(9)
Radiotherapy	372	(38)	480	(42)	533	(45)	507	(43)
Chemotherapy	56	(5)	36	(3)	16	(1)	11	(1)
'Other or none'	172	(18)	199	(18)	186	(16)	229	(19)
Age ≥70 years								
Surgery	42	(8)	61	(9)	99	(13)	140	(17)
Surgery+radiotherapy	8	(2)	19	(3)	22	(3)	27	(4)
Radiotherapy	238	(47)	347	(51)	359	(46)	386	(47)
Chemotherapy	30	(6)	8	(1)	6	(1)	2	(0)
'Other or none'	193	(37)	247	(36)	292	(37)	264	(32)
total	1490		1812		1966		2005	

* only data on tumour stage collected since 1980 can be considered to be reliable.

Treatment (only recorded when given within the first 6 months after diagnosis) was divided into five categories: surgery, surgery and radiotherapy, radiotherapy, chemotherapy, and 'other or none', including palliative therapy other than surgery, chemotherapy or radiotherapy.

Relative survival for patients diagnosed up to 1992 was calculated as the ratio of observed to expected actuarial rates. Expected survival rates were calculated from life tables for regional male and female populations (supplied by Statistics Netherlands), compiled according to 5-year age groups and year of diagnosis. The risk of death due to lung cancer was estimated using a program from the Finnish Cancer Registry.[13] The standard errors of survival rates were calculated according to Greenwood's formula.[14] Survival rates were computed according to sex, age group (<70 years, ≥70 years), histological subtype and stage of disease for the periods 1975-79, 1980-84, 1985-89 and 1990-92. Patients who were diagnosed at autopsy or died within the first month of diagnosis were excluded from the survival analysis (N=475, 8%).

Table 2 *Trends in stage distribution of non-small-cell lung cancer, according to histological type (%).*

Histology	Stage	1980-84 %	1985-89 %	1990-94 %
Squamous cell	Localized	30	37	39
	Non-localized	58	51	49
	Unknown	12	12	12
	Total	N=1324	N=1300	N=1243
Adenocarcinoma	Localized	38	34	32
	Non-localized	52	58	59
	Unknown	10	8	9
	Total	N=295	N=397	N=425
Large-cell undiff.	Localized	15	20	18
	Non-localized	78	71	75
	Unknown	7	9	7
	Total	N=189	N=239	N=298

Results

General characteristics

In total 7273 patients with non-small-cell lung cancer were diagnosed between 1975 and 1994 (6616 men and 657 women). The age-standardized incidence rate (WSR) for men increased from 59 per 100,000 person-years in 1975 to 67 in 1983 and then decreased to 52 in 1995. The peak incidence rate for squamous cell carcinoma was reached in 1978, while for adenocarcinoma it was 1985. The incidence rate for women increased from 3 per 100,000 in 1975 to 9 in 1995. The incidence increased for every histological type. The male/female ratio decreased from 21 in 1975-79 to 6 in 1990-94

and the proportion of elderly patients increased from 34% to 41%. The characteristics of the patients are shown in table 1. Squamous cell carcinoma was the most frequent histological type, but the proportions with adenocarcinoma (only among men) or large-cell undifferentiated carcinoma have increased markedly. Most patients (50%) received radiotherapy and almost 30% of all patients underwent surgical resection (almost 40% of younger and 15% of older patients), of whom 6% had combined surgery and radiotherapy. The use of chemotherapy (in the 1970s mainly endoxan) has decreased markedly.

Trends in stage distribution and treatment policy

The proportion of those with squamous cell carcinoma who were aged 70 years or more increased from 37% in 1975-79 to 46% in 1990-94, for those with adenocarcinoma from 24% to 28% and for those with large-cell undifferentiated carcinoma from 27% to 38%. For patients with squamous cell carcinoma the proportion with localized tumours has increased since 1980. However, for those with adenocarcinoma, the opposite trend was found. For patients with large-cell undifferentiated carcinoma, the proportion with localized tumours has not changed and was clearly lower than for patients with squamous cell carcinoma or adenocarcinoma (table 2). Between 1980 and 1994, just over 85% of all adenocarcinoma patients with a localized tumour underwent surgical resection, in contrast to 55-65% of patients with squamous cell or large-cell undifferentiated carcinoma. For patients with a non-localized tumour the percentages undergoing surgical resection were similar for all three histological types (5-10%). Most patients with a non-localized tumour received radiotherapy (figure 1).

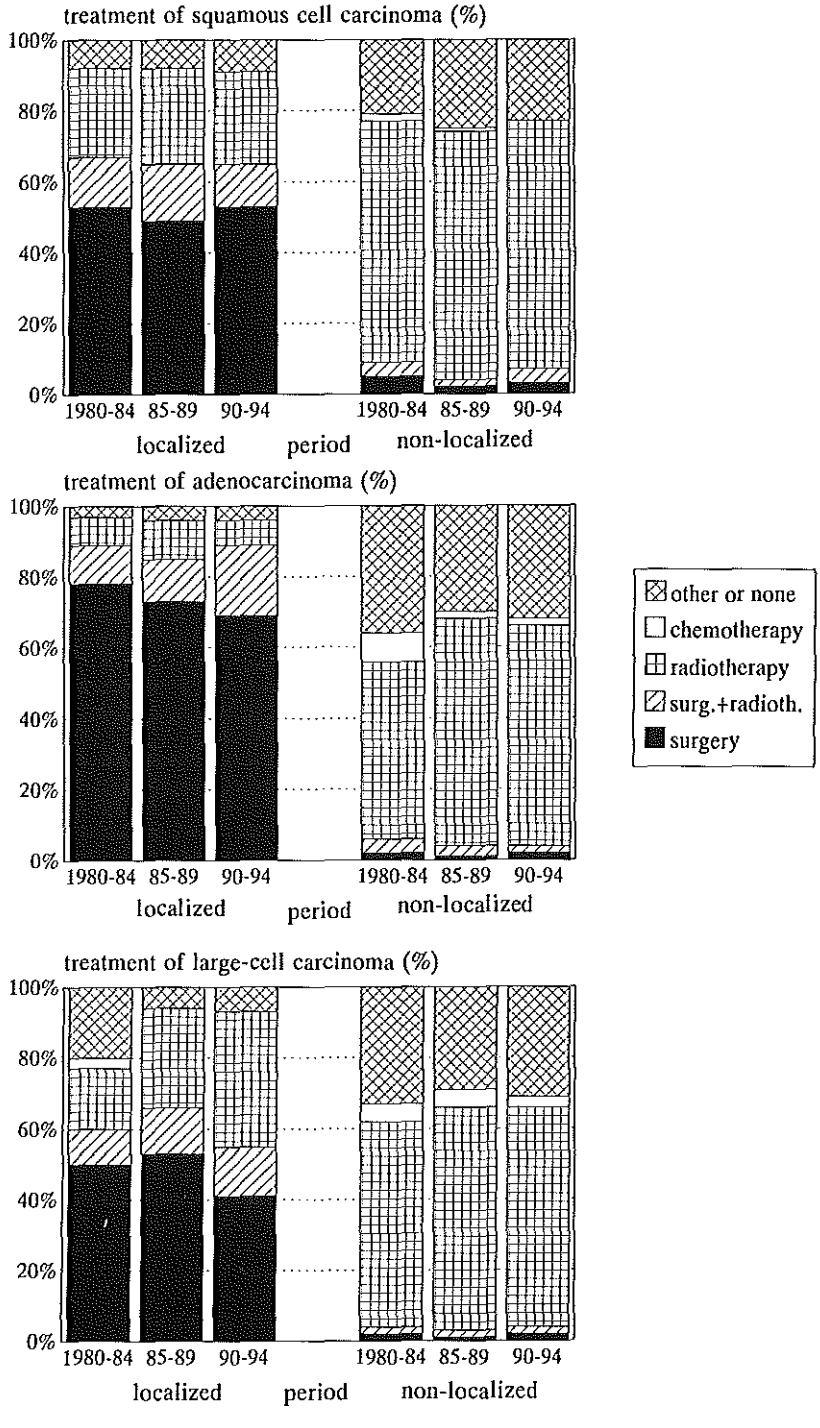
Table 3 *Relative 1- and 5-year survival rates for patients with non-small-cell lung cancer, according to period.*

	Relative 1-year survival				Relative 5-year survival		
	1975-79	1980-84	1985-89	1990-92	1975-79	1980-84	1985-89
	%(SE#)	%(SE#)	%(SE#)	%(SE#)	%(SE#)	%(SE#)	%(SE#)
All NSCLC	48 (1)	47 (1)	48 (1)	47 (2)	15 (1)	15 (1)	17 (1)
Squamous cell	48 (2)	49 (1)	51 (2)	51 (2)	14 (1)	14 (1)	16 (1)
Adenocarcinoma	59 (4)	49 (3)	46 (3)	45 (4)	28 (4)	24 (3)	18 (2)
Large-cell undiff.	32 (4)	31 (4)	30 (3)	26 (4)	11 (3)	7 (2)	10 (2)
Men	47 (1)	47 (1)	48 (1)	47 (2)	15 (1)	15 (1)	16 (1)
Women	54 (7)	45 (5)	46 (4)	44 (5)	21 (6)	18 (4)	17 (3)
Age <70 years	50 (2)	50 (2)	52 (2)	48 (2)	18 (1)	19 (1)	19 (1)
Age ≥70 years	42 (2)	41 (2)	41 (2)	46 (3)	8 (2)	6 (1)	11 (1)
Localized	*	76 (2)	78 (2)	75 (2)	*	37 (2)	38 (2)
Non-localized	*	32 (2)	30 (2)	29 (2)	*	4 (1)	4 (1)

#Standard Error

*Only data on tumour stage collected since 1980 can be considered reliable.

Figure 1 *Trends in treatment of patients with non-small-cell lung cancer, according to histological type.*



Survival

Overall, relative 1-, 5- and 10-year survival rates for patients with non-small-cell lung cancer (48%, 16% and 10% respectively) did not change between 1975 and 1992 and were similar for men and women. Relative 1- and 5-year survival rates were highest for patients younger than 70 years of age and for those with a localized tumour. In addition to being dependent on age and stage, survival clearly varied according to histological subtype. The relative 1-year survival rate for patients with squamous cell carcinoma has increased slightly from 48% in 1975-79 to 51% in 1990-92, while that for patients with adenocarcinoma decreased markedly from 59% to 45%; the same trends were found for the 5-year survival rates. Relative survival rates for patients with large-cell undifferentiated carcinoma were much lower and have not changed significantly over time (table 3). The decrease in survival found for adenocarcinoma was greatest for patients younger than 70 years of age (1-year survival rates decreasing from 63% to 46%) and for men (1-year survival rates decreasing from 61% to 45%). After stratification according to stage, relative 1- and 3-year survival rates for all three histological subtypes did not change over time.

Discussion

In the southeastern part of the Netherlands, the prognosis for patients with non-small-cell lung cancer has remained constant between 1975 and 1992, despite an increase in the number of chest physicians from 10 to 20 per one million inhabitants. Among patients with non-small-cell lung cancer, the proportions with adenocarcinoma and large-cell undifferentiated carcinoma increased, while that with squamous cell carcinoma decreased. The percentage of localized tumours among patients with adenocarcinoma has decreased in contrast to squamous cell carcinoma. The survival rate for patients with squamous cell carcinoma has increased slightly since 1975, while that for adenocarcinoma has decreased markedly, especially among patients younger than 70 years of age and men. However, the changes in survival disappeared after stratification according to stage of disease. While the incidence of large-cell undifferentiated carcinoma increased, neither stage distribution nor prognosis for these patients has changed over time, both being much worse than those found for squamous cell carcinoma and adenocarcinoma.

The incidence rates for squamous cell lung cancer have been decreasing in Western countries,[5,6,15,16] 15-25 years after the decrease in the percentage of smokers. Absolute and proportional increases in the incidence of pulmonary adenocarcinoma have been noticed in many countries.[5-8,15-17] The extent to which changes in diagnostic techniques and/or classification criteria were responsible for the increase in adenocarcinoma is

likely to be limited; despite increased application of better diagnostic techniques applied by more chest physicians, the percentage of localized tumours has decreased. The few solid carcinomas with mucus production, only classified as adenocarcinoma after 1981,[11] cannot be responsible for the increase. Furthermore, in our data set the rise in adenocarcinoma was not caused by an increase in bronchioloalveolar carcinoma, as has been observed by others.[18,19] Changes in exposure to risk factors, such as the increased use of filter cigarettes,[20,21] probably play a role.
Large-cell undifferentiated carcinoma has frequently been called a 'waste-basket' or nonentity, because the carcinomas are so poorly differentiated that squamous or glandular differentiation is no longer evident at the light microscopic level. Thus, the incidence varies with the criteria used to classify the other forms of non-small-cell lung cancer. Together, strict criteria for the diagnosis of squamous cell carcinoma and adenocarcinoma and small biopsies which diminish the chance of detecting focal signs of differentiation may have led to more large-cell undifferentiated carcinomas;[22] sometimes the term is used to distinguish them from small-cell tumours. In the mid-1990s 18 of 52 large-cell undifferentiated carcinomas (35%) could be reclassified as squamous cell carcinoma and seven (13%) as adenocarcinoma. Thus, the observed decrease in squamous cell carcinoma may also be because of the increase in large-cell undifferentiated carcinoma, whereas the observed increase in adenocarcinoma may be even greater.

In 1975-79 relative 1-year survival was highest for patients with adenocarcinoma, but in 1980-84 the relative survival for patients with squamous cell carcinoma surpassed that for adenocarcinoma. A shift of the more aggressive squamous cell tumours toward large-cell undifferentiated tumours or earlier diagnosis because of the use of more refined techniques may have occurred.
Despite increased application of better diagnostic techniques applied by more chest physicians, the percentage patients with localized adenocarcinoma has decreased, with a corresponding decrease in survival. The question is whether adenocarcinoma, especially among younger patients, has become a more aggressive tumour.
Despite a higher resection rate and more younger patients the survival rate for patients with localized adenocarcinoma was not much higher than that for patients with localized squamous cell carcinoma, as was also found in the USA[23] but not in Scotland.[4] In a study in Germany micrometastases in patients with apparently localized lung cancer occurred more often in adenocarcinoma patients.[24]

Between 1978 and 1985, 1-year survival rates in Europe varied between 21% and 42%, and 5-year rates between 6% and 15%. The rates were highest in the southeastern part of the Netherlands, Finland, Switzerland and France and lowest in England, Denmark and Scotland.[25] Since the Eindhoven Cancer Registry is a registry

without death certificate only (DCO) cases, some elderly patients and patients with poor chances of survival may have been missed. However, the proportion missing lung cancer patients in a similar Dutch cancer registry was estimated to be less than 5%.[10] Survival of lung cancer, regardless of histological type, in European countries has not improved over time.[25] In Yorkshire, England, UK, a modest improvement in 2-year survival between 1976 and 1983 was found for patients with non-small-cell lung cancer, especially for patients over 70 years and those with squamous cell carcinoma;[26] however, the percentage with an unknown histology in Yorkshire was very high.[27]

In conclusion, the prognosis for patients with non-small-cell lung cancer did not change significantly between 1975 and 1994. However, there were changes between morphological subtypes: the prognosis for squamous cell carcinoma improved slightly, probably because of an increase in the proportion with localized tumours, while the stage of disease at diagnosis and the prognosis for adenocarcinoma patients became worse, especially for younger patients. For patients with large-cell undifferentiated carcinoma neither stage distribution nor prognosis changed during that period. The divergent trends may be partly explained by changes in histological tumour typing, but changes in patterns of risk and biological behaviour of adenocarcinoma cannot be excluded.

References

1. Capewell S. Patients presenting with lung cancer in South East Scotland. Thorax 1987; 42: 853.
2. Sant M, Gatta G, Capocaccia R, et al. Survival for lung cancer in northern Italy. Cancer Causes Control 1992; 3: 223-30.
3. Hilsenbeck SG, Raub WA, Sridhar KS. Prognostic factors in lung cancer based on multivariate analysis. Am J Clin Oncol (CCT) 1993; 16: 301-9.
4. Travis WD, Travis LB, Devesa SS. Lung cancer. Cancer suppl 1995; 75: 191-202.
5. Zheng T, Holford T, Boyle P, et al. Time trend and the age-period-cohort effect on the incidence of histologic types of lung cancer in Connecticut, 1960-1989. Cancer 1994; 74: 1556-67.
6. Janssen-Heijnen MLG, Nab HW, van Reek J, et al. Striking changes in smoking behaviour and lung cancer incidence by histological type in the south-east Netherlands, 1960-1991. Eur J Cancer 1995; 31A: 949-52.
7. Levi F, Franceschi S, La Vecchia C, et al. Lung carcinoma trends by histologic type in Vaud and Neuchâtel, Switzerland, 1974-1994. Cancer 1997; 79: 906-14.
8. Russo A, Crosignani P, Franceschi S, et al. Changes in lung cancer histological types in Varese Cancer Registry, Italy 1976-1992. Eur J Cancer 1997; 33: 1643-47.
9. Clerci M, Panvini D, Torri V, et al. Patterns of care and survival in non small cell lung cancer: 15 years' experience in a general hospital. Tumori 1994; 80: 106-12.
10. Schouten LJ, Hoppener P, van den Brandt PA, et al. Completeness of cancer registration in Limburg, the Netherlands. Int J Epidemiol 1993; 22: 369-76.
11. WHO. The World Health Organization histological typing of lung tumours. Am J Clin Path 1982; 77: 123-36.
12. Mountain CF. A new international staging system for lung cancer. Chest 1986; 89: (suppl) 225-33.

13. Hakulinen T, Abeywickrama KH. A computer package for relative survival analysis. Computer Programmes in Biomedicine 1985; 19: 197-207.
14. Greenwood M. Reports on Public Health and Medical Subjects No 33, appendix 1: the "errors of sampling" of the survivorship tables. London: Her Majesty's Stationary Office, 1926.
15. Dodds L, Davis S, Polissar L. A population-based study of lung cancer incidence trends by histologic type, 1974-81. J Natl Cancer Inst 1986; 76: 21-9.
16. Wu AH, Henderson BE, Thomas DC, et al. Changing patterns of lung cancer incidence by histological type. J Natl Cancer Inst 1986; 77: 53-6.
17. Travis WD, Lubin J, Ries L, et al. United States lung carcinoma incidence trends: declining for most histologic types among men, increasing among females. Cancer 1996; 77: 2464-70.
18. Barsky SH, Cameron R, Osann KE, et al. Rising incidence of bronchioloalveolar lung carcinoma and its unique clinicopathologic features. Cancer 1994; 73: 1163-70.
19. Barkley JE, Green MR. Bronchioloalveolar carcinoma. J Clin Oncol 1996; 14: 2377-86.
20. Morabia A, Wynder EL. Cigarette smoking and lung cancer cell types. Cancer 1991; 68: 2074-8.
21. Thun MJ, Lally CA, Flannery JT, et al. Cigarette smoking and changes in the histopathology of lung cancer. J Natl Cancer Inst 1997; 89: 1580-6.
22. Gazdar AF, Linnoila RI. The pathology of lung cancer: changing concepts and newer diagnostic techniques. Semin Oncol 1988; 15: 215-25.
23. Humphrey EW, Smart CR, Winchester DP, et al. National survey of the pattern of care for carcinoma of the lung. J Thorac Cardiovasc Surg 1990; 100: 837-43.
24. Pantel K, Izbicki J, Passlick B, et al. Frequency and prognostic significance of isolated tumour cells in bone marrow of patients with non-small-cell lung cancer without overt metastases. Lancet 1996; 347: 649-53.
25. Berrino F, Sant M, Verdecchia A, et al. (eds.) Survival of cancer patients in Europe: the EUROCARE study. IARC Scientific Publications No. 132, Lyon 1995: 232-44.
26. Connolly CK, Ones WG, Thorogood J, et al. Investigation, treatment and prognosis of bronchial carcinoma in the Yorkshire Region of England 1976-1983. Br J Cancer 1990; 61: 579-83.
27. Crawford SM, Atherton F. Lung cancer: histological aspects of diagnosis in England and the south-east Netherlands. J Epidemiology and Community Health 1994; 48: 420-1.

4.1.2 Common factor for the rising incidence and decreasing survival of adenocarcinoma of the lung?

Abstract

Possible explanations for the negative changes in population-based survival rates for adenocarcinoma of the lung between 1975 and 1994 were studied against the background of changes in incidence, using data from the Eindhoven Cancer Registry. While the peak in the age-standardized incidence rate for squamous cell carcinoma of the lung among men was reached in 1978, the rate for adenocarcinoma has increased until 1985. The proportion of adenocarcinoma among men has been increasing since 1975 and for those born after 1920. Among women, the incidence of both squamous cell carcinoma and adenocarcinoma increased until the 1990s. There was a trend toward a more advanced tumour stage among patients with adenocarcinoma younger than 70 years (the proportion advanced tumours increasing from 52% to 64%), but not among the elderly. At the same time the relative 1-year survival rate for younger patients decreased from 64% to 46%; this decline was greatest for men. However, survival according to stage has remained unchanged. In a multivariate analysis, survival for adenocarcinoma decreased for male patients born since 1930 and for those diagnosed since 1980, whereas survival slightly decreased for women born after 1940. Since it is unlikely that the decreasing survival rate for younger patients with adenocarcinoma is due to changes in cancer detection or treatment, it may point to the emergence of a more rapidly metastasizing tumour. Both the rising incidence and the decreasing survival may be related to changes in exposure to smoking, the increased use of low-tar filter cigarettes being the most likely candidate.

Introduction

Among the various histological subtypes of non-small-cell lung cancer, a marked absolute and proportional increase in the incidence rates for adenocarcinoma among men has been observed in the southeastern part of the Netherlands as well as in many other countries, whereas the incidence of squamous cell carcinoma decreased.[1-7] A recent analysis in this area with high incidence rates for lung cancer, indicated declining survival rates for patients with adenocarcinoma but unchanged survival rates for squamous cell carcinoma and large-cell undifferentiated carcinoma.[8] Since such a decrease in survival for patients with one of the histological subtypes of non-small-cell lung cancer is unusual in an area with good access to specialized care (medically, financially and geographically), we report in more detail on the changes in survival rates for adenocarcinoma among men and women against the background of the changes in incidence, taking both effects of period of diagnosis and birth cohort into account.

Patients and methods

The Eindhoven Cancer Registry collects data on patients with cancer newly diagnosed in the Dutch province of North Brabant and the northern part of the adjacent province of Limburg. Despite the lack of access to death certificates, the infrastructure of Dutch health care facilities and the notification procedures used have made it possible to establish cancer registries with a completeness exceeding 95%.[9] The number of chest physicians has increased from 10 per one million inhabitants in the 1970s to 20 in the mid-1980s. During the period 1975-94 the percentage clinical diagnoses without histological or cytological confirmation remained steady at 5% for patients younger than 70 and 11% for those older than 70 years of age. The morphological diagnoses of lung cancer were made by 8 pathologists in 3 laboratories. The microscopic diagnosis of adenocarcinoma was based on tabuloacinar or papillary growth pattern and/or the production of epithelial type mucins by the tumour cells.[10] Stage of disease was recorded on the basis of clinical and/or pathological examination: if available, the postsurgical TNM was used, otherwise the clinical TNM.[11] The patients were divided into two categories: localized (stages I and II) and non-localized (stages III (A&B) and IV). Data on tumour stage can be considered consistent since 1980.
Incidence rates were computed per 100,000 person-years for each sex and displayed as 3-year moving means. Age-adjustment was performed by direct standardization according to the European Standard Population (ESR: European Standardized Rate).[12] We also calculated the proportional distribution of histological subtypes for each 10-year birth cohort, according to 10-year age groups.

A combination of passive and active follow-up of all patients diagnosed between 1975 and 1992 was performed, the latest life-status check being on 1 April 1994. Of all lung cancer patients, only 0.4% were lost to follow-up. Patients who were diagnosed at autopsy or died within the first month of diagnosis were excluded from the survival analysis (N=99, 9%). Relative survival is defined as the ratio of the crude to the expected rates (calculated from life tables for regional male and female populations, compiled according to 5-year age groups and year of diagnosis). The univariate risk of death due to lung cancer, according to period of diagnosis, was predicted from a model prepared by the Finnish Cancer Registry.[13] We used a relative survival analysis (Relsurv programme)[14,15] for estimating the prognostic value on the hazard rate of period of diagnosis and birth cohort simultaneously. Birth cohorts were classified as 10-year periods of birth and period of diagnosis as 1975-79, 1980-84, 1985-89 and 1990-92. We estimated the effect of age at the time of diagnosis (<50, 50-69 and ≥70 years) in the model, because the mean age decreased with more recent birth cohorts and survival has appeared better for younger patients.[8] Each birth cohort and period of diagnosis was classified by a new dummy, with birth cohort 1920-29 and period 1975-79 as reference categories. We stratified, according to gender. The likelihood ratio test was used for calculating P-values. Effects are defined as net hazard rate ratios for each birth cohort and each period compared with the reference categories.

Results

A total of 7273 patients with non-small-cell lung cancer was diagnosed between 1975 and 1994; 1287 had adenocarcinoma (1030 men and 257 women). The peak in incidence rates (ESR) for adenocarcinoma among men was reached in 1985, while that for squamous cell carcinoma was already reached in 1978. Among women the incidence rates for all histological subtypes of non-small-cell lung cancer increased until 1994. The proportion of adenocarcinoma among non-small-cell lung cancer for men increased from 10% in 1975-79 to 18% in 1990-94, while this proportion for women remained about 40%. The proportion of adenocarcinoma among non-small-cell lung cancer has been increasing among men born since 1920, while there was no such trend among women (table 1).

There was a trend toward a more advanced stage among younger patients (the proportion of patients with advanced tumour stage increasing from 52% to 64%), while the trend among the elderly was opposite (decreasing from 54% to 44%). The proportion of tumours of unknown stage remained constant in both age groups. Between 1975 and 1992 the relative 1- and 3-year survival rates for younger patients with adenocarcinoma have decreased markedly from 63% to 46% and from 38% to 26%, respectively (table 2); this decrease was most marked for men. After

stratification according to stage, relative 1- and 3-year survival rates for adenocarcinoma remained approximately steady (table 2).

Table 1 Percentage of adenocarcinoma among histological subtypes of non-small-cell lung cancer (1975-94), according to sex, birth cohort and age.

Men Birth cohort	Age cohort 20-49 yrs			Age cohort 50-59 yrs			Age cohort 60-69 yrs			Age cohort 70-79 yrs			Age cohort 80-99 yrs		
	% **AC**	*mean age**	N*	% **AC**	*mean age**	N*	% **AC**	*mean age**	N*	% **AC**	*mean age**	N*	% **AC**	*mean age**	N*
1890-1899										**11**	*78.3*	66	**8**	*83.9*	121
1900-1909							**10**	*68.3*	173	**8**	*74.8*	868	**9**	*83.0*	285
1910-1919				**9**	*58.5*	91	**12**	*65.8*	1141	**12**	*74.0*	1114	**9**	*81.2*	67
1920-1929	**12**	*48.6*	25	**19**	*56.4*	596	**20**	*64.8*	1139	**16**	*71.5*	190			
1930-1939	**20**	*46.3*	139	**30**	*55.3*	531	**22**	*61.5*	162						
1940-1949	**27**	*43.7*	139	**34**	*51.7*	41									
1950-1959	**44**	*33.9*	18												

Women Birth cohort	Age cohort 20-49 yrs			Age cohort 50-59 yrs			Age cohort 60-69 yrs			Age cohort 70-79 yrs			Age cohort 80-99 yrs		
	% **AC**	*mean age**	N*	% **AC**	*mean age**	N*	% **AC**	*mean age**	N*	% **AC**	*mean age**	N*	% **AC**	*mean age**	N*
1890-1899										----	----	3	**50**	*84.9*	12
1900-1909							----	----	9	**34**	*74.6*	35	**44**	*84.2*	32
1910-1919				----	----	2	**42**	*66.1*	53	**30**	*74.1*	76	----	----	6
1920-1929	----	----	2	**44**	*56.6*	50	**42**	*64.9*	142	**39**	*71.2*	18			
1930-1939	**50**	*46.7*	34	**34**	*55.5*	100	**40**	*61.8*	20						
1940-1949	**50**	*43.1*	52	**42**	*52.2*	12									
1950-1959	**35**	*37.9*	23												

* The mean age and the number of patients reflect all patients with non-small-cell lung cancer.

We studied the effects of period of diagnosis and birth cohort simultaneously. Addition of age group did not substantially improve the model (P=0.2). The hazard rate ratio decreased in men born between 1890 and 1930, whereafter it increased again (P<0.01). The hazard rate ratio for period of diagnosis increased from 1975-79 to 1985-89 (P<0.01). The hazard rate ratio in women increased for those born since 1940, but there was no significant effect for period of diagnosis (P=0.4).

Table 2 *Trends in relative 1- and 3-year survival rates for patients with adenocarcinoma, according to age, gender and stage.*

	Relative 1-year survival				Relative 3-year survival			
	1975-79	1980-84	1985-89	1990-92	1975-79	1980-84	1985-89	1990-92
	%(SE#)	%(SE#)	%(SE#)	%(SE#)	%(SE#)	%(SE#)	%(SE#)	%(SE#)
Overall	59 (4)	49 (3)	46 (3)	45 (4)	36 (4)	27 (3)	25 (2)	24 (3)
Age <70 years	63 (4)	56 (4)	49 (3)	46 (4)	38 (5)	33 (1)	27 (3)	26 (4)
Age ≥70 years	47 (9)	29 (6)	34 (6)	40 (7)	29 (9)	-	20 (5)	-
Men	61 (4)	48 (3)	47 (3)	45 (4)	39 (5)	26 (3)	24 (3)	23 (4)
Women	53 (10)	51 (7)	43 (6)	44 (7)	-	30 (7)	27 (6)	26 (7)
Localized	*	81 (4)	84 (3)	77 (4)	*	54 (4)	57 (4)	49 (5)
Non-localized	*	22 (3)	22 (2)	23 (3)	*	5 (2)	6 (1)	8 (2)

Standard Error

* Only data collected since 1980 can be considered reliable.

Discussion

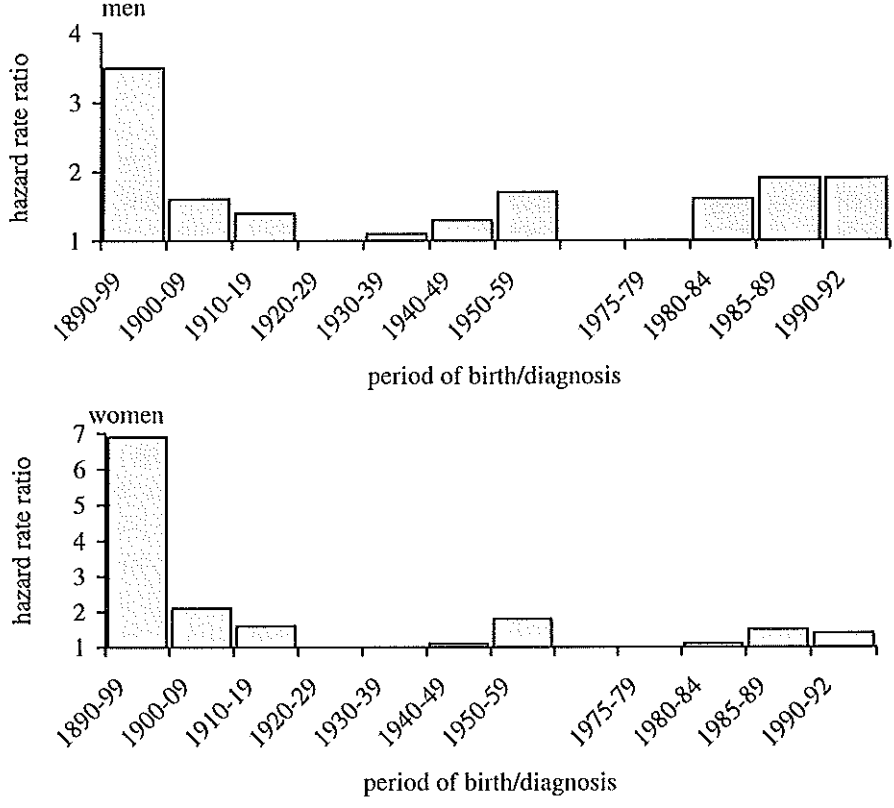
Among men with non-small-cell lung cancer in the southeastern part of the Netherlands the proportion of adenocarcinoma increased since 1975 and for those born since 1920, while among women this proportion remained roughly unchanged. For male patients with adenocarcinoma born since 1930 and for those diagnosed since 1975 the survival rate decreased, whereas the survival rate for female patients slightly decreased for those born since 1940.

The role of changes in detection or histological tumour typing in the increase in incidence for male patients born after 1920 is likely to be limited: despite better diagnostic techniques and the increase in the number of chest physicians, the majority of adenocarcinomas were not diagnosed in an earlier stage of disease. Furthermore, the rise in adenocarcinoma was not caused by an increase in bronchioloalveolar carcinoma, as was found in the United States.[16,17] Most of the increase in the incidence rate for adenocarcinoma among men appears to be real. It has been previously suggested that this increase may be due to the increased use of low-tar filter cigarettes since the 1960s, especially since they only found an increase in adenocarcinoma among smokers.[6,17] The use of filters in longstanding smokers generally results in different inhalation behaviour, e.g. taking larger puffs and retaining smoke longer in

order to compensate for the lower nicotine yield of filter cigarettes. The subsequent increased deposits of smoking particles in the bronchioles could enhance the risk for tumours in the peripheral lung zones, where a substantial number of pulmonary adenocarcinomas arise.[18] Furthermore, low-tar filter cigarettes may increase the risk for adenocarcinoma because of their higher nitrate content.[19] Younger people in the Netherlands were more inclined to smoke low-tar filter cigarettes than the elderly (data derived from periodic surveys in the Netherlands). The change in exposure to filter cigarettes has been less marked for women, because the proportion of smoking women only increased markedly since the 1960s. They mainly smoked low-tar filter cigarettes and the proportion of adenocarcinoma has been considerably higher than for men during the whole study period.

Figure 1 *Hazard rate ratios for birth cohort and period of diagnosis, stratified according to gender.*

Reference categories: *birth cohort 1920-29*
period of diagnosis 1975-79



While the prognosis for patients with the other histological subtypes of non-small-cell lung cancer remained unchanged,[8] we have searched for explanations for the decline in the survival rate since 1975 for male patients with adenocarcinoma of the lung who were born since 1930. Among these patients the proportion with early disease has also been decreasing. It is unlikely that this is due to an increase in patient delay or doctor delay. First, there is an increased awareness among the public of the importance of early diagnosis of cancer in general, and of the major signs of cancer. Second, the number of chest physicians has increased twofold and detection has improved by the increased use of flexible bronchoscopy. We hypothesize that the biological behaviour of adenocarcinomas may have shifted toward a more rapidly metastasizing tumour. This could be associated with the shift to smoking more low-tar filter cigarettes since the 1960s, especially since younger men were more likely to switch from high-tar non-filter cigarettes to low-tar filter cigarettes than the elderly. The percentage smoking low-tar filter cigarettes in the Netherlands has steadily been increasing since the 1960s, up to 78% among male cigarette smokers and up to 92% among female cigarette smokers in 1997 (data derived from periodic surveys in the Netherlands). As described above, filter use could result in a deeper penetration of carcinogens in the peripheral lung zones. In this respect, cigarette smoke-induced K-ras mutations, which are known to be associated with the adenocarcinoma phenotype in lung cancer, have been shown in several studies to be associated with a poor prognosis.[20-22]

We hypothesize that a shift in smoking-related risk factors, such as the increased use of low-tar filter cigarettes, may explain the increase in incidence as well as the decrease in survival for adenocarcinoma, especially in male patients who were born after 1920.

References

1. Janssen-Heijnen MLG, Nab HW, van Reek J, et al. Striking changes in smoking behaviour and lung cancer incidence by histological type in the south-east Netherlands, 1960-1991. Eur J Cancer 1995; 31A: 949-52.
2. Vincent RG, Pickren JW, Lane WW, et al. The changing histopathology of lung cancer: a review of 1682 cases. Cancer 1977; 39: 1647-55.
3. Wu AH, Henderson BE, Thomas DC, et al. Changing patterns of lung cancer incidence by histological type. J Natl Cancer Inst 1986; 77: 53-6.
4. Devesa SS, Shaw GL, Blot WJ. Changing patterns of lung cancer incidence by histological type. Cancer Epidemiol Biomarkers Prev 1991; 1: 29-34.
5. Travis WD, Travis LB, Devesa SS. Lung cancer. Cancer suppl 1995; 75: 191-202.
6. Thun MJ, Lally CA, Flannery JT, et al. Cigarette smoking and changes in the histopathology of lung cancer. J Natl Cancer Inst 1997; 89: 1580-6.
7. Levi F, Franceschi S, La Vecchia C, et al. Lung carcinoma trends by histologic type in Vaud and Neuchatel, Switzerland, 1974-1994. Cancer 1997; 79: 906-14.

8. Janssen-Heijnen MLG, Schipper RM, Klinkhamer PJJM, et al. Divergent changes in survival for histological types of non-small-cell lung cancer in southeastern Netherlands since 1975. Br J Cancer 1998; 77: 2053-7.
9. Schouten LJ, Höppener P, van den Brandt PA, et al. Completeness of cancer registration in Limburg, the Netherlands. Int J Epidemiol 1993; 22: 369-76.
10. WHO. The World Health Organization histological typing of lung tumours. Am J Clin Path 1982; 77: 123-36.
11. Mountain CF. A new international staging system for lung cancer. Chest 1986; 89 (suppl): 225-33.
12. Parkin DM, Muir CS, Whelan SL, et al. (eds.) Cancer incidence in five continents, vol VI. Lyon: IARC Scientific Publications No.120, 1992: 865-70.
13. Hakulinen T, Abeywickrama KH. A computer package for relative survival analysis. Computer Programmes in Biomedicine 1985; 19: 197-207.
14. Estève J, Benhamou E, Croasdale M, et al. Relative survival and the estimation of net survival: elements for further study. Stat Medicine 1990; 9: 529-38.
15. Hedelin G. RELSURV 2.0: a program for relative survival. Technical report Department of epidemiology and public health. Strasbourg: Louis Pasteur University, 1997.
16. Barkley JE, Green MR. Bronchioloalveolar carcinoma. J Clin Oncol 1996; 14: 2377-86.
17. Barsky SH, Cameron R, Osann KE, et al. Rising incidence of bronchioloalveolar lung carcinoma and its unique clinicopathologic features. Cancer 1994; 73: 1163-70.
18. Stellman SD, Muscat JE, Thompson S, et al. Risk of squamous cell carcinoma and adenocarcinoma of the lung in relation to lifetime filter cigarette smoking. Cancer 1997; 80: 382-8.
19. Morabia A, Wynder EL. Cigarette smoking and lung cancer cell types. Cancer 1991; 68: 2074-8.
20. Hecht SS, Hoffmann D. Tobacco-specific nitrosamines, an important group of carcinogens in tobacco and tobacco smoke. Carcinogenesis 1988; 17: 116-28.
21. Van de Wetering ML, Mooi WJ, Wagenaar SjSc, et al. K-ras oncogene activation in adenocarcinoma of the lung: incidence and relation to smoking. Cancer Res 1988; 48: 5738-41.
22. Kern JA, Slebos RJC, Top B, et al. C-erbB-2 expression and codon 12 K-ras mutations both predict shortened survival for patients with pulmonary adenocarcinomas. J Clin Invest 1994; 93: 516-20.
23. Rodenhuis S, Boerrigter L, Top B, et al. Mutational activation of the K-ras oncogene and the effect of chemotherapy in advanced adenocarcinoma of the lung: a prospective study. J Clin Oncol 1997; 15: 285-91.

4.2 Improvement and plateau in survival of small-cell lung cancer since 1975: a population-based study*

Summary

Background: Cytotoxic therapy appears to have improved short-term survival for patients with small-cell lung cancer, but little is known about the results for unselected patients and trends in long-term survival.
Patients and methods: One thousand seven hundred ninety six patients with small-cell lung cancer diagnosed between 1975 and 1994 in the southeastern part of the Netherlands. We studied treatment policy for and survival of unselected patients since 1975, when cytotoxic therapy emerged.
Results: The proportion patients receiving chemotherapy, with or without irradiation, almost tripled from 30% to 82% for patients younger than 70 years of age and from 15% to 56% for those over 70, whereas the proportion receiving only radiotherapy decreased from 36% to 5% in both age groups. The short-term (<2-year) survival rate improved markedly between 1975 and 1989, especially for patients younger than 70 (median survival increased from 5 to 10 months). Two-year survival remained poor (8%). Two percent of all patients younger than 70 years at diagnosis survived for at least 8 years, but these patients still represent an excess five-year mortality of 39%.
Conclusion: In the southeastern part of Netherlands short-term survival of patients with small-cell lung cancer improved markedly up to the end of the 1980s, but a major impact on cure rates has not been achieved.

* Reprinted from Ann Oncol, 9. Janssen-Heijnen MLG, Schipper RM, Klinkhamer PJJM, Crommelin MA, Coebergh JWW. Improvement and plateau in survival of small-cell lung cancer since 1975, a population-based study, pp 543-7, Copyright (1998), with kind permission from Kluwer Academic Publishers.

Introduction

Small-cell lung cancer (SCLC) accounts for approximately 20% of all lung tumours among males and 25% among females in the southeastern part of the Netherlands.[1] SCLC has the poorest prognosis of all lung cancer cell types, particularly because of the rapid growth rate and early metastatic spread;[2,3] median survival for selected and unselected patients is about 12 months for limited disease and only about six months for extensive disease.[4-6] Since the end of the 1970s chemotherapy has become therapy-of-first-choice except for those rare patients with a localized peripheral lesion which should be resected. With the improvement of cytotoxic therapy over the last two decades, survival for patients with SCLC appears to have improved,[7-9] but only little is known about trends in long-term survival for unselected patients.[7,10] We studied treatment policy for and both short-term and long-term survival of unselected patients with SCLC diagnosed in the southeastern part of the Netherlands since 1975, the period of development of cytotoxic therapy.

Patients and methods

Data were obtained from the Eindhoven Cancer Registry, which contains data on patients with newly diagnosed cancer in the Dutch province of North Brabant and the northern part of the adjacent province of Limburg. The area is characterized by good access to specialised care (medically, financially and geographically) in community hospitals, served by three regional pathology laboratories and one Department of Radiotherapy.[11] Between 1975 and 1994 the number of chest physicians, who mainly treated these patients, increased from 10 to 20 per one million inhabitants. The data were derived directly from clinical records of the community hospitals and the Department of Radiotherapy, upon notification by pathological laboratories and hospital administrations. Despite the lack of 'Death Certificate Only' (DCO) cases, the infrastructure of the Dutch health care system has made it possible to establish cancer registries with a completeness exceeding 95%.[12]

Between 1975 and 1994 10,149 lung cancer patients were diagnosed in the southeastern part of the Netherlands: 7273 non-small-cell lung cancer, 1796 small-cell lung cancer, 471 other lung tumours and 609 clinically diagnosed lung tumours.

All patients diagnosed up to 1992 (N=1585) were included in survival analysis: there was active follow-up until 1 April 1994. Of these 1585 SCLC patients 30 (2%) were still alive and 1555 (98%) were dead; none were untraceable. Patients who were diagnosed at autopsy or died within the first month of diagnosis were excluded from the survival analysis (N=242, 15%). Tumour stage at diagnosis was based on physical examination. Tumours were classified according to the Veterans Administration Lung

Table 1 *General characteristics of patients with small-cell lung cancer diagnosed between 1975 and 1994.*

	1975-79		1980-84		1985-89		1990-94	
	No.	(%)	No.	(%)	No.	(%)	No.	(%)
Sex								
Male	372	(93)	398	(92)	369	(85)	427	(81)
Female	27	(7)	35	(8)	65	(15)	103	(19)
Mean age (range)	64 (34-91)		64 (31-88)		65 (37-89)		66 (36-92)	
Therapy								
Age <70 years (N=1207)								
Surgery	29	(10)	14	(5)	12	(4)	11	(3)
Radiotherapy (RT)	98	(35)	20	(7)	7	(2)	12	(4)
Chemotherapy (CT)	36	(13)	116	(39)	150	(51)	191	(56)
CT + RT	47	(17)	77	(26)	77	(26)	88	(26)
Other or none	70	(25)	67	(23)	47	(16)	38	(11)
Age ≥70 years (N=589)								
Surgery	6	(5)	3	(2)	2	(1)	6	(3)
Radiotherapy (RT)	45	(38)	16	(12)	12	(9)	11	(6)
Chemotherapy (CT)	7	(6)	58	(42)	66	(47)	81	(43)
CT + RT	11	(9)	14	(10)	17	(12)	25	(13)
Other or none	50	(42)	48	(35)	44	(31)	67	(35)
Total	**399**		**433**		**434**		**530**	

Cancer Study Group (VALG).[13] Two categories were considered: limited disease (confined to one hemithorax including hilar, ipsilateral and contralateral mediastinal, and ipsilateral and contralateral supraclavicular lymph nodes) and extensive disease (any disease at sites beyond the definition of limited disease). Data on tumour stage collected since 1990 were used for this analysis.

Treatment (only recorded when given within the first six months, except for radiotherapy) was divided into five categories: surgery, chemotherapy alone, radiotherapy alone, chemotherapy + radiotherapy, and 'other or none', including palliative care other than surgery, chemotherapy or radiotherapy.

We analysed the trends in treatment policy and survival for SCLC since 1975. Some of the patients died of causes other than the underlying cancer, particularly long-term survivors and older patients, thus the observed survival (irrespective of the cause of death) may not always reflect the disease-specific survival. Since causes of death are not included in this cancer registry, it is not possible to calculate disease-specific survival. In order to estimate the latter, the relative survival rate was calculated as the ratio of the observed to the expected actuarial rates. Expected survival rates were estimated from life tables for regional male and female populations with the same 5-year age groups (supplied by Statistics Netherlands). The risk of death due to small-cell lung cancer and the P-values of equality of relative survival on the basis of maximum likelihood ratio tests were calculated using a program of the Finnish Cancer Registry.[14,15] For patients younger than 70 years of age diagnosed between 1975 and

1989 the conditional relative 5-year survival rates were computed for patients who were still alive after one, three, five and eight years. The standard errors of survival rates were calculated according to Greenwood's formula.[16]

Table 2 Treatment (%) of small-cell lung cancer, according to age and stage (1990-1994).

Age (years)		Stage of disease Limited	Extensive	unknown
<70	**Number (%)**	139 (41)	128 (38)	73 (21)
	Treatment (%)			
	Surgery	6	0	4
	Radiotherapy	3	4	4
	Chemotherapy	49	62	60
	Chemo+radiotherapy	35	19	21
	Other or none	7	16	11
≥70	**Number (%)**	68 (36)	62 (33)	60 (31)
	Treatment (%)			
	Surgery	7	0	2
	Radiotherapy	9	5	3
	Chemotherapy	41	45	42
	Chemo+radiotherapy	28	8	2
	Other or none	15	42	52

Results

Distribution of prognostic factors

The general characteristics of the patients, according to period of diagnosis, are listed in table 1. Between 1975 and 1994 1796 patients with small-cell lung cancer were diagnosed (1566 men and 230 women); the male/female ratio decreased from 14 in 1975-79 to 4 in 1990-94. The mean age remained about 65 years (range 31-92 years). For patients diagnosed between 1990 and 1994 the proportion with limited disease was 41% for patients younger than 70 years of age and 36% for those over 70, whereas the proportions with extensive disease were 38% and 33%, respectively. The proportion with disease of unknown stage was higher for older patients (31%) than for younger patients (21%). Most patients (58%) received chemotherapy, with or without irradiation, a proportion which almost tripled from 30% to 82% of patients younger than 70 and from 15% to 56% of those over 70. The proportion patients who underwent surgical resection or irradiation decreased markedly in both age groups (table 1). Treatment for each stage of disease and for both age groups (1990-1994) is shown in table 2. Elderly patients (≥70 years) were treated less aggressively, especially

those with cancer of the extensive or unknown stage. Furthermore, patients with limited stage small-cell lung cancer more often underwent surgery or received a combination of chemotherapy and radiotherapy.

Table 3 Relative survival#, according to gender, age and stage, in all SCLC patients diagnosed between 1975 and 1992.

		1975-79	1980-84	1985-89	1990-92
Diagnosed at autopsy or dead within 1 month		14%	14%	16%	18%
All SCLC (N=1585)	median (months)	5	7	9	9
	0.5 yr (SE*)	43% (3)	58% (3)	70% (2)	71% (3)
	1 yr (SE*)	16% (2)	25% (2)	34% (2)	35% (3)
	1.5 yrs (SE*)	10% (2)	11% (2)	13% (2)	16% (2)
	2 yrs (SE*)	7% (1)	8% (1)	8% (1)	8% (2)
Gender					
Males (N=1395)	median (months)	5	7	9	9
Females (N=190)	median (months)	6	9	11	9
Age					
<70 yrs (N=1073)	median (months)	5	8	10	10
≥70 yrs (N=512)	median (months)	5	5	6	6
Stage of disease					
Age < 70 yrs					
Limited (N=85)	median (months)				13
Extensive (N=76)	median (months)				8
Unknown (N=45)	median (months)				8
Stage of disease					
Age ≥ 70 yrs					
Limited (N=29)	median (months)				10
Extensive (N=43)	median (months)				5
Unknown (N=41)	median (months)				3

Conditional on being alive at 1 month since diagnosis
* Standard Error

Survival

Of all patients with SCLC diagnosed between 1975 and 1992 242 (15%) were diagnosed at autopsy or died within one month of diagnosis, i.e. 12% of patients younger than 70 and 22% of those over 70. For those alive after 1 month the median survival increased from five months in 1975-79 to nine months in 1985-89 and 1990-92. The improvement only applied for short-term (<2 years) survival (figure 1). The overall 2-year relative survival rate remained only 8%. The increase in short-term survival was found for both males and females and was most marked for patients younger than 70 years. Survival was better for females, patients younger than 70 and patients with limited disease (table 3).

Testing of equality of the two-year survival patterns showed a levelling off of the improvement for patients younger than 70 years: P<0.01 for 1980-84 vs. 1975-79, P=0.32 for 1985-89 vs. 1980-84 and P=0.63 for 1990-92 vs. 1985-89. For elderly the

improvement in survival was less marked: P=0.42 for 1980-84 vs. 1975-79, P=0.24 for 1985-89 vs. 1980-84 and P=0.34 for 1990-92 vs. 1985-89.
Ninety patients (6%) survived for at least 2 years. The distribution of prognostic factors at diagnosis for these 'long-term' survivors differed from that found for the initial group: the mean age was 3.5 years younger, there were more females (16% versus 12%) and the proportion with a surgically resected tumour was also much higher (25% versus 5%). Two of the 90 'long-term' survivors developed a second malignancy. One had a pancreatic tumour 4.2 years after diagnosis of the first tumour; the patient survived only two days after diagnosis of this second tumour. The other had a squamous cell lung tumour 6.2 years after diagnosis, with a survival of 4.6 years.
The relative 5-year survival rate, calculated for patients younger than 70 years of age at diagnosis who were still alive after 1, 3, 5, and 8 years, respectively, increased from 12% conditional on being alive after 1 year to 61% conditional on being alive after 8 years (table 4).

Table 4 Relative 5-year survival (%) for patients (<70 yrs) who were still alive at given intervals after diagnosis (1975-1989).

	Interval after diagnosis			
	year 1 (se*)	**year 3 (se*)**	**year 5 (se*)**	**year 8 (se*)**
Survival	12% (2)	56% (10)	59% (13)	61% (16)
proportion of initial group	*24*	*4*	*3*	*2*

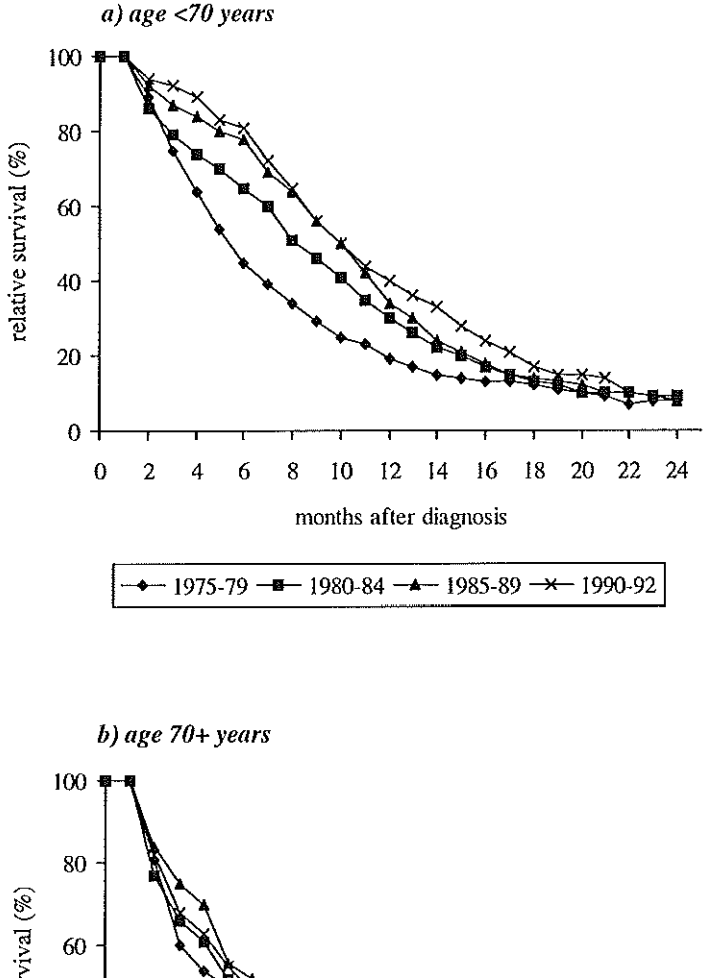
* Standard error

Discussion

In the southeastern part of the Netherlands chemotherapy has been first-choice therapy for patients with SCLC since the beginning of the 1980s. Short-term survival (<2 years) has almost doubled since 1975, especially for patients younger than 70 years; however, 'long-term' survival (>2 years) remained poor and excess mortality for patients who were alive after eight years was 39%.

The improved short-term survival is likely to be due to the increased use of chemotherapy since the end of the 1970s. Cyclophosphamide-Doxorubicin-Etoposide (CDE) has been the standard combination in the southeastern part of the Netherlands and had not evolved to a platinum containing regimen during the study period. Nonetheless, despite initial chemosensitivity, the majority of patients relapse or develop a second tumour and die;[17,18] results of chemotherapy seem to have reached a plateau and ascending from here seems impossible with the current available tools.[9] The percentage patients receiving radiotherapy alone or radiotherapy after chemotherapy decreased, even though meta-analyses showed that survival for patients

Figure 1 *Trends in relative survival of small-cell lung cancer (1975-92), according to age.*



with limited disease who received chemotherapy and radiotherapy was significantly better than for those receiving chemotherapy alone.[19,20]
Our data do not show an improvement in median survival over time for older patients, which may be due to less aggressive treatment because of poor performance status. The latter is related to the high prevalence of co-morbidity in these cases: according to unpublished data from our Cancer Registry, 60% of patients over 70 with small-cell lung cancer diagnosed between 1993 and 1995 in the southeastern part of the Netherlands had one or more serious co-morbid conditions such as cardiovascular diseases or chronic obstructive lung diseases (COPD). The proportion receiving chemotherapy (of patients over 70) decreased slightly from 73% for those without concomitant diseases to 65% for those with two or more concomitant diseases. Nonetheless, in several other studies on unselected patients it was found that even elderly patients with co-morbidity are likely to benefit from combination chemotherapy.[6,21] Moreover, doxorubicin appeared to have no influence on cardiac arrhythmias in small-cell lung cancer patients with cardiac disease.[22] In a Canadian study elderly patients were treated less aggressively than younger patients, but survival was similar for the two age groups.[23]

In our study only six percent of all SCLC patients (N=90) survived for at least two years, a finding similar to that of the SEER (Surveillance, Epidemiology and End Results) project in the United States.[24] Two of these 'long-term' survivors developed a second malignancy: a non-small-cell lung tumour and a pancreatic tumour. In other studies non-small-cell lung cancer developed in 0.5% to 24% and other malignancies in 3% to 11%.[9,10,25-31] However, the numbers with second malignancies in these studies were very small.

Conclusion: in the southeastern part of the Netherlands short-term survival of patients with small-cell lung cancer improved markedly up to the end of the 1980s, but a major impact on cure rates has not been achieved.

References

1. Janssen-Heijnen MLG, Nab HW, van Reek J, et al. Striking changes in smoking behaviour and lung cancer incidence by histological type in the south-east Netherlands, 1960-1991. Eur J Cancer 1995; 31A: 949-52.
2. Fox W, Scadding JG. Medical Research Council comparative trial of surgery and radiotherapy for primary treatment of small-celled or oat-celled carcinoma of bronchus: ten-year follow up. Lancet 1973;2:63-5.
3. Matthews MJ, Kanhouwa S, Pickren J, et al. Frequency of residual and metastatic tumors in patients undergoing curative surgical resection for lung cancer. Cancer Chemother 1973; 4: 63-7.
4. George TK, Fitzgerald D, Brown BS, et al. Long-term survival in limited-stage small-cell lung carcinoma: experience in Rochester, New York from 1975 to 1981. Cancer 1986; 58: 1193-9.

5. Osterlind K, Andersen PK. Prognostic factors in small-cell lung cancer: multivariate model based on 788 patients treated with chemotherapy with or without irradiation. Cancer Res 1986; 46: 4189-94.
6. Shepherd FA, Amdemichael E, Evans WK, et al. Treatment of small-cell lung cancer in the elderly. J Am Geriatr Soc 1994; 42: 64-70.
7. Choi NC, Carey RW, Kaufman D, et al. Small-cell carcinoma of the lung: a progress report of 15 years' experience. Cancer 1987; 59: 6-14.
8. Skarin AT. Analysis of long-term survivors with small-cell lung cancer. Chest 1993; 103: 440S-4S.
9. Lassen U, Osterlind K, Hansen M, et al. Long-term survival in small-cell lung cancer: posttreatment characteristics in patients surviving 5 ot 18+ years: an analysis of 1,714 consecutive patients. J Clin Oncol 1995; 13: 1215-20.
10. Souhami RL, Law K. Longevity in small-cell lung cancer: a report to the Lung Cancer Subcommittee of the United Kingdom Coordinating Committee for Cancer Research. Br J Cancer 1990; 61: 584-9.
11. Coebergh JWW, van der Heijden LH, Janssen-Heijnen MLG (eds.). Cancer incidence and survival in the south-east of the Netherlands 1955-1994: a report from the Eindhoven Cancer Registry. Eindhoven, The Netherlands, 1995.
12. Schouten LJ, Höppener P, van den Brandt PA, et al. Completeness of cancer registration in Limburg, the Netherlands. Int J Epidemiol 1993; 22: 369-76.
13. Stahel RA, Ginsberg R, Havemann K, et al. Staging and prognostic factors in small-cell lung cancer: a consensus report. Lung Cancer 1989; 5: 119-26.
14. Hakulinen T, Abeywickrama KH. A computer package for relative survival analysis. Computer Programmes in Biomedicine 1985; 19: 197-207.
15. Hakulinen T, Tenkanen L, Abeywickrama K, Päivärinta L. Testing equality of relative survival patterns based on aggregated data. Biometrics 1987; 43: 313-25.
16. Greenwood M. Reports on Public Health and Medical Subjects No. 33, appendix 1: the "errors of sampling" of the survivorship tables. London, 1926: Her Majesty's Stationary Office.
17. Findlay MPN, Griffin AM, Baghavan D, et al. Retrospective review of chemotherapy for small-cell lung cancer in the elderly: does the end justify the means? Eur J Cancer 1991; 27: 1597-1601.
18. Schiller JH, Ettinger DS, Larson MM, et al. Phase II trial of oral etoposide plus cisplatin in extensive stage small-cell carcinoma of the lung: an Eastern Cooperative Oncology Group Study. Eur J Cancer 1994; 30A: 158-61.
19. Pignon J-P, Arriagada R, Ihde DC, et al. A meta-analysis of thoracic radiotherapy for small-cell lung cancer. N Engl J Med 1992; 327: 1618-24.
20. Arriagada R, Pignon JP, Ihde DC, et al. Effect of thoracic radiotherapy on mortality in limited small-cell lung cancer: a meta-analysis of 13 randomized trials among 2,140 patients. Anticancer Res 1994; 14: 333-5.
21. Clamon GH, Audeh MW, Pinnick S. Small-cell lung carcinoma in the elderly. J Am Geriatrics Soc 1982; 30: 299-302.
22. Raabe NK, Storstein L. Cardiac arrhythmias in patients with small-cell lung cancer and cardiac disease before, during and after doxorubicin administration: an evaluation of acute cardiotocicity by continuous 24-hour Holter monitoring. Acta Oncol 1991; 30: 843-6.
23. Dajczman E, Fu LY, Small D, et al. Treatment of small-cell lung carcinoma in the elderly. Cancer 1996; 77: 2032-8.
24. Davis S, Wright PW, Schulman SF, et al. Long-term survival in small-cell carcinoma of the lung: a population experience. J Clin Oncol 1985; 3: 80-91.
25. Albain KS, Crowley JJ, Livingston RB. Long-term survival and toxicity in small-cell lung cancer: expanded Southwest Oncology Group experience. Chest 1991; 99: 1425-32.
26. Heyne KH, Lippman SM, Lee JJ, et al. The incidence of second primary tumors in long-term survivors of small-cell lung cancer. J Clin Oncol 1992;10:1519-24.
27. Van der Gaast A, Postmus PE, Burghouts J, et al. Long term survival of small-cell lung cancer patients after chemotherapy. Br J Cancer 1993; 67: 822-4.

28. Johnson BE, Linnoila RI, Williams JP, et al. Risk of second aerodigestive cancers increases in patients who survive free of small-cell lung cancer for more than 2 years. J Clin Oncol 1995; 13: 101-11.
29. Verhagen AF, Tavilla G, van de Wal HJ, et al. Multiple primary lung cancers. Thorac Cardiovasc Surg 1994; 42: 404.
30. Moro D, Jacoulet P, Quoix E, et al. Small-cell lung cancer: patients surviving longer than thirty months. Anticancer Res 1994; 14: 301-4.
31. Osterlind K, Hansen HH, Hansen M, et al. Mortality and morbidity in long-term surviving patients treated with chemotherapy with or without irradiation for small-cell lung cancer. J Clin Oncol 1986; 4: 1044-52.

4.3 Prevalence of co-morbidity in lung cancer patients and its relationship with treatment: a population-based study*

Abstract

Background: with the rising mean age of lung cancer patients, the number of patients with serious co-morbidity at diagnosis is increasing. As a result, co-morbidity may become an important factor in both the choice of treatment and survival. We studied the prevalence of serious co-morbidity among newly diagnosed lung cancer patients and its association with morphology, stage and treatment.
Patients: a total of 3864 lung cancer patients registered in the population-based registry of the Comprehensive Cancer Centre South between 1993 and 1995.
Results: during the study period, the mean age of patients was 67 years (range: 29-93). The most frequent concomitant diseases were cardiovascular diseases (23%), chronic obstructive pulmonary diseases (COPD) (22%) and other malignancies (15%). The prevalence of concomitant diseases was highest for men (60%), patients with squamous cell carcinoma (64%) and those with a localized tumour (66%). The resection rate for patients <70 years, with a localized non-small-cell lung tumour, was especially low for those with COPD (67%) or diabetes (64%) compared with patients without concomitant diseases (94%). The association between co-morbidity and chemotherapy for patients with small-cell lung cancer was limited.
Conclusions: the prevalence of co-morbidity, especially cardiovascular diseases and COPD, among lung cancer patients is about twice as high as in the general population. Co-morbidity seems to be associated with earlier diagnosis of lung cancer, but it may also lead to less accurate staging and less aggressive treatment. Thus, prognosis is likely to be negatively influenced by co-morbidity.

* Reprinted from Lung Cancer (in press). Janssen-Heijnen MLG, Schipper RM, Razenberg PPA, Crommelin MA, Coebergh JWW. Prevalence of co-morbidity in lung cancer patients and its relationship with treatment: a population-based study, Copyright (1998), with permission from Elsevier Science.

Introduction

Lung cancer is the most common type of cancer among men in the Netherlands and ranks third for women; incidence increases sharply with age.[1] With the rising mean age of lung cancer patients diagnosed in the southeastern part of the Netherlands from 61 years in 1960 to 67 years in 1995, care for cancer patients with serious concomitant diseases is becoming increasingly complex, because of complications and quality-of-life after treatment.[2-5] The prognosis for patients with co-morbidity may also be worse, independent of age, disease stage, and type of treatment.[6-8] The Eindhoven Cancer Registry, at the request of clinicians, has been collecting data on clinically relevant concomitant diseases on all cancer patients since 1993. We analysed the age-specific prevalence of serious co-morbidity for lung cancer patients in relation to cancer morphology, stage of disease and treatment. Since mortality in our area, especially due to tobacco-related causes of death such as respiratory diseases, cancer and cardiovascular diseases, is almost twice as high for men as women,[9] we evaluated the prevalence of co-morbidity for each sex separately.

Table 1 *Classification of co-morbidity, according to an adapted version list of Charlson et al. (1987).*

COPD
Cardiovascular diseases (myocardial infarction, cardiac decompensation, angina pectoris, intermittent claudication, abdominal aneurysm)
Cerebrovascular diseases (cerebrovascular accident, hemiplegia)
Other malignancies (except basal cell skin carcinoma)
Hypertension
Diabetes Mellitus (medically treated)
Other:
soft tissue diseases (Besnier Boeck disease (sarcoidosis), Wegener's granulomatosis, SLE (systemic lupus erythematosis))
rheumatoid arthritis (only severe)
kidney diseases (chronic glomerulonephritis, chronic pyelonephritis)
bowel diseases (Crohn's disease, ulcerative colitis)
liver diseases (cirrhosis, hepatitis)
dementia
tuberculosis

Patients and methods

Data were derived from the Eindhoven Cancer Registry, which has collected data on patients with newly diagnosed cancer since 1955 in the Dutch province of North Brabant and since 1970 also in the northern part of the adjacent province of Limburg. This registry serves a population of about 2 million inhabitants. The access to specialized care is good, supplied by 16 community hospitals and two large

Radiotherapy Institutes. Data on clinically relevant concomitant diseases, noted in the clinical records (history, preoperative report or correspondence between specialists and the general practitioner), has been registered since 1993, according to a slightly adapted version of the list of Charlson and colleagues (table 1).[10]

We validated if the registration clerks had recorded co-morbidity correctly from the medical records by evaluating the records of 127 consecutive lung cancer patients diagnosed in 1995 in three hospitals. The registration clerks had underestimated the total number of diseases by 8%. Underestimation was found mainly for cardiovascular diseases (27% of the originally recorded prevalence), because terms such as coronary artery bypass grafting (CABG), bypass and percutaneous transluminal coronary angioplasty (PTCA) had sometimes been disregarded. The occurrence of chronic obstructive pulmonary disease (COPD) was overestimated by 6% of the originally recorded prevalence, due to vague description in the medical record. Because the methods of registration were only improved in 1996 and the registration clerks recognized the deficiency recording cardiovascular diseases and COPD, we increased the prevalence of cardiovascular diseases recorded in the period 1993-95 by 27% of the originally recorded prevalence and we decreased the prevalence of COPD by 6%.

Lung cancer was classified as small-cell and non-small-cell carcinoma; the latter includes squamous cell carcinoma, adenocarcinoma, large-cell undifferentiated carcinoma and some rare subtypes.[11] Tumour stage was recorded in the Eindhoven Cancer Registry on the basis of clinical examination, according to the Tumour-Node-Metastasis (TNM) system of the Union Internationale Contre le Cancer, version 4, 1987.[12] Non-small-cell tumours were classified as: localized (stages I and II) and non-localized (stages IIIa, IIIb and IV). Small-cell lung tumours were classified as limited (confined to one hemithorax including hilar, ipsilateral and contralateral mediastinal, and ipsilateral and contralateral supraclavicular lymph nodes) and extensive disease (any disease at sites beyond the definition of limited disease). However, for almost 30% of small-cell lung tumours the stage was unknown.

In this survey we analysed the prevalence of co-morbidity for lung cancer patients according to gender, age (<70 and ≥ 70 years), morphology and tumour stage. The association between co-morbidity and treatment was also analysed, according to age, histology and stage of disease. Differences in the prevalence of co-morbidity for the subgroups were tested with the χ^2 test. We estimated the age-adjusted effects of co-morbidity on treatment by use of the logistic regression model.

Results

Prevalence of co-morbidity

Between 1993 and 1995, 3864 lung cancer patients were diagnosed (3183 men and 681 women), whereas 3551 serious concomitant conditions in 2258 patients were recorded; 34% of patients did not have a concomitant disease and the existence of other diseases was unknown in 8% of cases. The mean age of patients was 67 years (range: 29-93).

Table 2 *Number of concomitant diseases per patient, according to age.*

Number of concomitant diseases	Age (years) < 70	70-99
None (%)	40	24
1 (%)	34	36
2 (%)	13	22
≥ 3 (%)	5	11
Unknown (%)	8	7
Number of patients	*2331*	*1533*

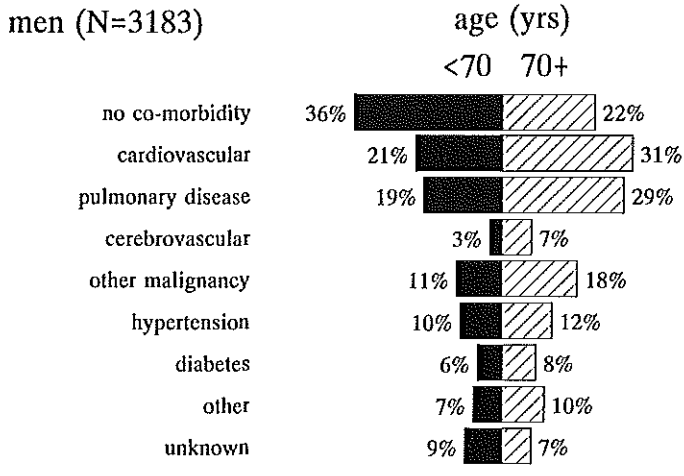
The prevalence of co-morbidity for lung cancer patients of 70 years or older (69%) was higher than for younger patients (52%) (P=0.001) (table 2). Figure 1 shows the prevalence of co-morbidity for lung cancer patients according to gender and age. The most frequent concomitant disease was cardiovascular disease (23%), followed by COPD (22%), other malignancies (15%), hypertension (12%) and diabetes mellitus (7%). Most of the other malignancies were cancers of the respiratory tract (36%); other frequently occurring malignancies were cancers of the urogenital (27%) and digestive (13%) tract and the breast in women (20%). The prevalence of co-morbidity was 8% higher for men than for women (P=0.001) (figure 1). For patients younger than 70 years of age, the prevalence of cardiovascular diseases was 12% lower for women than for men. For women of 70 years and older the prevalences of COPD and cardiovascular diseases were almost 10% lower than for men; in contrast the prevalences of hypertension and diabetes were almost 10% higher. The most frequent combinations of diseases were COPD and cardiovascular diseases (17%), COPD and other malignancies (13%), and COPD and hypertension (11%).

The prevalence of concomitant diseases, especially COPD, was lower for patients with adenocarcinoma, large-cell undifferentiated carcinoma or small-cell carcinoma (about 52%) than for those with squamous cell carcinoma of the lung (64%) (table 3) (P=0.001).

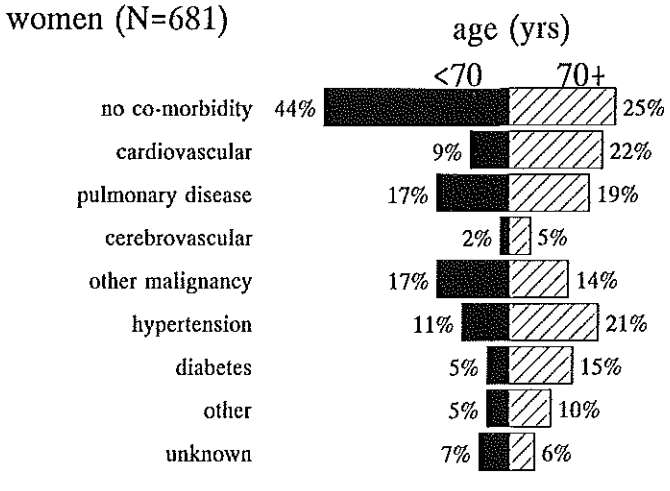
The prevalence rates for COPD (P=0.001), cardiovascular diseases (P=0.02) and other malignancies (P=0.002) were higher for patients with localized non-small-cell lung cancer than for those with non-localized disease. For patients with small-cell lung

cancer the prevalence of COPD (P=0.05) was higher among those with limited than those with extensive disease. The prevalence of co-morbidity, especially COPD and other malignancies, was also high in patients with unknown stage of disease (table 4).

Figure 1 *Age-specific prevalence of concomitant diseases for men and women.*



percentages corrected after validation study
more concomitant diseases per patient possible



percentages corrected after validation study
more concomitant diseases per patient possible

Treatment

The resection rate for patients with localized (clinical stage I or II) non-small-cell lung cancer decreased with an increasing number of concomitant diseases from 94% to 70% for patients younger than 70 years of age (P=0.001) and from 63% to 49% for older patients (P=0.4). The resection rate was especially low for younger patients with COPD (only 67%, P=0.001) or diabetes (64%, P=0.001). In contrast, the proportion patients who received radiotherapy increased with the rising number of concomitant diseases from 4% to 18% for younger and from 20% to 37% for older patients (figure 2a). The age-adjusted effect of co-morbidity on surgery of localized non-small-cell lung cancer was evaluated by use of a multivariate logistic regression model. Both age and co-morbidity were independently associated with surgery (P for age was 0.0001 and P for the presence of co-morbidity was 0.002). Treatment choice for patients with non-localized non-small-cell lung cancer did not differ with the presence of co-morbidity (figure 2b). We also analysed the influence of co-morbidity on the extent of staging, according to age, within the group 'localized' and 'non-localized' non-small-cell lung tumours. The extent of staging, being clearly lower in the elderly, was not influenced by the presence of co-morbidity (data not shown).

The proportion of patients with small-cell lung cancer receiving chemotherapy did not differ with the number of concomitant diseases for patients younger than 70 years of age. However, there was a slight, but not significant, decrease among older patients (from 73% for those without co-morbidity to 63% for those with at least 2 concomitant conditions) (P=0.2) (figure 2c). In the multivariate logistic regression model, only age was independently associated with chemotherapy for small-cell lung cancer (P=0.0001 for age and P=0.25 for co-morbidity).

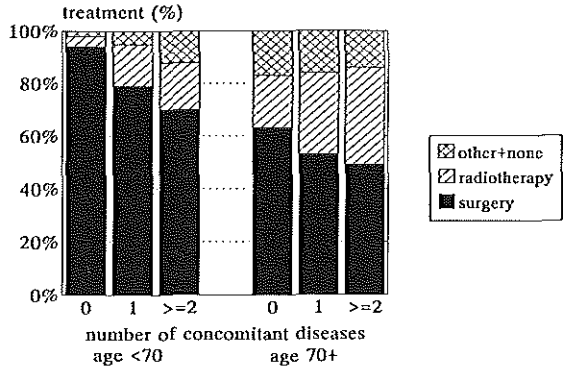
Table 3 *Proportional distribution of co-morbidity* in lung cancer patients, according to histological type and age.*

	Squamous-cell		Adenocarcinoma		Large-cell undiff.		Small-cell	
Age (yrs)	<70	≥70	<70	≥70	<70	≥70	<70	≥70
Co-morbidity	%	%	%	%	%	%	%	%
	N=852	N=681	N=391	N=148	N=347	N=198	N=435	N=232
COPD	23	31	17	23	14	24	14	22
Cardiovascular	20	30	17	29	16	28	20	28
Cerebrovascular	3	7	2	6	3	5	3	6
Other malignancy	14	19	12	15	15	17	9	14
Hypertension	11	13	10	19	9	11	11	13
Diabetes mellitus	7	9	3	11	3	7	7	8
Other	7	11	7	11	7	9	7	9
None	34	19	40	24	43	27	39	30
Unknown	7	6	11	5	8	10	9	6

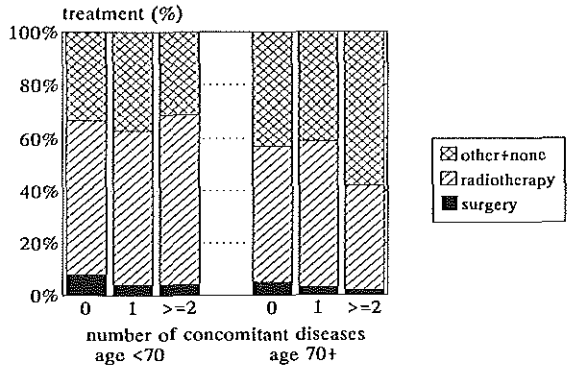
* more per patient, total >100%

Figure 2 *Choice of therapy for patients with lung cancer, according to number of concomitant diseases and age.*

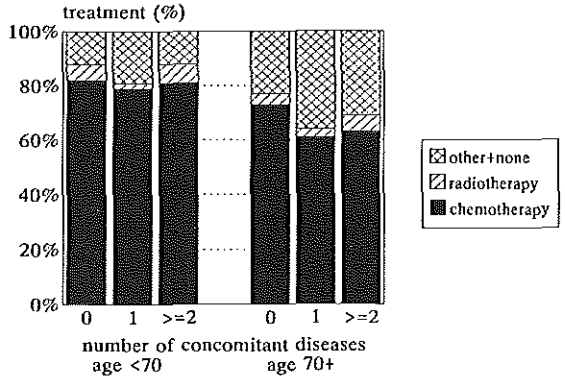
a) localized non-small-cell lung cancer



b) non-localized non-small-cell lung cancer



c) small-cell lung cancer



Discussion

The most common concomitant diseases among patients with lung cancer were cardiovascular diseases, COPD, other malignancies, hypertension and diabetes mellitus; the prevalences were the highest for men, patients with squamous cell carcinoma and those with a localized tumour. As expected, the prevalence increased with age. The resection rate for patients with a localized non-small-cell lung tumour decreased with an increasing number of concomitant diseases, whereas the percentage undergoing radiotherapy increased, especially for patients younger than 70 years. For patients with small-cell lung cancer, chemotherapy decreased slightly with the number of co-morbid conditions, but only for patients over 70 years of age.

Table 4 *Proportional distribution of co-morbidity*, according to stage.*

	Non-small-cell carcinoma			Small-cell carcinoma		
Stage	Localized	Non-localized	Unknown	Limited	Extensive	Unknown
Co-morbidity	%	%	%	%	%	%
	N=1006	N=1380	N=231	N=268	N=254	N=145
COPD	28	18	33	20	13	19
Cardiovascular	26	20	21	23	23	21
Cerebrovascular	4	3	6	4	3	6
Other malignancy	18	13	19	9	8	16
Hypertension	13	10	13	11	13	10
Diabetes mellitus	7	6	8	8	5	9
Other	9	7	12	10	6	6
None	26	37	19	37	40	27
Unknown	6	8	10	5	9	12

*more per patient, total >100%

Prevalence of co-morbidity

Comparison of prevalences of chronic diseases is full of biases due to selection, detection and classification. We compared our population-based prevalences with those obtained by population-based screening and case finding. In the general population, the prevalences of cerebrovascular diseases, diabetes mellitus and dementia increased with age,[13-17] as was also found in our study. In Dutch general practices, 19.5% of those aged 65 and older have one, 3.2% have two and 0.3% have three chronic diseases.[18] As expected, the prevalence of smoking-related diseases, such as cardiovascular and chronic pulmonary diseases, for lung cancer patients in our study was higher than that for patients with other tumours and in general practices.[18,19] The fact that smoking is by far the most important risk factor for lung cancer most likely explains the high prevalence of other smoking-related diseases, such as COPD, cardiovascular diseases and malignancies of the respiratory, urogenital and digestive tract.[20] The higher prevalence of these diseases among men (the same as was found in a study by Havlik et al.)[19] and patients with squamous cell carcinoma, supports this

hypothesis because these two groups contain the highest proportions of smokers.[21,22] The fact that the diet of smokers usually contains more sugar and saturated fat and less fruit and fibre than that of non-smokers may play a role in the high prevalence of cardiovascular diseases and diabetes among lung cancer patients.[23]

The relationship between stage of disease and co-morbidity may be subject to confounding (by age), detection bias and ascertainment bias. In the elderly group, both the proportion with unknown stage of disease and the occurrence of co-morbidity are higher. However, the association between stage of disease and co-morbidity persisted after adjustment for age. Detection bias can affect diagnosis in different ways: on the one hand, patients with another disease which produces symptoms similar to those of lung cancer may be diagnosed in a more advanced stage of their lung cancer because the symptoms of lung cancer are overshadowed ('camouflage' bias).[24] On the other hand, lung cancer patients may be diagnosed in an earlier stage as a result of regular surveillance of other chronic diseases (screening bias). For our patients, the latter seems to prevail, because those with localized lung cancer suffered more co-morbidity. The data on co-morbidity may also be subject to ascertainment bias: for (older) patients with advanced disease the assessment of co-morbidity by chest physicians may not be optimum and more information on co-morbidity may be recorded for resectable patients because of the required pre-operative examination. However, since the Eindhoven Cancer Registry only records serious, clinically relevant concomitant diseases which are listed in the clinical records, this will play only a minor role. The high prevalence of co-morbidity among patients with an unknown stage of disease (table 4) may point to the fact that co-morbidity leads to less accurate staging. The relationship between stage of disease and co-morbidity differed between the various diseases, suggesting different mechanisms; e.g. the prevalence of COPD is more likely to be subject to 'camouflage' bias than that of diabetes. For breast cancer patients with localized disease the prevalence of co-morbidity was also higher than for those with non-localized disease.[6]

Treatment

Surgery offers the best chance of cure for patients with localized non-small-cell lung tumours. However, given the potential for serious, especially cardiorespiratory complications of lung surgery,[25-28] the lower resection rate for patients with a localized non-small-cell lung tumour and serious co-morbidity is not surprising. In previous studies, cancer patients with higher levels of co-morbidity were treated less aggressively than those with lower levels, independent of age and stage of disease.[2,5] However, age alone appeared to be a more important factor in influencing treatment choice than co-morbidity (figure 2), which is probably related to the higher postoperative mortality in the elderly.[26] In the United Kingdom the lower resection rate in the elderly could not be explained by performance status at presentation.[29] The

proportion elderly patients with small-cell lung cancer receiving chemotherapy was also slightly lower, although not significantly. However, the dosis of chemotherapy was probably also lower in case of co-morbidity. In two other studies, no relationship was found between co-morbidity and treatment for small-cell lung cancer.[30,31] Furthermore, when doxorubicin was administered to small-cell lung cancer patients with cardiac disease it appeared to have no influence on cardiac arrhythmias.[32] For patients with breast or endometrial cancer, the number of concomitant diseases was closely associated with an increased risk for death after adjustments for age, stage of disease and type of treatment.[6,33] However, there was no difference in survival rates for lung cancer patients in Finland between those with and without bronchial asthma after adjustment for differences in histology and stage.[34]

Conclusion

The prevalence of co-morbidity, especially cardiovascular diseases and COPD, among lung cancer patients is about twice as high as in the general population. Co-morbidity is associated with earlier diagnosis of lung cancer, but it may also lead to less accurate staging and less aggressive treatment. Thus, prognosis is likely to be negatively influenced by co-morbidity.

References

1. Visser O, Coebergh JWW, Schouten LJ (eds.). Incidence of cancer in the Netherlands, 1993: fifth report of the Netherlands Cancer Registry. Utrecht, 1996.
2. Guadagnoli E, Weitberg A, Mor V, et al. The influence of patient age on the diagnosis and treatment of lung and colorectal cancer. Arch Intern Med 1990; 150: 1485-90.
3. Monfardini S, Aapro M, Ferrucci L, et al. Commission of the European Communities "Europe Against Cancer" programme European School of Oncology Advisory Report Cancer Treatment in the Elderly. Eur J Cancer 1993; 29A: 2325-30.
4. Wei JY. Cardiovascular comorbidity in the older cancer patient. Semin Oncol 1995;22:9-10.
5. Greenfield S, Aranow HU, Elashoff RM, et al. Flaws in mortality data: the hazards of ignoring comorbid disease. JAMA 1988; 260: 2253-55.
6. Satariano WA, Ragland DR. The effect of comorbidity on 3-year survival of women with primary breast cancer. Ann Intern Med 1994; 120: 104-10.
7. Piccirillo JF, Feinstein AR. Clinical symptoms and comorbidity: significance for the prognostic classification of cancer. Cancer 1996; 77: 834-42.
8. Feinstein AR, Wells CK. A clinical-severity staging system for patients with lung cancer. Medicine 1990; 69: 1-33.
9. Coebergh JWW, van der Heijden LH, Janssen-Heijnen MLG (eds.). Cancer incidence and survival in the south-east of the Netherlands 1955-1994: a report from the Eindhoven Cancer Registry. Eindhoven, The Netherlands, 1995: 116.
10. Charlson ME, Pompei P, Ales KL, et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chron Dis 1987; 40: 373-83.
11. WHO. The World Health Organization histological typing of lung tumours. Am J Clin Path 1982; 77: 123-36.
12. Mountain CF. A new international staging system for lung cancer. Chest 1986; 89 (suppl): 225-33.

13. Looman SJ, Bots ML, Hofman A, et al. Stroke in the elderly: prevalence and frequency of hospitalization; the Rotterdam study. [in Dutch] Ned Tijdschr Geneeskd 1996; 140: 312-16.
14. Ott A, Breteler MMB, van Harskamp F, et al. Prevalence of Alzheimer's disease and vascular dementia: association with education: the Rotterdam Study. Br Med J 1995; 310: 970-3.
15. Stolk RP, Pols HAP, Lamberts SWJ, et al. Diabetes mellitus, impaired glucose tolerance, and hyperinsulinemia in an elderly population: the Rotterdam Study. Am J Epidemiol 1997; 145: 24-32.
16. Grobbee DE, van der Bom JG, Bots ML, et al. Cardiovascular disease among elderly people; the 'Rotterdam elderly study'. [in Dutch] Ned Tijdschr Geneeskd 1995; 139: 1978-82.
17. Mennen LI, Witteman JCM, Geleijnse JM, et al. Risk factors for cardiovascular disease among elderly people; the Rotterdam study. [in Dutch] Ned Tijdschr Geneeskd 1995; 139: 1983-8.
18. Schellevis FG, van der Velden J, van de Lisdonk E, et al. Comorbidity of chronic diseases in general practice. J Clin Epidemiol 1993; 46: 469-73.
19. Havlik RJ, Yancik R, Long S, et al. The National Institute on Aging and the National Cancer Institute SEER collaborative study on comorbidity and early diagnosis of cancer in the elderly. Cancer 1994; 74: 2101-6.
20. Doll R, Peto R, Wheatly K, et al. Mortality in relation to smoking: 40 years' observations on male British doctors. Br Med J 1994; 309: 901-11.
21. McDuffie HH, Klaassen DJ, Dosman JA. Determinants of cell type in patients with cancer of the lungs. Chest 1990; 98: 1187-93.
22. Siemiatycki J, Krewski D, Franco E, et al. Associations between cigarette smoking and each of 21 types of cancer: a multisite case-control study. Int J Epidemiol 1995; 24; 504-14.
23. Margetts BM, Jackson AA. Interactions between people's diet and their smoking habits: the dietary and nutritional survey of British adults. Br Med J 1993; 307: 1381-4.
24. Yancik R, Kessler L, Yates JW. The elderly population: opportunities for cancer prevention and detection. Cancer 1988; 62 (suppl 8): 1823-8.
25. Nagasaki F, Flehinger BJ, Martini N. Complications of surgery in the treatment of carcinoma of the lung. Chest 1982; 82: 25-9.
26. Ginsberg RJ, Hill LD, Eagan RT, et al. Modern thirty day operative mortality for surgical resections in lung cancer. J Thorac Cardiovasc Surg 1983; 86: 654-8.
27. Damhuis RAM, Schütte PR. Resection rates and postoperative mortality in 7,899 patients with lung cancer. Eur Respir J 1996; 9: 7-10.
28. Thomas P, Sielezneff I, Ragni J, et al. Is lung cancer resection justified in patients aged over 70 years? Eur J Cardiothorac Surg 1993; 7: 246-51.
29. Brown JS, Eraut D, Trask C, et al. Age and the treatment of lung cancer. Thorax 1996; 51; 564-8.
30. Shepherd FA, Amdemichael E, Evans WK, et al. Treatment of small-cell lung cancer in the elderly. J Am Geriatr Soc 1994; 42: 64-70.
31. Dajczman E, Fu LY, Small D, et al. Treatment of small cell lung carcinoma in the elderly. Cancer 1996; 77: 2032-8.
32. Raabe NK, Storstein L. Cardiac arrhythmias in patients with small cell lung cancer and cardiac disease before, during and after doxorubicin administration: an evaluation of acute cardiotoxicity by continuous 24-hour Holter monitoring. Acta Oncol 1991; 30: 843-6.
33. Wells CK, Stoller JK, Feinstein AR, et al. Comorbid and clinical determinants of prognosis in endometrial cancer. Arch Intern Med 1984; 144: 2004-9.
34. Vesterinen E, Karjalainen S, Timonen T, et al. Survival rates in lung cancer patients with and without bronchial asthma. Acta Oncologica 1993; 32: 517-20.

Chapter 5. Trends in incidence and survival within Europe

5.1 Trends in incidence and survival of histological subtypes of lung cancer in European cancer registries, 1978-1992

5.1 Trends in incidence and survival of histological subtypes of lung cancer in European cancer registries, 1978-1992

Abstract

Trends in the incidence and survival of the histological subtypes of lung cancer were studied in Europe, especially in order to determine international variations and changes in incidence and survival rates over time.

We used data of lung cancer patients diagnosed between 1978 and 1992 in eleven cancer registries with a high proportion of histologically verified cases (N=141,480). These registries were selected from the EUROCIM and Eurocare databases.

Incidence rates of squamous cell carcinoma for men in northern Europe have been decreasing since the mid-1980s, while that of adenocarcinoma has been increasing. The incidence rates for men in southern and eastern Europe and for women have been increasing for every histological subtype. One-year survival rates for patients with small-cell carcinoma increased in Denmark and the Netherlands, probably due to the introduction of chemotherapy in the 1970s. For patients with non-small-cell carcinoma one-year survival remained approximately constant in most regions, but varied from 25% in Denmark and England to over 40% in Finland, France and the Netherlands. However, survival of squamous cell carcinoma decreased slightly in Finland and France, and survival of adenocarcinoma decreased in Finland and the Netherlands.

Geographical variations in incidence rates of lung cancer can be largely explained by differences in past smoking behaviour and variations in survival rates can be largely explained by differences in access to specialized care. The increase in the incidence of adenocarcinoma, which in previous studies was associated with the increased use of low-tar filter cigarettes, may be worrying, because survival for these patients has also been decreasing in some regions.

Introduction

Lung cancer is often classified as small-cell lung cancer and non-small-cell lung cancer. The latter group contains squamous cell carcinomas, adenocarcinomas, large-cell undifferentiated carcinomas and some rare subtypes such as adenosquamous cell carcinoma, adenoid cystic carcinoma and mucoepidermoid carcinoma.[1] In Italy, the Netherlands and Switzerland a proportional increase in the incidence of adenocarcinoma was found.[2-4] Overall survival for lung cancer in European cancer registries has not improved between 1978 and 1985.[5] However, there have been divergent trends for the histological subtypes of lung cancer. In previous studies an improvement was found for survival of small-cell carcinoma since the introduction of chemotherapy in the 1970s,[6-9] while survival of non-small-cell carcinoma had remained approximately constant.[10-12] In the southeastern part of the Netherlands substantial variations were found for trends in survival of the histological subtypes of non-small-cell lung cancer: survival of adenocarcinoma decreased markedly since the 1970s, while survival of squamous cell carcinoma increased slightly and that of large-cell undifferentiated carcinoma remained approximately constant.[11] In this study variations in the incidence and survival of the histological subtypes of lung cancer and trends therein were studied in European cancer registries. We discussed if the trends were associated with changes in smoking behaviour, detection, classification or treatment.

Patients and methods

We used data of patients diagnosed with lung cancer between 1978 and 1992 and recorded in eleven European population-based cancer registries. Registries were selected from the EUROCARE database (a concerted action among European cancer registries)[5] on the basis of: (1) data of at least two periods of 5 years and (2) a substantial proportion of histological verification of diagnoses (>75%). The selected cancer registries are shown in table 1. For Yorkshire only data of patients younger than 65 years were used, because the percentage histologically verified cases among the elderly was too low. For international comparison and for comparison with clinical studies, cases incidentally discovered at autopsy were excluded, as were those known to registries from the death-certificate-only (DCO). In case of multiple metachronous tumours, only the first-diagnosed tumour was included for survival analysis.
Small-cell lung tumours were classified as ICD (international classification of diseases) -codes 8040-8043. Non-small-cell lung tumours comprised squamous cell carcinoma (ICD 8070-8080), adenocarcinoma (ICD 8140, 8230, 8250, 8260, 8480, 8481, 8550), large-cell undifferentiated carcinoma (ICD 8012, 8020, 8021, 8030,

8031, 8310), and some rare subtypes such as adenosquamous cell carcinoma (ICD 8560), adenoid cystic carcinoma (ICD 8200) and mucoepidermoid carcinoma (ICD 8430), according to the WHO classification.[1]

Incidence rates were derived from the EUROCIM (European cancer incidence and mortality) database and were computed per 100,000 person-years, according to gender, histological subtype and period of diagnosis. Age-adjustment was performed by direct standardization according to the World Standard Population (WSR: World Standardized Rate).[13]

We calculated crude 1-year survival rates using the life table method. The standard errors of survival rates were calculated according to Greenwood's formula.[14] Survival rates for patients diagnosed in the registry areas were computed according to histological subtype for the periods 1978-82, 1983-87, 1988-92. For patients diagnosed between 1985 and 1989 comparisons between countries were presented in terms of age-adjusted relative survival, computed by the direct method; the population of cases from the whole set of data was used as a standard.[5]

Table 1 *Selected cancer registries.*

				% histological verification* age (years)		
	Available years	% DCO	N	all	<65	65-99
Calvados (France)	1978-1989	N.A.#	2084	90	94	87
Doubs (France)	1978-1992	N.A.#	2312	87	94	83
Denmark	1978-1992	1	43,969	97	98	96
Eindhoven (The Netherlands)	1978-1992	N.A.#	6849	94	97	92
Finland	1978-1992	2	30,944	73	84	66
Geneva (Switzerland)	1978-1989	1	2068	97	99	95
Slovenia	1985-1992	5	5810	94	97	88
South-Sweden	1978-1992	N.A.#	7092	98	99	97
Tarragona (Spain)	1985-1992	6	1382	85	92	80
Varese (Italy)	1978-1987	4	4263	79	87	70
Yorkshire (United Kingdom)	1978-1990	7	34,707	66	75	60

* death certificates only (DCO) excluded
\# not available

Results

Incidence

Between 1978 and 1992 141,480 lung cancer patients were diagnosed: 80,071 with a non-small-cell tumour (56%), 21,514 with a small-cell tumour (15%), 10,594 with another lung tumour (7%) and 29,301 with a clinically diagnosed tumour (21%). Among the patients with non-small-cell carcinoma 44,895 (56%) had squamous cell carcinoma, 21,659 (27%) adenocarcinoma, 12,750 (16%) large-cell undifferentiated carcinoma and 767 (1%) another non-small-cell lung tumour.

Table 2 *Trends in age-standardized incidence rates (WSR), according to gender, cancer registry and histological subtype, 1978-92.*

Source: EUROCIM

		WSR (men)			WSR (women)		
		1978-82	1983-87	1988-92	1978-82	1983-87	1988-92
Denmark	**Non-small-cell**	**34**	**36**	**32**	**10.1**	**13.9**	**15.3**
	Squamous cell	21	20	17	3.4	4.4	4.5
	Adenocarcinoma	8	11	11	5.0	7.6	8.6
	Large-cell undiff.	5	5	4	1.8	2.0	2.1
	Small-cell	**10**	**11**	**10**	**3.2**	**5.0**	**5.5**
	All types	*58*	*58*	*52*	*17*	*23*	*25.4*
Finland	**Non-small-cell**	**40**	**37**	**29**	**4.1**	**4.7**	**4.4**
	Squamous cell	23	23	18	1.1	1.6	1.3
	Adenocarcinoma	7	8	7	2.0	2.3	2.5
	Large-cell undiff.	10	6	4	1.0	0.8	0.6
	Small-cell	**11**	**11**	**9**	**1.0**	**1.4**	**1.5**
	All types	*72*	*64*	*53*	*6.7*	*7.8*	*8.0*
France	**Non-small-cell**	**34**	**37**	**41**	**1.9**	**2.5**	**3.9**
	Squamous cell	26	28	28	0.7	1.1	1.7
	Adenocarcinoma	4	5	8	0.8	1.1	1.9
	Large-cell undiff.	4	4	5	0.4	0.3	0.3
	Small-cell	**6**	**8**	**8**	**0.2**	**0.8**	**0.9**
	All types	*49*	*50*	*53*	*3.0*	*4.0*	*5.4*
Italy	**Non-small-cell**	**45**	**52**	**53**	**2.9**	**4.5**	**4.9**
	Squamous cell	32	35	31	1.1	1.4	1.6
	Adenocarcinoma	9	13	18	1.7	2.5	2.8
	Large-cell undiff.	4	4	4	0.2	0.6	0.4
	Small-cell	**7**	**11**	**11**	**0.5**	**1.3**	**1.1**
	All types	*81*	*83*	*80*	*5.9*	*8.3*	*7.9*
Netherlands	**Non-small-cell**	**69**	**66**	**57**	**3.6**	**5.6**	**6.3**
	Squamous cell	55	47	40	1.6	2.5	2.4
	Adenocarcinoma	7	13	11	1.5	2.3	2.6
	Large-cell undiff.	7	6	7	0.5	0.9	1.3
	Small-cell	**17**	**15**	**14**	**1.4**	**1.7**	**3.4**
	All types	*94*	*87*	*81*	*5.7*	*7.9*	*11.5*
Slovenia	**Non-small-cell**		**39**	**43**		**4.2**	**5.8**
	Squamous cell		24	25		0.9	1.3
	Adenocarcinoma		8	10		2.7	3.4
	Large-cell undiff.		7	8		0.6	1.1
	Small-cell		**11**	**11**		**1.5**	**1.7**
	All types		*59*	*65*		*7.2*	*9.2*
Spain	**Non-small-cell**	**13**	**22**	**26**	**0.5**	**1.5**	**2.2**
	Squamous cell	9	16	17	0	0.6	0.3
	Adenocarcinoma	2	3	6	0.4	0.8	1.7
	Large-cell undiff.	2	2	3	0.1	0.1	0.3
	Small-cell	**4**	**7**	**9**	**0.2**	**0.2**	**0.2**
	All types	*31*	*39*	*43*	*3.0*	*2.7*	*3.1*
Sweden	**Non-small-cell**	**27***	**26**	**22**	**7.4***	**8.8**	**9.3**
	Squamous cell	10	10	9	1.5	1.6	1.8
	Adenocarcinoma	4	6	6	2.6	3.3	4.6
	Large-cell undiff.	12*	9	6	2.8*	3.6	2.6
	Small-cell	**-**	**2**	**6**	**-**	**0.9**	**2.5**
	All types	*27*	*28*	*29*	*7.6*	*10.1*	*12.3*

Table 2 (continued)

		WSR (men)			WSR (women)		
		1978-82	1983-87	1988-92	1978-82	1983-87	1988-92
Switzerland	**Non-small-cell**	**55**	**46**	**39**	**7.0**	**11**	**8.5**
	Squamous cell	38	28	22	2.8	4.1	2.6
	Adenocarcinoma	13	13	13	3.9	5.8	5.0
	Large-cell undiff.	4	4	3	0.4	1.1	0.9
	Small-cell	**10**	**11**	**8**	**1.9**	**2.3**	**3.5**
	All types	*71*	*61*	*54*	*10.4*	*14.8*	*14.3*
UK	**Non-small-cell**		**31**	**31**		**8.6**	**10.8**
	Squamous cell		23	21		5.2	6.1
	Adenocarcinoma		4	6		2.3	3.1
	Large-cell undiff.		4	4		1.2	1.6
	Small-cell		**7**	**8**		**4.0**	**4.5**
	All types		*71*	*64*		*22.8*	*24.9*

* includes small-cell lung cancer

European male lung cancer incidence rates in the selected cancer registries between 1978 and 1992 were highest (>75 per 100,000 person-years) in the Netherlands (Eindhoven) and Italy (Varese), moderate (50-74 per 100,000) in Denmark, Finland, France (Calvados and Doubs), Slovenia, Switzerland (Geneva) and the United Kingdom (Yorkshire), and low (<50 per 100,000) in Spain (Tarragona) and Sweden (south). Among women lung cancer incidence rates were high (>20 per 100,000) in Denmark and the United Kingdom, moderate (10-19 per 100,000) in Sweden and Switzerland, and low (<10 per 100,000) in Finland, France, Italy, the Netherlands, Slovenia and Spain. Age-standardized incidence rates for lung cancer have changed markedly in the past two decades (table 2). In northern Europe the incidence rate among men has been decreasing since the mid-1980s, while in southern and eastern European countries the peak in incidence rates among men was not reached in the beginning of the 1990s. Among women lung cancer incidence (being 5-10 times lower than among men) is still on the rise in most countries, except for Italy and Switzerland, where a plateau was reached in 1983-87. In most countries with declining incidence rates of lung cancer, the incidence rate of adenocarcinoma among men increased.

Survival

Age-standardized relative 1-year survival rates for patients with lung cancer diagnosed between 1985 and 1989 were highest in Finland, France, the Netherlands and Switzerland (about 40%), and lowest in Denmark and the United Kingdom (about 20%). One-year survival rates for all cancer registries combined remained 29% (36% for non-small-cell carcinoma and 22% for small-cell carcinoma). Table 3 shows that overall 1-year survival rates remained constant in all regions, except for Finland, where survival decreased since 1988 and for Switzerland (a slight increase). The same trends were found for patients with non-small cell cancer. However, the prognosis for

patients with squamous cell carcinoma increased slightly in the Netherlands, Slovenia and Switzerland, remained constant in Denmark, Italy and the United Kingdom, but decreased in Finland and France. The prognosis for patients with adenocarcinoma remained approximately constant in most regions, but decreased in Finland and the Netherlands. The prognosis for patients with large-cell undifferentiated carcinoma has remained more or less constant, except for a decrease in France and Italy and an increase in Denmark and the United Kingdom. Survival for patients with small-cell carcinoma has been increasing Denmark, France and the Netherlands, but has remained approximately constant in the other regions.

Table 3 *Trends in 1-year survival (%) and standard error (SE) of histological subtypes of lung cancer.*

a) all types, non-small-cell lung cancer, small-cell lung cancer

	All histological types			Non-small-cell carcinoma			Small-cell carcinoma		
	1978-82	1983-87	1988-92	1978-82	1983-87	1988-92	1978-82	1983-87	1988-92
Registry	% (SE)	% (SE)	% (SE)	% (SE)	% (SE)	% (SE)	% (SE)	% (SE)	% (SE)
Denmark	22 (0.4)	22 (0.3)	22 (0.3)	25 (0.5)	25 (0.5)	25 (0.5)	17 (1)	21 (1)	22 (1)
Finland	37 (0.5)	38 (0.5)	33 (0.5)	43 (1)	45 (1)	40 (1)	26 (1)	24 (1)	23 (1)
France	35 (1)	35 (1)	34 (2)	38 (2)	38 (1)	34 (2)	27 (3)	27 (4)	32 (4)
Italy	28 (1)	30 (1)		34 (1)	34 (1)		25 (3)	26 (2)	
Netherlands	35 (1)	37 (1)	37 (1)	40 (1)	41 (1)	41 (1)	17 (2)	26 (2)	24 (2)
Slovenia		27 (1)	29 (1)		31 (1)	32 (1)		25 (2)	26 (2)
Sweden	29 (1)	29 (1)	30 (1)	29 (1)[@]	30 (1)	31 (1)	-	21 (3)	25 (2)
Switzerland	34 (2)	37 (2)	38 (3)	33 (2)	38 (2)	39 (3)	29 (4)	26 (4)	-
UK*	22 (1)	25 (1)	24 (1)	32 (1)	34 (1)	31 (1)	16 (1)	18 (1)	17 (2)

b) histological subtypes of non-small-cell lung cancer

	Squamous cell carcinoma			Adenocarcinoma			Large-cell undifferentiated		
	1978-82	1983-87	1988-92	1978-82	1983-87	1988-92	1978-82	1983-87	1988-92
Registry	% (SE)	% (SE)	% (SE)	% (SE)	% (SE)	% (SE)	% (SE)	% (SE)	% (SE)
Denmark	30 (1)	28 (1)	28 (1)	24 (1)	23 (1)	24 (1)	12 (1)	13 (1)	17 (1)
Finland	50 (1)	50 (1)	44 (1)	44 (2)	45 (1)	39 (1)	29 (1)	30 (1)	26 (2)
France	44 (2)	42 (2)	35 (3)	37 (4)	31 (4)	42 (5)	23 (3)	25 (3)	18 (3)
Italy	38 (2)	37 (2)		27 (3)	30 (3)		25 (4)	17 (3)	
Netherlands	41 (1)	44 (2)	45 (2)	44 (4)	40 (3)	38 (3)	24 (3)	29 (4)	24 (3)
Slovenia		34 (2)	37 (1)		29 (2)	26 (2)		24 (3)	26 (2)
Sweden	36 (2)	36 (2)	33 (2)	33 (2)	34 (2)	35 (2)	21 (2)[@]	22 (2)	23 (2)
Switzerland	35 (2)	41 (3)	43 (4)	34 (4)	37 (3)	36 (5)	18 (5)	25 (5)	-
UK*	36 (1)	36 (1)	33 (2)	30 (3)	36 (2)	31 (3)	15 (2)	17 (3)	23 (3)

*only patients younger than 65 years of age
[@] includes small-cell lung cancer

Discussion

We analysed the trends in the incidence and survival of the histological subtypes of lung cancer in 11 European cancer registries between 1978 and 1992. Incidence rates for men in northern Europe have been decreasing since the mid-1980s, but the peak in

rates for men in southern and eastern Europe and for women was not reached in the beginning of the 1990s. While the incidence of squamous cell carcinoma among men in northern Europe has been decreasing, that of adenocarcinoma has been increasing. Among women the incidence rate increased for every histological subtype. Prognosis for patients with lung cancer was best in Finland, France, the Netherlands and Switzerland and worst in Denmark and the United Kingdom. One-year survival rates for patients with small-cell carcinoma increased in Denmark, France and the Netherlands. For patients with squamous cell carcinoma one-year survival increased slightly in the Netherlands, Slovenia and Switzerland, but decreased in Finland and France. The survival rates for patients with adenocarcinoma remained stable in most cancer registries, but decreased in Finland and the Netherlands.

Since smoking is the major risk factor for lung cancer,[15] trends in the incidence can be largely explained by trends in past smoking behaviour. The percentage of male smokers has been very high in the Netherlands (95% in 1960), which has resulted in a very high lung cancer incidence rate among males in the 1980s.[2] In contrast, both the percentage of smokers and the lung cancer incidence rate among Swedish men have been very low.[16] The percentage of female smokers has always been lower than that of male smokers,[17] thus the incidence of lung cancer among women has also been lower than among men. The incidence of lung cancer among women was relatively high in Denmark and Yorkshire, where the percentage of female smokers has been high.[17,18] The decrease in the percentage of male smokers since the 1960s in most northern European countries has resulted in a decrease in incidence since the 1980s. Since the percentage of smokers in southern and eastern Europe and among women in most European countries has been increasing until the 1980s,[17] the peaks in incidence were still not reached at the early 1990s.

Since smoking is more closely associated with squamous cell carcinoma and small-cell carcinoma than adenocarcinoma and large-cell undifferentiated carcinoma,[19-20] the decrease in incidence rates since the 1980s has mainly occurred in squamous cell carcinoma and small-cell carcinoma. Several authors have suggested that the increase in the incidence of adenocarcinoma is related to the increased use of low-tar filter cigarettes.[19,21-24] Filter use could result in taking larger puffs and retaining smoke longer to compensate for the lower nicotine yield. This may have increased the incidence of adenocarcinoma, which often develops in the peripheral lung zones. Smoking low-tar filter cigarettes may also increase the risk for adenocarcinoma because of the higher nitrate content.[25] Since Thun and colleagues found that the rise in adenocarcinoma only occurred in smokers,[23] the increased use of low-tar filter cigarettes seems a plausible explanation. The increase in the incidence of adenocarcinoma was also found in the United States,[23,26,27] where adenocarcinoma is now the leading histological type of lung cancer among both males and females. This

is probably due to the higher proportion of low-tar filter cigarette smokers in the United States compared with Europe.[28,29]

There were considerable variations in prognosis for patients with lung cancer in Europe. Age-standardized relative 1-year survival rates were highest in Finland, France, the Netherlands and Switzerland (about 40%) and lowest in Denmark and the United Kingdom (about 20%).[5] Variations in survival rates could, in theory, be caused by differences in registration-procedures, but this probably did not play an important role. Firstly, the comparability of data was checked in the Eurocare study, secondly, patients known to registries from the death-certificate-only (DCO) were excluded and thirdly, survival rates in Denmark and Finland differed markedly, despite equally reliable registration-procedures. Variations in survival can probably be explained by differences in access to specialized care (medically, financially and geographically); this may explain the poor survival rates in the United Kingdom, where the number of consultants and the percentage patients receiving curative treatment is lower than in most other European countries.[30-32]

Overall 1-year survival remained approximately constant in every region, except for Finland, where the survival for all histological subtypes has been decreasing since 1988. We were not able to explain this decrease in survival. The improved survival for patients with small-cell carcinoma in Denmark, France and the Netherlands was probably due to the introduction of chemotherapy in the 1970s. In 1987 the percentage of patients with small-cell lung cancer receiving chemotherapy varied between 50% (United Kingdom) and 70% (the Netherlands).[32] Survival for patients with squamous cell carcinoma increased in the Netherlands, Slovenia and Switzerland, probably due to the improvement in detection and treatment. The observed decrease in survival for patients with squamous cell carcinoma in France may be explained by a shift of large-cell undifferentiated carcinomas – with a lower survival rate – to the group of squamous cell carcinomas. The inter-observer reproducibility of large-cell undifferentiated carcinoma is rather low and it can be reclassified as squamous cell carcinoma or adenocarcinoma in 10-30% of all cases.[33-35]. This should have caused a decrease in survival for all three histological groups. The latter was not found in this study. We are not aware of any other explanation for the decrease in survival of squamous cell carcinoma in France.

The decrease in survival for patients with adenocarcinoma in the Netherlands, was probably not due to a change in classification.[11] In the southeastern part of the Netherlands adenocarcinoma was diagnosed in a more advanced stage in the recent years, despite good access to medical care.[11] We wondered if the decrease in survival could be explained by the increased preference for low-tar filter cigarettes since the 1960s, because of the deeper penetration of carcinogens in the peripheral lung zones.

Conclusion: Geographical variations in incidence rates of lung cancer can be largely explained by differences in past smoking behaviour and variations in survival rates can be largely explained by differences in access to specialized care. The increase in the incidence of adenocarcinoma, which in previous studies was associated with the increased use of low-tar filter cigarettes, may be worrying, because survival for these patients has also been decreasing in some regions.

References

1. WHO. The World Health Organization histological typing of lung tumours. Am J Clin Path 1982; 77: 123-36.
2. Janssen-Heijnen MLG, Nab HW, van Reek J, et al. Striking changes in smoking behaviour and lung cancer incidence by histological type in the south-east Netherlands, 1960-1991. Eur J Cancer 1995; 31A: 949-52.
3. Levi F, Franceschi S, La Vecchia C, et al. Lung carcinoma trends by histologic type in Vaud and Neuchâtel, Switzerland, 1974-1994. Cancer 1997; 79: 906-14.
4. Russo A, Crosignani P, Franceschi S, et al. Changes in lung cancer histological types in Varese Cancer Registry, Italy 1976-1992. Eur J Cancer 1997; 33: 1643-7.
5. Berrino F, Sant M, Verdecchia A, et al. (eds.). Survival of cancer patients in Europe: the EUROCARE study. IARC Scientific Publications No. 132, Lyon, 1995: 232-44.
6. Choi NC, Carey RW, Kaufman D, et al. Small-cell carcinoma of the lung: a progress report of 15 years' experience. Cancer 1987; 59: 6-14.
7. Skarin AT. Analysis of long-term survivors with small-cell lung cancer. Chest 1993; 103: 440S-4S.
8. Lassen U, Osterlind K, Hansen M, et al. Long-term survival in small-cell lung cancer: posttreatment characteristics in patients surviving 5 ot 18+ years: an analysis of 1,714 consecutive patients. J Clin Oncol 1995; 13: 1215-20.
9. Janssen-Heijnen MLG, Schipper RM, Klinkhamer PJJM, et al. Improvement and plateau in survival of small-cell lung cancer since 1975: a population-based study. Ann Oncol 1998; 9: 543-7.
10. Clerci M, Panvini D, Torri V, et al. Patterns of care and survival in non small cell lung cancer: 15 years' experience in a general hospital. Tumori 1994; 80: 106-12.
11. Janssen-Heijnen MLG, Schipper RM, Klinkhamer PJJM, et al. Divergent changes in survival for histological types of non-small-cell lung cancer in the southeastern area of the Netherlands since 1975. Br J Cancer 1998; 77: 2053-7.
12. Connolly CK, Crawford SM, Rider PL, et al. Carcinoma of the bronchus in the Yorkshire region of England 1976-1990: trends since 1984. Eur Resp J 1997; 10: 397-403.
13. Parkin DM, Whelan SL, Ferlay J, et al. (eds.). Cancer indicence in five continents, volume VII. IARC Scientific Publications No. 143, Lyon, 1997.
14. Greenwood M. Reports on Public Health and Medical Subjects No. 33, appendix 1: the "errors of sampling" of the survivorship tables. London: Her Majesty's Stationary Office, 1926.
15. Doll R, Peto R, Wheatly K, et al. Mortality in relation to smoking: 40 years' observations on male British doctors. Br Med J 1994; 309: 901-11.
16. Wersäll JP, Eklund G. The decline of smoking among Swedish men. Int J Epidemiol 1998; 27: 20-6.
17. Franceschi S, Naett C. Trends in smoking in Europe. Eur J Cancer Prev 1995; 4: 271-84.
18. Prescott E, Osler M, Andersen PK, et al. Has risk associated with smoking increased? Results from the Copenhagen Center for Prospective Populaiton Studies. Int J Epidemiol 1997; 26: 1214-8.
19. Lubin JH, Blot WJ. Assessment of lung cancer risk factors by histologic category. J Natl Cancer Inst 1984; 73: 383-9.

20. Engeland A, Haldorsen T, Andersen A, et al. The impact of smoking habits on lung cancer risk: 28 years' observation of 26,000 Norwegian men and women. Cancer Causes and Control 1996; 7: 336-76.
21. Morabia A, Wynder EL. Cigarette smoking and lung cancer cell types. Cancer 1991; 68: 2074-8.
22. Stellman SD, Garfinkel L. Lung cancer risk is proportional to cigarette tar yield: evidence from a prospective study. Prev Medicine 1989; 18: 518-25.
23. Thun MJ, Lally CA, Flannery JT, et al. Cigarette smoking and changes in the histopathology of lung cancer. J Natl Cancer Inst 1997; 89: 1580-6.
24. Wynder EL, Covey LS. Epidemiologic patterns in lung cancer by histologic type. Eur J Cancer Clin Oncol 1987; 23: 1491-6.
25. Hecht SS, Hoffmann D. Tobacco-specific nitrosamines, an important group of carcinogens in tobacco and tobacco smoke. Carcinogenesis 1988; 17: 116-28.
26. Zheng T, Holford T, Boyle P, et al. Time trend and the age-period-cohort effect on the incidence of histologic types of lung cancer in Connecticut, 1960-1989. Cancer 1994; 74: 1556-67.
27. Travis WD, Lubin J, Ries L, et al. United States lung carcinoma incidence trends: declining for most histologic types among males, increasing among females. Cancer 1996; 77: 2464-70.
28. Wynder EL, Muscat JE. The changing epidemiology of smoking and lung cancer histology. Environ Health Perspect 1995; 103(suppl 8): 143-8.
29. Giovino GA, Henningfield JE, Tomar SL, et al. Epidemiology of tobacco use and dependence. Epid Rev 1995; 17: 48-65.
30. Farthing MJ, Williams R, Swan CH, et al. Nature and standards of gastrointestinal and liver services in the United Kingdom. Gut 1993; 34: 1728-39.
31. Schroeder SA. Western European responses to physician oversupply: lessons for the United States. J Am Med Assoc 1984; 252: 373-84.
32. Gatta G, Sant M (on behalf of the EUROCARE working group). Patterns of treatment of lung cancer patients in Europe (abstract). Annual meeting of the International Association of Cancer Registries. Bratislava, Slovakia, 1993.
33. Greenberg ER, Korson R, Baker J, et al. Incidence of lung cancer by cell type: a population-based study in New Hampshire and Vermont. J Natl Cancer Inst 1984; 72: 599-603.
34. Campobasso O, Andrion A, Ribotta M, et al. The value of the 1981 WHO histological classification in interobserver reproducibility and changing pattern of lung cancer. Int J Cancer 1993; 53: 205-8.
35. Gazdar AF, Linnoila RI. The pathology of lung cancer – changing concepts and newer diagnostic techniques. Semin Oncol 1988; 15: 215-25.

Chapter 6. Incidence and survival of uncommon tumours

6.1 Increased but low incidence and poor survival of malignant mesothelioma in the southeastern part of the Netherlands since 1970: a population-based study

6.2 Trends in incidence and survival of uncommon lung tumours since 1970: a population-based study in the southeastern part of the Netherlands

6.1 Increased but low incidence and poor survival of malignant mesothelioma in the southeastern part of the Netherlands since 1970: a population-based study

Background

Malignant mesothelioma represents only 0.5% of all cancers in the Netherlands, but mortality has increased markedly since 1970.[1] The major risk factor is exposure to asbestos; the association was first noted in 1960 in South Africa[2] and confirmed in the Netherlands in 1971.[3] The latency time is usually 30-40 years.[4] Changes in the incidence and survival rates for malignant mesothelioma since 1970 in the southeastern part of the Netherlands, an area with presumably limited exposure to asbestos, were investigated.

Patients and methods

Data of the Eindhoven Cancer Registry, which has collected data on patients with newly diagnosed cancer since 1955 in the southeastern part of the Netherlands, were used. Only since the 1960s has mesothelioma been considered a morphological entity. About sixty percent of all histological specimens of (suspected) mesothelioma have been reviewed by two or three experts of the Netherlands Mesothelioma Panel since 1969. Age-specific (according to 15-year age groups) and age-adjusted (ESR: European Standardized Rate) incidence rates were computed per one million person-years, according to sex, tumour site and 5-year periods of diagnosis. The ESR for the southeastern part of the Netherlands was compared to that found in other European areas using data from the European Cancer Incidence and Mortality (EUROCIM) database.

There was a combination of passive and active follow-up of all patients diagnosed up to 31 December 1992. The latest follow-up to determine vital status by the municipal population administrations occurred on 1 April 1994. Relative survival was calculated as the ratio of observed to expected actuarial rates. Expected survival rates were calculated from life tables for regional male and female populations (supplied by Statistics Netherlands), compiled according to 5-year age groups and year of

diagnosis. The risk of death due to lung cancer was estimated using a program from the Finnish Cancer Registry.[5] The standard errors of survival rates were calculated according to Greenwood's formula.[6] Patients who were diagnosed at autopsy or died within the first month of diagnosis were excluded from the survival analysis (N=6, 5%).

Results

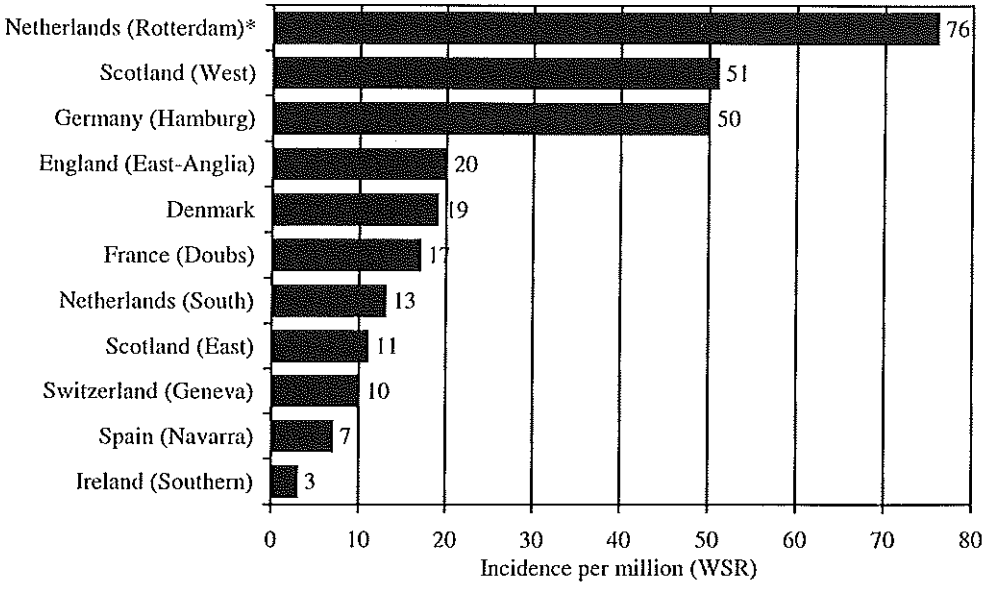
Between 1970 and 1994 136 patients with malignant mesothelioma were diagnosed: 108 (79%) men and 28 (21%) women. Most of the mesotheliomas occurred in the pleura (N=119, 88%) versus 15 (11%) in the peritoneum and 2 in the tunica vaginalis testis. The incidence rates for malignant pleural mesothelioma have increased twofold since 1975, while those for peritoneal mesothelioma remained constant (table). Compared to other European cancer registries the incidence of mesothelioma in the southeastern part of the Netherlands in the late 1980s was fairly low (figure). The incidence rates for mesothelioma in Rotterdam (the southwestern part of the Netherlands including Walcheren Island), Western Scotland and Hamburg (the northern part of Germany) were extremely high.
Survival rates for mesothelioma were poor. Six patients (5%) were diagnosed at autopsy or died within one month of diagnosis. Between 1970 and 1992 the overall relative 0.5-, 1- and 3-year survival rates remained constant at 68%, 42% and 8%, respectively. There was no significant difference between men and women. Survival for peritoneal mesothelioma (79% alive at 1 year, standard error 28%) seemed better than for pleural mesothelioma (38% alive at 1 year, standard error 10%). None of the patients survived longer than five years after diagnosis.

Table *Trends in age-specific and age-adjusted (ESR) incidence, per one million person-years.*

Men		age (years)				pleural	peritoneal
period	N	30-44	45-59	60-74	75 +	ESR	ESR
1970-74	6	-	7	26	-	2.9	1.5
1975-79	17	-	24	44	39	10.2	-
1980-84	14	5	10	49	-	6.8	0.6
1985-89	26	7	31	35	46	11.2	1.5
1990-94	45	2	37	84	143	19.3	2.0
Women							
1970-74	1	-	-	-	-	-	0.9
1975-79	1	2	-	-	-	0.5	-
1980-84	6	4	5	-	12	2.4	0.5
1985-89	8	2	5	7	25	3.3	-
1990-94	12	2	7	27	8	3.8	0.12

Figure *Age-standardized incidence rates (ESR) for mesothelioma in Europe (1985-89, males).*

*1986-1989



Discussion

Nowadays, about one out of every 40 patients with cancer of the lower respiratory tract in the southeastern part of the Netherlands has a mesothelioma versus one out of every 120 patients in the 1970s. Initial misdiagnosis of mesothelioma may have been common and was probably attributable to misclassification of adenocarcinoma of the lung, breast, ovary, stomach, kidney, or prostate that can metastasize to the pleura.[7] Peritoneal mesotheliomas can be confused with adenocarcinomas arising from any abdominal organ. Nonetheless, it is not likely that diagnostic trends explain to any large extent the recent increase in recorded rates, because the experts of the Netherlands Mesothelioma Panel reviewed a large proportion (±60%) of the histological specimens of mesotheliomas collected since 1969. The incidence of mesothelioma in the southeastern part of the Netherlands was fairly low compared to other cancer registries, because of the presumably limited exposure to asbestos. Although low, the incidence rate for pleural mesothelioma for (especially elderly) men has increased twofold since 1975. This might be explained by the migration of men who were exposed to asbestos while employed in the shipbuilding industry from the southwestern to the southeastern part of the Netherlands.

The very high incidence rates for the southwestern part of the Netherlands – which includes the Walcheren Island and the Rijnmond shipbuilding area –,[8] western Scotland and the northern part of Germany probably reflect the high exposure to asbestos due to shipbuilding. Asbestos remains the predominant cause of pleural, peritoneal, and probably epididymal mesothelioma.[9] After legal measures to prevent or reduce exposure to asbestos were introduced in the Netherlands, unfortunately not until 1977, the import of asbestos decreased dramatically. Given the mean latency time of 30-40 years, incidence rates for malignant mesothelioma among Dutch men will probably increase until 2015-2020.[10]
Between 1970 and 1992 the prognosis for patients with mesothelioma remained poor, being similar to the southwestern part of the Netherlands, the United States and Canada.[11,12]

Conclusion: in view of the presumably limited exposure to asbestos, the incidence of mesothelioma in the southeastern part of the Netherlands will probably remain low, despite the increase in the past few decades.

References

1. Meijers JMM, Planteydt HT, Slangen JJM, et al. Trend and geographical patterns of pleural mesotheliomas in the Netherlands 1970-1987. Br J Ind Med 1990; 47: 775-81.
2. Wagner JC, Sleggs CA, Marchand P. Diffuse pleural mesothelioma and asbestos exposure in the North Western Cape Province. Br J Ind Med 1960; 17: 266-71.
3. Stumphius J. Epidemiology of mesothelioma on Walcheren Island. Br J Ind Med 1971; 28: 59-66.
4. Woitowitz HJ, Grossgarten K. Pleural mesothelioma: etiology and practical consequences. [in German] Pneumologie 1991; 45: 153-8.
5. Hakulinen T, Abeywickrama KH. A computer package for relative survival analysis. Computer Programmes in Biomedicine 1985; 19: 197-207.
6. Greenwood M. Reports on Public Health and Medical Subjects No. 33, appendix 1: the "errors of sampling" of the survivorship tables. London: Her Majesty's Stationary Office, 1926.
7. Walz R, Koch HK. Malignant pleural mesothelioma: some aspects of epidemiology, differential diagnosis and prognosis. Histological and immunohistochemical evaluation and follow-up of mesotheliomas diagnosed from 1964 to January 1985. Path Res Pract 1990; 186: 124-34.
8. Damhuis RAM, van Gelder T. Malignant mesothelioma in the Rotterdam Area, 1987-1989. Eur J Cancer 1993; 29A: 1478-9.
9. McDonald AD, McDonald JC. Mesothelioma after crocidolite exposure during gas mask manufacture. Environ Res 1978; 17: 340-6.
10. Burdorf A, Barendregt JJ, Swuste PHJJ, et al. Future increase of the incidence of mesothelioma due to occupational exposure to asbestos in the past. [in Dutch] Ned Tijdschr Geneeskd 1997; 141: 1093-8.
11. Van Gelder T, Damhuis RAM, Hoogsteden HC. Prognostic factors and survival in malignant pleural mesothelioma. Eur Respir J 1994; 7: 1035-8.
12. Ribak J, Selikoff IJ. Survival of asbestos insulation workers with mesothelioma. Br J Ind Med 1992; 49: 732-5.

6.2 Trends in incidence and survival of uncommon lung tumours since 1970: a population-based study in the southeastern part of the Netherlands

Introduction

The two major histological types of epithelial lung cancer are small-cell cancer and non-small-cell cancer. The latter includes squamous cell carcinoma, adenocarcinoma, large-cell undifferentiated carcinoma and some rare subtypes such as adenosquamous cell carcinoma, adenoid cystic carcinoma and mucoepidermoid carcinoma. The less common tumours can be subclassified as mesothelioma (chapter 6.1), carcinoid tumours, carcinosarcomas and sarcomas, all clearly different with respect to aetiology and prognosis.
Because they are so rare, uncommon lung tumours are usually described in case series. In this study we described and interpreted trends in incidence rates and survival rates for uncommon tumours in the southeastern part of the Netherlands between 1970 and 1994.

Methods

For this study data from the Eindhoven Cancer Registry were used. This registry started to record data on all cancer patients diagnosed in the eastern part of the Dutch province of North-Brabant in 1955; since 1970 the northern part of the adjacent province of Limburg is included. It serves an area with 1 million inhabitants and good access to specialized care.
The uncommon lung tumours are carcinoid tumour (ICD 8240), carcinosarcoma (ICD 8980), sarcoma (ICD 8800-8900) and malignant melanoma (ICD 8720). Pulmonary carcinoid tumours are defined as tumours of the diffuse endocrine system derived from Kultschitsky-type cells; carcinosarcomas are tumours that have an admixture of carcinoma and sarcoma. The age-adjusted incidence rates, according to the European Standardized Rate (ESR) for each histological type, were computed per one million person-years for the periods 1970-79, 1980-89 and 1990-94.
Relative survival was calculated as the ratio of the crude to the expected rates (calculated from life tables for regional male and female populations, compiled according to 5-year age groups and year of diagnosis). The risk of death due to uncommon lung tumours was predicted from a model prepared by the Finnish Cancer Registry.[1]

Results

During the period 1970-94 11,047 lung cancer patients were diagnosed in the southeastern part of the Netherlands, whereby 6% were clinically diagnosed. Less than 1% of these patients suffered from an uncommon lung tumour: 54 carcinoid tumours (0.5%), 11 carcinosarcomas (0.1%), 9 sarcomas (0.1%) and 1 malignant melanoma (0.01%). The male/female ratio was 1.3 for carcinoid tumours, 2.7 for carcinosarcomas and 2 for sarcomas. The male/female ratio for carcinoid tumours was lower for patients younger than 50 years of age (m/f-ratio = 1) than for those 50 and older (m/f-ratio = 1.4). Carcinoid tumours developed mainly in the lower lung lobe (41%). The mean age of patients with carcinoid tumour was 54 years (range 24-84), those with carcinosarcoma 61 years (range 36-74) and patients with sarcoma 63 years (range 45-69).

The age-standardized incidence rate (ESR) for carcinoid tumours increased from 3 per one million inhabitants in 1970-79 to 7 in 1980-89 and 1990-94 (table); the increase occurred in both the younger and older age groups. For carcinosarcomas and sarcomas the incidence rates were about 1 per one million inhabitants (table). Most carcinoid tumours, carcinosarcomas and sarcomas were surgically resected (85%, 60% and 71%, respectively).

The relative 1-, 5- and 10-year survival rates for patients with carcinoid tumour remained constant at 97%, 83% and 77%, respectively. The median survival time for patients with a carcinoid tumour was 6.5 years. The relative 1-year survival rates for patients with carcinosarcoma or sarcoma were 26% and 46%, respectively.

Table *Age-standardized incidence rates per one million person-years (ESR) of uncommon lung tumours diagnosed between 1970 and 1994, according to histological subtype.*

	Carcinoid		Carcinosarcoma		Sarcoma	
	N	ESR	N	ESR	N	ESR
1970-79	7	3	3	0.9	4	1.0
1980-89	30	7	2	0.5	3	0.8
1990-94	17	7	6	3.0	2	0.9
1970-94	**54**	**6**	**11**	**1.1**	**9**	**1.0**

Discussion

The most frequent uncommon lung tumour was the carcinoid tumour, which occurred mainly in younger age groups.[2] It is usually localized centrally and accounts for less than 1% of all lung tumours.[3] An increase in the incidence of carcinoid tumours in all

age groups was also found in the SEER cancer registry.[4] This may in part be due to improved diagnostic technology and increased awareness, but there is also some evidence that hormonal factors play a role in the aetiology of carcinoid tumours.[5] The male/female ratio was lower in the reproductive period (younger than 50). The prognosis for patients with carcinoid tumour was rather good; the 5-year survival rate was over 80%, as was also found in other western countries.[4,6-10]

Sarcomas originating in the lung usually represent less than 0.1% of all malignant lung tumours;[11] they are usually aggressive tumours, with 60-90% fatality 5 years after diagnosis.[2,12,13] The single most important differential diagnosis for cases of suspected primary sarcoma of the lung is metastatic spread from an extrapulmonary tumour. Therapy is usually surgery;[14] radiotherapy and chemotherapy have proven to be of little benefit thus far.[3] Little is known about aetiological factors,[15] and the relationship with smoking has not been confirmed.[12] If sarcomas were closely related to smoking the incidence in the southeastern part of the Netherlands should have increased markedly until the early 1980s, since the percentage male smokers was about 95% in the 1950s.[16] However this could not be demonstrated in this study.

Carcinosarcomas are difficult to distinguish from squamous cell carcinomas unless differentiation into specific tissues such as neoplastic bone, cartilage and striated muscle occurs. Only about 1 out of 1000 lung tumours will be a carcinosarcoma and they are very rarely diagnosed preoperatively.[17] The prognosis for carcinosarcoma was poor (26% alive after 1 year), as in Germany.[17]

It was found to be particularly difficult to establish with certainty the diagnosis of primary melanomas in the lung, because the lung is such a common site for metastases (particularly from ocular melanoma) which may arise many years after the primary tumour was excised.[18] Furthermore, primary cutaneous melanomas can regress but still give rise to metastases.[19] There are, moreover, rare instances of primary melanoma arising in the bronchus.[20] It is important to be able to identify those cases which are recognized as primary tumours, so that the clinical and pathological features can be analysed and diagnosed during life in order to achieve appropriate treatment and management. The majority of melanomas in the lung reported in other studies are believed to be primary tumours. The aetiology might be related to smoking, but the number of cases in previous studies was too small to exclude the possibility that this relationship was due to chance.

Conclusion: although carcinoid tumours, sarcomas, carcinosarcomas and malignant melanomas very rarely occur in the lung, they should be distinguished from small-cell lung cancer or non-small-cell lung cancer, because different treatment is required and there are differences in prognosis.

References

1. Hakulinen T, Abeywickrama KH. A computer package for relative survival analysis. Computer Programmes in Biomedicine 1985; 19: 197-207.
2. Travis WD, Travis LB, Devesa SS. Lung cancer. Cancer 1995; 75: 191-202.
3. Williams CJ, Krikorian JG, Green MR, Raghavan D (eds.). Textbook of uncommon cancer. John Wiley & Sons Ltd, Oxford, 1988, 335-97.
4. Modlin IM, Sandor A. An analysis of 8305 cases of carcinoid tumors. Cancer 1997; 79: 813-29.
5. Newton JN, Swerdlow AJ, dos Santos Silva IM, et al. The epidemiology of carcinoid tumours in England and Scotland. Br J Cancer 1994; 70: 939-42.
6. Godwin JD. Carcinoid tumors: an analysis of 2837 cases. Cancer 1975; 36: 560.
7. Marty-Ane CH, Costes V, Pujol JL, et al. Carcinoid tumors of the lung: do atypical features require aggressive management? Ann Thorac Surg 1995; 59: 78-83.
8. Perkins P, Kemp BL, Putnam JB Jr, et al. Pretreatment characteristics of carcinoid tumors of the lung which predict aggressive behavior. Am J Clin Oncol 1997; 20: 285-8.
9. Shah R, Sabanathan S, Mearns J, et al. Carcinoid tumour of the lung. J Cardiovasc Surg 1997; 38: 187-9.
10. Crocetti E, Buiatti E, Amorosi A. Epidemiology of carcinoid tumours in central Italy. Eur J Epidemiol 1997; 13: 357-9.
11. Paulsen SM, Egeblad K, Christensen J. Malignant fibrous histiocytoma of the lung. Virchows Arch Pathol Anat 1981; 394: 167-76.
12. Guccion JG, Rosen SH. Bronchopulmonary leiomyosarcomas and fibrosarcomas: a study of 32 cases and review of the literature. Cancer 1972; 30: 835-47.
13. Dail DH, Liebow AA, Gmelich JT, et al. Intravascular, bronchiolar, and alveolar tumor of the lung (IVBAT): an analysis of twenty cases of a peculiar sclerosing endothelial tumor. Cancer 1983; 51: 452-64.
14. Gebauer C. The postoperative prognosis of primary pulmonary sarcomas. Scand J Thorac Cardiovasc Surg 1982; 16: 91-7.
15. Yang JC, Rosenberg SA, Glatstein EJ, et al. Sarcomas of soft tissues. In: DeVita VT Jr, Hellman S, Rosenberg SA (eds.). Principles & Practice of Oncology, Fouth Edition, JB Lippencott Co., Philadelphia, 1993: 1436-88.
16. Janssen-Heijnen MLG, Nab HW, van Reek J, et al. Striking changes in smoking behaviour and lung cancer incidence by histological type in the south-east Netherlands, 1960-1991. Eur J Cancer 1995; 31A: 949-52.
17. Summerman E, Huwer H, Seitz G. Carcinosarcoma of the lung, a tumour which has a poor prognosis and is extremely rarely diagnosed preoperatively. Thorac Cardiovasc Surg 1990; 38: 247-50.
18. Reed RJ, Kent EM. Solitary pulmonary melanomas. J Thorac Cardiovasc Surg 1964; 48: 226-31.
19. Smith JL, Stehlin JS Jr. Spontaneous regression of primary malignant melanoma with regional metastases. Cancer 1965; 18: 1399-415.
20. DasGupta TK, Brasfield RD, Paglia MA. Primary melanomas at unusual sites. Surg Gynecol Obstet 1969; 128: 841-8.

Chapter 7. General discussion

In this thesis changes in the incidence and survival of the histological subtypes of lung cancer in the southeastern part of the Netherlands have been described and interpreted. For men the age-standardized incidence rate increased markedly until 1983 and then decreased. The incidence among middle-aged men increased until the beginning of the 1970s, that for men aged 60-74 until the end of the 1970s and that for men aged 75 and older until the mid-1980s. The decrease in incidence among men started earlier for squamous cell and small-cell carcinoma (1978) than for adenocarcinoma (1985). For women the incidence rate increased from the initially very low level in the 1960s until the 1990s in every age group and for every histological subtype. The incidence rates for pleural mesothelioma and carcinoid tumours have increased but have remained low.

The prognosis for patients with lung cancer was dependent on age and stage and varied markedly between the various histological subtypes. For non-small-cell lung cancer overall survival did not improve significantly, but subsite-specific survival increased slightly for patients with squamous cell carcinoma, decreased for patients with adenocarcinoma and remained stable for those with large-cell undifferentiated carcinoma. For small-cell lung cancer short-term survival has improved considerably since the introduction of chemotherapy, but long-term survival has remained poor.

Quality of the data

When reporting on trends, it must be realised that the precision of detection, classification and staging has gradually improved, especially due to the introduction of flexible bronchoscopy and the increase in the number of chest physicians. In contrast, the direct and multiple source registration process in the Eindhoven Cancer Registry has remained largely the same.

Completeness

The analyses were confined to a core region of municipalities that were covered by the Eindhoven Cancer Registry. This is a registry without Death Certificate Only (DCO) cases and with good access to medical care; some elderly patients and patients with poor chances of survival may have been missed, but the percentage missing patients (mainly elderly) was estimated to be less than 5%. Since survival of lung cancer is poor, mortality should be almost equal to the incidence. We compared incidence and mortality rates – determined by Statistics Netherlands – in order to assess the completeness of the cancer registry. Incidence rates were slightly higher than mortality rates, except for the very elderly (section 2.1).

It should be noted that there are differences in completeness of data between the various countries, depending on the ascertainment in hospitals and cancer registries, the access to medical care, and the availability and quality of death certificates (section 1.2).

Classification

For histological typing of lung cancer the classification of the WHO was used. The same classification was used throughout the whole study period. Interobserver bias exists, especially for large-cell undifferentiated carcinoma;[1] this was also found in a review of a sample of lung cancer patients taken from the Eindhoven Cancer Registry: almost 50% of large-cell undifferentiated carcinomas could be reclassified as squamous cell carcinoma and almost 15% as adenocarcinoma. For adenocarcinoma it is sometimes difficult to distinguish between primary adenocarcinoma of the lung and metastases from adenocarcinoma elsewhere, such as the breast, prostate, colon, rectum or stomach. As soon as the primary tumour was found, the diagnosis was corrected in the registry.

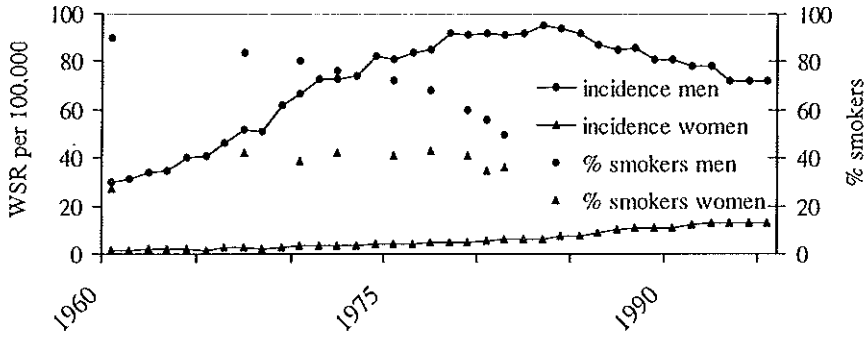
The recording of co-morbidity by cancer registry personnel was validated in a study of 127 patients (section 2.4): there was an underestimation of the total number of diseases of 8%; the number of cardiovascular diseases was underestimated by 27% of the originally recorded prevalence, while the occurrence of COPD (chronic obstructive pulmonary disease) was overestimated by 6%. Since this was only corrected in registration procedures in the second half of 1996 we adjusted the originally recorded

prevalences of cardiovascular diseases and COPD by the above-mentioned percentages.
When reporting on trends in stage distribution one should take into account 'stage migration': through improved diagnostic techniques lymph node metastases and distant metastases can now be found more easily, thus some tumours that were recorded as localized in the earlier period will be recorded as regional nowadays.[2]

Trends in incidence

Age-standardized lung cancer incidence rates (World Standardized Rate, WSR) for men in the southeastern part of the Netherlands increased markedly from 30 per 100,000 person-years in 1960 to 95 in 1983 and then declined to 70 in 1994; the incidence increased until birth cohort 1910-19. The decrease in incidence rates first occurred among middle-aged men (peak in 1974) and later also among the elderly. Incidence rates for women were much lower than those for men but increased from 1 per 100,000 person-years in 1960 to a plateau of 13 since 1992. The incidence of lung cancer among men in municipalities with tobacco-processing industries was clearly higher than in other urban and rural municipalities. In contrast, incidence of lung cancer among women was much higher in urban than in rural areas, and the presence of tobacco industries did not make any notable difference. For men the peak incidences of squamous cell carcinoma and small-cell carcinoma were reached in 1978, while that for adenocarcinoma was reached in 1985. The proportion with adenocarcinoma has increased, especially for men born after 1920. Among women the incidence rates have increased for every histological subtype.
The trends in lung cancer incidence were most likely related to changing smoking habits, the major risk factor for lung cancer (figure).[3-11] The relative risk for smokers depends on multiple aspects of smoking behaviour, including age at starting smoking, the number of cigarettes smoked, the products smoked and the inhaling pattern. It varies between 3 and 55 for men and between 4 and 147 for women.[12] The decline in male smokers from 95% in 1960 to 50% in 1981 was followed by a drop in male lung cancer incidence after 20-25 years (section 3.1). The decrease in incidence for men born since 1920 could be explained by the fact that these men (who were younger than 40 years in 1960) were more likely to quit smoking or to switch to low-tar filter cigarettes compared to the older birth cohorts. The trends in the incidence of female lung cancer (increase and plateau) also reflect changes in smoking behaviour: the percentage female smokers increased from a low 27% in 1960 to 40% in 1967; after 1979 it decreased to 36% in 1981.

Figure Age-standardized incidence (WSR) and % smokers.



The trends in lung cancer incidence in the southeastern part of the Netherlands seem to represent an extreme situation: male lung cancer incidence was one of the highest in Europe (section 5) and between 1969 and 1990 regional mortality was also higher than in other parts of the Netherlands.[13-16] Between 1960 and 1980 the percentage male smokers was 5% higher in the southern part of the Netherlands than in the rest of the country, which might possibly be attributed to high social acceptance of smoking due to the presence of many tobacco-processing industries (section 3.2). On the other hand, female lung cancer incidence and mortality in the southeastern part of the Netherlands were among the lowest in the Netherlands and in Europe up to 1980,[13-16] due to the very low initial percentage female smokers in this part of the Netherlands. This was probably related to the traditional lifestyle of, largely Roman-Catholic, women.

Another argument for the role of smoking habits is the fact that among men the peak incidence rates for squamous cell carcinoma and small-cell carcinoma, both of which correlate with smoking better than adenocarcinoma,[7,17-23] were reached in 1978, while that for adenocarcinoma was reached in 1985. The same phenomenon was seen in other European countries (section 5) and in North America;[24-32] in North America adenocarcinoma is now even the leading lung cancer cell type among men. The strength of the association between smoking and histology seems to be related to tumour location: adenocarcinoma develops primarily in the peripheral lung zones, whereas squamous cell carcinoma and small-cell carcinoma occur mainly in central or hilar locations.[7,19,33,34]

Since squamous cell carcinoma and small-cell carcinoma are closely related to smoking the decrease in incidence rates for men was probably due to a decrease in the percentage smokers since the 1960s and the change to low-tar filter cigarettes (figure).[25,26,28]

The increase in the incidence of adenocarcinoma – which exhibits the lowest correlation with smoking – is more difficult to explain. It was not caused by an

increase in bronchioloalveolar carcinoma, as was suggested in three studies conducted in the United States in the 1990s.[35-37] Furthermore, inter-observer reproducibility for adenocarcinoma was good.[1,38,39] Other authors suggest that the increase might be due to changes in exposure to risk factors, such as the increased preference for low-tar filter cigarettes since the 1960s, especially since the increase in adenocarcinoma only occurred in smokers.[32] Filters could lead to larger puffs and retaining smoke longer to compensate for the lower nicotine yield. The subsequently increased deposits of smoking particles in the bronchioles could enhance the risk for adenocarcinoma, which usually occurs in the peripheral lung zones.[7,32,33,40,41] Furthermore, low-tar filter cigarettes have a higher nitrate content. The subsequently increased production of N-nitrosamines induced lung adenocarcinomas in laboratory animals.[42] Stellman and colleagues indeed found that the risk of adenocarcinoma for filter cigarette smokers was not reduced when compared with non-filter cigarette smokers, in contrast to the risk for squamous cell carcinoma.[41] Younger men were more inclined to smoke low-tar filter cigarettes than the elderly; this explains why the increase in adenocarcinoma mainly occurred in men born after 1920 (section 4.1.2). The percentage smoking women just started to increase in the 1960s, and the proportion smoking low-tar filter cigarettes has always been higher than for men. This may have contributed to the higher baseline proportion of women with adenocarcinoma.

Uncommon tumours

Section 6.1 shows that the incidence of pleural mesothelioma in the southeastern part of the Netherlands was fairly low compared to some other Dutch cancer registries, but it has increased twofold since 1975 (from 10 to 19 per one million person-years), especially among (elderly) men. This may be explained by the migration of men who were exposed to asbestos while employed in the shipbuilding industry from the southwestern to the southeastern part of the Netherlands. However, in view of the presumably limited exposure to asbestos of the population in the southeastern part of the Netherlands, the incidence of mesothelioma in this area will probably remain low.

After mesothelioma, the most frequent uncommon lung tumour was carcinoid tumour, which develops especially in younger age groups.[29] The incidence of carcinoid tumours seems to have increased slightly in all age groups (section 6.2), as was also demonstrated by the SEER cancer data.[43] This may in part be due to improved diagnostic technology and increased awareness. There is also some evidence that hormonal factors play an important role in the aetiology of carcinoid tumours.[44] This may explain the lower male/female ratio in the reproductive period (younger than 50).

Sarcomas, carcinosarcomas and melanomas in the lung are very rare and a trend could not be identified. It is unlikely that these tumours are closely associated with smoking; otherwise a marked increase would have been seen since the 1960s.

Conclusion on trends in incidence
In view of the trends in known risk factors and latency time, the incidence rates for male lung cancer will probably decline further in the near future, but the proportion of adenocarcinoma will increase further. A decrease in the incidence of female lung cancer is not expected before the beginning of the next century.

Trends in survival

Besides being dependent on age and tumour stage, survival for lung cancer patients was closely related to histology of the tumour. Survival was best for patients with carcinoid tumour (1-year survival was 97%), followed by non-small-cell carcinoma and sarcoma (1-year survival almost 50%), mesothelioma (1-year survival was 42%) and small-cell carcinoma (1-year survival about 35%), and was poorest for patients with carcinosarcoma (1-year survival about 25%). Although the overall prognosis for patients with non-small-cell lung cancer has remained unchanged, there have been divergent changes between morphological subtypes (section 4.1.1). Relative survival for squamous cell carcinoma improved slightly between 1975 and 1994, while relative 1-year survival for patients with adenocarcinoma has decreased markedly since 1975 and for those born after 1930. The relative survival rate for large-cell undifferentiated carcinoma was markedly lower than that for the above-mentioned two types and has remained roughly unchanged.
Short-term survival (<2 years) for patients with small-cell carcinoma has almost doubled since 1975, especially for patients younger than 70 years; for this group median survival has increased from 5 to 10 months. However, 'long-term' survival (≥2 years) remained poor and excess 5-year mortality for patients who were alive after eight years was 39%.
Survival of lung cancer for patients in the southeastern part of the Netherlands was among the highest in Europe (section 5).

Non-small-cell lung cancer
In section 4.1.2 we searched for an explanation for the decline in survival found for younger patients with adenocarcinoma of the lung. Among these patients the proportion with early disease has also been decreasing, thus the biological behaviour of adenocarcinomas might have shifted towards a more rapidly metastasizing tumour. This may be caused by the higher concentration of carcinogens in the peripheral lung zones. The most likely explanation is the introduction of low-tar filter cigarettes, especially because the decrease in survival occurred in those born after 1930. In this respect, cigarette smoke-induced K-ras mutations, which are known to be associated with the adenocarcinoma phenotype in lung cancer, have been shown in several

studies to be associated with a poor prognosis.[45-47] Monitoring of microalbuminuria or cytokeratin-18 may also indicate the prognosis for patients with non-small-cell lung cancer.[48-50]

The mean age of lung cancer patients is rising due to the combined effect of a decrease in incidence among younger men, an increase in the incidence among the elderly and the growing mean age of the general population. Therefore, co-morbidity is becoming more important for the clinical management of cancer patients, especially surgical resection, because of peroperative and postoperative complications.[51-54] Co-morbidity is also an independent prognostic factor.[55-60] Section 4.3 shows that the presence of co-morbidity in patients with localized non-small-cell lung cancer was indeed associated with fewer resections.

Small-cell lung cancer

Section 4.2 shows that the improved short-term survival found for small-cell lung cancer in the southeastern part of the Netherlands is likely to be due to the increased use of chemotherapy since the end of the 1970s. Cyclophosphamide-Doxorubicin-Etoposide (CDE) has been the standard combination since the end of the 1980s. It had not yet evolved to the platinum-containing regimen during the study period. Nonetheless, despite initial chemosensitivity, the majority of patients relapse or develop a second tumour.[61-64] Results of chemotherapy have reached a plateau and further improvement seems impossible with currently available tools.[65-67] For older patients only a small improvement in median survival was found, which may be due to less aggressive treatment because of poor performance status. The latter is probably related to the high prevalence of co-morbidity (60%) among these patients: the proportion patients over 70 receiving chemotherapy decreased slightly from 73% for those without concomitant diseases to 65% for those with two or more concomitant diseases, but doses were probably also adapted (section 4.3). There is some disagreement about the benefit of chemotherapy for older patients with small-cell lung cancer. Some authors have argued that survival for the elderly is similar to that for younger patients, despite less aggressive treatment,[68] while others found that even elderly patients with co-morbidity are likely to benefit from combination chemotherapy.[69-73]

Conclusion on trends in survival

Despite better access to medical care and improvement in diagnostic techniques and treatment, overall survival for non-small-cell lung cancer has not improved over time, and prognosis for adenocarcinoma has even been decreasing, especially for those born after 1930. This might indicate that adenocarcinoma is becoming a more rapidly metastasizing tumour type, possibly caused by smoking low-tar filter cigarettes. Progress was noted for short-term survival of small-cell lung cancer after the

introduction of chemotherapy, but a plateau was reached at the end of the 1980s and long-term survival (≥2 years) has not improved.
Furthermore, the proportion of elderly patients is growing, thus co-morbidity will become an important factor in treatment choice and survival. This means that there is a need for adapted guidelines for these patients, who are usually excluded from clinical trials.

Conclusions and recommendations for further studies

Lung cancer is one of the major side-effects of nicotine addiction through tobacco smoking. The incidence has increased dramatically since the World War II, mainly due to smoking habits. The decrease in the percentage smokers since the 1960s reduced lung cancer incidence after the mid-1970s, first among middle-aged men. However, the percentage smokers has not decreased further since 1988 (remaining about 35%) and teenagers have even been smoking more since 1990. Thus the decrease in incidence will probably reach a plateau at the beginning of the next century and the incidence among people born since 1970 might even increase again. Age-period-cohort analysis is the propor method for following these trends.
Furthermore, the proportion of patients with adenocarcinoma has been increasing; in previous studies this was found to be due to the increase in smoking low-tar filter cigarettes since the 1960s. This may be worrying, especially since the prognosis has also been decreasing. Since the relationship between smoking low-tar filter cigarettes and an increase in incidence and decrease in survival for patients with adenocarcinoma has not been confirmed, there is a need for more studies on the health risks of these popular cigarettes and also on other putative risk factors for adenocarcinoma, especially since this tumour type also develops relatively often in non-smokers.
Besides giving health warnings, two possible ways to prevent lung cancer are (1) to decrease the availability of cigarettes or raise the price or (2) to develop better strategies for handling nicotine addiction. The latter could be achieved e.g. by offering less harmful nicotine delivery systems such as chewing gum or 'plasters'. The effectiveness of these strategies needs to be studied in the various groups of addicted smokers.
Insight into the relationship between mutational activation of oncogenes or disruption of tumour suppressor gene function, such as K-ras, p53, or cytokeratin 18, and survival for the various histological subtypes among unselected patients with lung cancer could provide insight into tailor-made treatment for subgroups of patients, e.g. adjuvant chemotherapy shortly after surgery for patients with cytokeratin 18-positive stage I non-small-cell lung cancer. Through the cancer registry in collaboration with the

various pathological laboratories these prognostic factors can be studied in unselected patients.

Since a large proportion of patients with non-small-cell carcinoma do not qualify for surgical resection, palliative treatment is important. Now that new treatment strategies are emerging, progress in palliation can be studied in unselected patients with the help of cancer registries.

The rising proportion of elderly patients who present with co-morbidity at diagnosis indicates that there is a need for studies on the association between specific types of co-morbidity and determinants of prognosis, including complications during or after treatment. On the basis of these studies registration procedures for assessment of co-morbidity can be standardized and guidelines for treatment can be adapted or individualized.

Population-based cancer registries are helpful for monitoring trends in incidence, survival and adherence to guidelines for treatment, especially because these registries report exclusively on unselected patients.

Determinants of trends in incidence and survival of uncommon tumours should be studied on a national scale or even within Europe, because the numbers of patients in the separate cancer registries are too small to study these trends.

References

1. Campobasso O, Andrion A, Ribotta M, et al. The value of the 1981 WHO histological classification in inter-observer reproducibility and changing pattern of lung cancer. Int J Cancer 1993; 53: 205-8.
2. Feinstein AR, Sosin DM, Walls CE. The Will Rogers' phenomenon: stage migration and new diagnostic techniques as a source of misleading statistics for survival in cancer. New Engl J Med 1985; 312: 1604-6.
3. Wassink WF. The aetiology of lung cancer. [in Dutch] Ned Tijdschr Geneeskd 1948; 92: 3732-47.
4. Wynder EL, Graham EA. Tobacco smoking as a possible etiologic factor in bronchiogenic carcinoma. J Am Med Assoc 1950; 143: 329-36.
5. Doll R, Hill AB. Smoking and carcinoma of the lung: preliminary report. Br Med J 1950; September 30: 739-48.
6. Doll R, Peto R. Mortality in relation to smoking: 20 years' observation on male British doctors. Br Med J 1976; 2: 1525-36.
7. Lubin JH, Blot WJ. Assessment of lung cancer risk factors by histologic category. J Natl Cancer Inst 1984; 73: 383-9.
8. Lubin JH, Blot WJ, Berrino F, et al. Modifying risk of developing lung cancer by changing habits of cigarette smoking. Br Med J 1984; 288: 1953-6.
9. Pathak DR, Samet JM, Humble CG, et al. Determinants of lung cancer risk in cigarette smokers in New Mexico. J Natl Cancer Inst 1986; 76: 597-604.
10. Samet JM. The epidemiology of lung cancer. Chest 1993; 103: 20S-9S.
11. Doll R, Peto R, Wheatly K, et al. Mortality in relation to smoking: 40 years' observations on male British doctors. Br Med J 1994; 309: 901-11.
12. Harris RE, Zang EA, Anderson JI, et al. Race and sex differences in lung cancer risk associated with cigarette smoking. Int J Epidemiol 1993; 22: 592-9.

13. CBS. Atlas of cancer mortality in the Netherlands, 1969-78. [in Dutch] The Hague: CBS publications, 1980.
14. CBS. Atlas of cancer mortality in the Netherlands, 1979-90. [in Dutch] The Hague: CBS publications, 1992.
15. Kunst AE, Mackenbach JP. Regional lung cancer death rates unrelated to smoking? The case of the Netherlands. Eur J Cancer 1993; 29A: 270-3.
16. La Vecchia C, Boyle P, Franceschi S, et al. Smoking and cancer with emphasis on Europe. Eur J Cancer 1991; 27: 94-104.
17. McDuffie HH, Klaassen DJ, Dosman JA. Determinants of cell type in patients with cancer of the lungs. Chest 1990; 98: 1187-93.
18. Jedrychowski W, Becher H, Wahrendorf J, et al. Effect of tobacco smoking on various histological types of lung cancer. J Cancer Res Clin Oncol 1992; 118: 276-82.
19. Pezzotto SM, Mahuad R, Bay ML, et al. Variation in smoking-related lung cancer risk factors by cell type among men in Argentina: a case-control study. Cancer Causes and Control 1993; 4: 231-7.
20. Ellard GA, de Waard F, Kemmeren JM. Uninary nicotine metabolite excretion and lung cancer risk in a female cohort. Br J Cancer 1995; 72: 788-91.
21. Siemiatycki J, Krewski D, Franco E, et al. Associations between cigarette smoking and each of 21 types of cancer: a multi-site case-control study. Int J Epidemiol 1995; 24: 504-14.
22. De Waard F, Kemmeren JM, van Ginkel LA, et al. Urinary cotinine and lung cancer risk in a female cohort. Br J Cancer 1995; 72: 784-7.
23. Engeland A, Haldorsen T, Andersen A, et al. The impact of smoking habits on lung cancer risk: 28 years' observation of 26,000 Norwegian men and women. Cancer Causes and Control 1996; 7: 336-76.
24. Vincent RG, Pickren JW, Lane WW, et al. The changing histopathology of lung cancer: a review of 1682 cases. Cancer 1977; 39: 1647-55.
25. Wu AH, Henderson BE, Thomas DC, et al. Secular trends in histologic types of lung cancer. J Natl Cancer Inst 1986; 77: 53-6.
26. Dodds L, Davis S, Polissar L. A population-based study of lung cancer incidence trends by histologic type, 1974-81. J Natl Cancer Inst 1986; 76: 21-9.
27. El-Torky M, El-Zeky F, Hall JC. Significant changes in the distribution of histologic types of lung cancer: a review of 4928 cases. Cancer 1990; 65: 2361-7.
28. Zheng T, Holford T, Boyle P, et al. Time trend and the age-period-cohort effect on the incidence of histologic types of lung cancer in Connecticut, 1960-1989. Cancer 1994; 74: 1556-67.
29. Travis WD, Travis LB, Devesa SS. Lung cancer. Cancer Suppl 1995; 75: 191-202.
30. Levi F, Franceschi S, La Vecchia C, et al. Lung carcinoma trends by histologic type in Vaud and Neuchâtel, Switzerland, 1974-1994. Cancer 1997; 79: 906-14.
31. Russo A, Crosignani P, Franceschi S, et al. Changes in lung cancer histological types in Varese Cancer Registry, Italy 1976-1992. Eur J Cancer 1997; 33: 1643-7.
32. Thun MJ, Lally CA, Flannery JT, et al. Cigarette smoking and changes in the histopathology of lung cancer. J Natl Cancer Inst 1997; 89: 1580-6.
33. Morabia A, Wynder EL. Cigarette smoking and lung cancer cell types. Cancer 1991; 68: 2074-8.
34. Wynder EL, Hoffmann D. Smoking and lung cancer: scientific challenges and opportunities. Cancer Res 1994; 54: 5284-95.
35. Auerbach O, Garfinkel L. The changing pattern of lung carcinoma. Cancer 1991; 68: 1973-7.
36. Barsky SH, Cameron R, Osann KE, et al. Rising incidence of bronchioloalveolar lung carcinoma and its unique clinicopathologic features. Cancer 1994; 73: 1163-70.
37. Barkley JE, Green MR. Bronchioloalveolar carcinoma. J Clin Oncol 1996; 14: 2377-86.
38. Greenberg ER, Korson R, Baker J, et al. Incidence of lung cancer by cell type: a population-based study in New Hampshire and Vermont. J Natl Cancer Inst 1984; 72: 599-603.
39. Brownson RC, Loy TS, Ingram E, et al. Lung cancer in nonsmoking women: histology and survival patterns. Cancer 1995; 75: 29-33.
40. Wynder EL, Covey LS. Epidemiologic patterns in lung cancer by histologic type. Eur J Cancer Clin Oncol 1987; 23: 1491-6.

41. Stellman SD, Muscat JE, Thompson S, et al. Risk of squamous cell carcinoma and adenocarcinoma of the lung in relation to lifetime filter cigarette smoking. Cancer 1997; 80: 382-8.
42. Hecht SS, Hoffmann D. Tobacco-specific nitrosamines, an important group of carcinogens in tobacco and tobacco smoke. Carcinogenesis 1988; 17: 116-28.
43. Modlin IM, Sandor A. An analysis of 8305 cases of carcinoid tumors. Cancer 1997; 79: 813-29.
44. Newton JN, Swerdlow AJ, dos Santos Silva IM, et al. The epidemiology of carcinoid tumours in England and Scotland. Br J Cancer 1994; 70: 939-42.
45. Van de Wetering ML, Mooi WJ, Wagenaar SjSc, et al. K-ras oncogene activation in adenocarcinoma of the lung: incidence and relation to smoking. Cancer Res 1988; 48: 5738-41.
46. Kern JA, Slebos RJC, Top B, et al. C-erbB-2 expression and codon 12 K-ras mutations both predict shortened survival for patients with pulmonary adenocarcinomas. J Clin Invest 1994; 93: 516-20.
47. Rodenhuis S, Boerrigter L, Top B, et al. Mutational activation of the K-ras oncogene and the effect of chemotherapy in advanced adenocarcinoma of the lung: a prospective study. J Clin Oncol 1997; 15: 285-91.
48. Pantel K, Izbicki J, Passlick B, et al. Frequency and prognostic significance of isolated tumour cells in bone marrow of patients with non-small-cell lung cancer without overt metastases. Lancet 1996; 347: 649-53.
49. Cohen R, Guber A, Siegal A, et al. The prognostic application of cytokeratin typing of nonsmall cell lung carcinoma: a retrospective study. Cancer 1997; 79: 468-73.
50. Pedersen LM, Milman N. Microalbuminuria in patients with lung cancer. Eur J Cancer 1998; 34: 76-80.
51. DeMaria LC, Cohen HJ. Characteristics of lung cancer in elderly patients. J Gerontol 1987; 42: 540-5.
52. Guadagnoli E, Weitberg A, Mor V, et al. The influence of patient age on the diagnosis and treatment of lung and colorectal cancer. Arch Intern Med 1990; 150: 1485-90.
53. Monfardini S, Yancik R. Cancer in the elderly: meeting the challenge of an aging population. J Natl Cancer Inst 1993; 85: 532-8.
54. Wei JY. Cardiovascular comorbidity in the older cancer patient. Semin Oncol 1995; 22: 9-10.
55. Burrows B, Earle RH. Course and prognosis of chronic obstructive lung disease: a prospective study of 200 patients. N Engl J Med 1969; 280: 379-404.
56. Postma DS, Burema J, Gimeno F, et al. Prognosis in severe chronic obstructive pulmonary disease. Am Rev Resp Dis 1979; 119: 357-67.
57. Merrilees MA, Scott PJ, Norris RM. Prognosis after myocardial infarction: results of 15 year follow up. Br Med J 1984; 288: 356-9.
58. Feinstein AR, Wells CK. A clinical-severity staging system for patients with lung cancer. Medicine 1990; 69: 1-33.
59. Satariano WA, Ragland DR. The effect of comorbidity on 3-year survival of women with primary breast cancer. Ann Intern Med 1994; 120: 104-10.
60. Wong DH, Weber EC, Schell MJ, et al. Factors associated with postoperative pulmonary complications in patients with severe chronic obstructive pulmonary disease. Anesth Analg 1995; 80: 276-84.
61. Findley MPN, Griffin AM, Raghaven D, et al. Retrospective review of chemotherapy for small cell lung cancer in the elderly: does the end justify the means? Eur J Cancer 1991; 27: 1597-1601.
62. Osterlind K, Hansen HH, Hansen M, et al. Mortality and morbidity in long-term surviving patients treated with chemotherapy with or without irradiation for small-cell lung cancer. J Clin Oncol 1986; 4: 1044-52.
63. Schiller JH, Ettinger DS, Larson MM, et al. Phase II trial of oral etoposide plus cisplatin in extensive stage small cell carcinoma of the lung: an Eastern Cooperative Oncology Group Study. Eur J Cancer 1994; 30A: 158-61.
64. Van der Gaast A, Postmus PE, Burghouts J, et al. Long term survival of small cell lung cancer patients after chemotherapy. Br J Cancer 1993; 67: 822-4.

65. Lassen U, Osterlind K, Hansen M, et al. Long-term survival in small-cell lung cancer: posttreatment characteristics in patients surviving 5 to 18+ years: an analysis of 1,714 consecutive patients. J Clin Oncol 1995; 13: 1215-20.
66. Souhami RL, Law K. Longevity in small cell lung cancer: a report to the Lung Cancer Subcommittee of the United Kingdom Coordinating Committee for Cancer Research. Br J Cancer 1990; 61: 584-9.
67. Skarin AT. Analysis of long-term survivors with small-cell lung cancer. Chest 1993; 103: 440S-4S.
68. Dajczman E, Fu LY, Small D, et al. Treatment of small cell lung carcinoma in the elderly. Cancer 1996; 77: 2032-8.
69. Clamon GH, Audeh MW, Pinnick S. Small cell lung carcinoma in the elderly. Am Geriatr Soc 1982; 30: 299-302.
70. Kelly CP, O'Donnell D, West B, et al. Small cell and squamous cell lung carcinomas: sequential occurrence at a single site. Thorax 1987; 42: 821-2.
71. Raabe NK, Storstein L. Cardiac arrhythmias in patients with small cell lung cancer and cardiac disease before, during and after doxorubicin administration. An evaluation of acute cardiotoxicity by continuous 24-hour Holter monitoring. Acta Oncol 1991; 30: 843-6.
72. Shepherd FA, Amdemichael E, Evans WK, et al. Treatment of small cell lung cancer in the elderly. J Am Geriatr Soc 1994; 42: 64-70.
73. Siu LL, Shepherd FA, Murray N, et al. Influence of age on the treatment of limited-stage small-cell lung cancer. J Clin Oncol 1996; 14: 821-8.

Lung cancer is by far the most frequent type of cancer among Dutch men and ranks third among women. Since the World War II, 250,000 Dutch people have died of lung cancer. The incidence rate among men was one of the highest in Europe. In the past few decades incidence rates of lung cancer and those of the histological subtypes have been changing markedly. Little is known about trends in population-based survival rates. Therefore, changes in incidence and survival rates for the histological subtypes of lung cancer were studied and interpreted against the background of smoking habits and changing therapy.
Data of the Eindhoven Cancer Registry were used, which originally served an area of about one million inhabitants in the southeastern part of the Netherlands and since 1987 an area of two million. For the study on variation in incidence and survival rates within Europe data of cancer registries participating in EUROCIM and Eurocare were used.

Since smoking is by far the most important risk factor for lung cancer, an aetiological background for males and females was obtained from period and birth cohort analyses. Among men, the age-standardized incidence rate increased strongly from 30 per 100,000 person-years in 1960 to 95 in 1983 and then decreased to 70 in 1994. The decrease occurred first among middle-aged men. The incidence increased until birth cohort 1910-19, whereafter it declined. Incidence rates for women were much lower than for men, but have been steadily increasing from 1 per 100,000 person-years in 1960 to 13 in 1994. The trends in lung cancer incidence for men and women followed the trends in smoking behaviour after 20-25 years. In this area the percentage of male smokers has been very high, but decreased from 95% in 1960 to 50% in 1981. The percentage of female smokers was rather low, but has been increasing from 27% in 1960 to 40% in 1967; after 1979 it decreased to 36% in 1981.
Since the southeastern part of the Netherlands contained many tobacco-processing industries, intraregional differences in incidence rates were studied in order to determine the effect of the different smoking habits for men and women in urban areas, rural areas and municipalities with tobacco-processing industries. Among men, lung cancer incidence was clearly higher in municipalities with tobacco-processing industries than in other urban and rural municipalities. In contrast, lung cancer incidence among women was much higher in urban than in rural municipalities and the presence of tobacco-processing industries did not make any difference. The high social acceptance of smoking due to the presence of tobacco-processing industries has very likely increased the percentage of male smokers and the amount smoked per day.
Another argument for the role of smoking habits is the fact that among men the peak incidence rates for squamous cell carcinoma and small-cell carcinoma, both of which correlate with smoking better than adenocarcinoma, were reached in 1978, while that for adenocarcinoma was reached in 1985. For men, the proportion of adenocarcinoma

among non-small-cell lung cancer increased from 10% in 1975-79 to 18% in 1990-94; it increased for men born since 1920. Among women the incidence rates increased for every histological subtype and the proportion of adenocarcinoma remained about 40%. In previous studies, the proportional increase in adenocarcinoma was found to be related to the increased preference for low-tar filter cigarettes since the 1960s. The smoke of these cigarettes is generally inhaled deeper, in order to compensate for the lower nicotine yield. Thus carcinogens penetrate deeper in the lung and can cause adenocarcinoma, which often develops in the peripheral lung zones.
Less than 1% of all tumours of the respiratory tract are very uncommon. Mesothelioma, carcinoid, carcinosarcoma and sarcoma clearly differ in aetiology and prognosis. The incidence rates of mesothelioma and carcinoid tumours have been increasing during the past decades, but have remained low.

Little is known about trends in long-term population-based survival rates for the histological subtypes of lung cancer. In the southeastern part of the Netherlands, short-term survival for patients with small-cell lung cancer has improved since the introduction of chemotherapy in the 1970s; median survival for patients younger than 70 years has increased from 5 months in 1975-79 to 10 months in 1985-92. However, 2-year survival has remained 8%. Overall prognosis for patients with non-small-cell lung cancer did not change over time, but there were divergent trends for the histological subtypes. Relative 1-year survival for patients with squamous cell carcinoma has improved slightly over time from 48% to 51%, while that for patients with adenocarcinoma has decreased markedly from 59% in 1975-79 to 45% in 1990-92; the decrease was found for those born since 1930. Among younger patients with adenocarcinoma, the proportion with early disease has also been decreasing, thus a more aggressive tumour type may have occurred. Since it is unlikely that changes in detection or classification play a major role, the higher concentration of carcinogens in the peripheral lung zones, due to the increased preference for low-tar filter cigarettes could have been responsible. Relative survival for patients with large-cell undifferentiated carcinoma was markedly lower than the above mentioned types of non-small-cell lung cancer and has remained roughly unchanged.
The number of patients that present with co-morbidity at diagnosis of lung cancer is increasing, because of the rising mean age of patients. Therefore, co-morbidity, one of the prognostic factors, was studied in depth. Co-morbidity has become a more important factor for the clinical management of patients, especially surgical resection, because of peroperative or postoperative complications. The presence of serious co-morbidity in patients younger than 70 years with localized non-small-cell lung cancer was indeed associated with less surgery: in absence of co-morbidity 94% of the tumours were surgically resected, compared with 70% in case of two or more co-morbid conditions.

Variations in the incidence and survival for patients with lung cancer within Europe between 1978 and 1992 were studied and were correlated with differences in smoking habits and access to specialized care. Incidence rates for men in northern Europe have been decreasing since the mid-1980s, while the peak in rates for men in southern and eastern Europe and for women was not reached in the beginning of the 1990s. The trends in incidence can be largely explained by the trends in past smoking behaviour. Age-standardized relative 1-year survival varied between 24% in Denmark and the United Kingdom, and 40% in Finland, France, the Netherlands and Switzerland. Most variations were probably due to differences in access to specialized care.

Lung cancer is one of the major side-effects of nicotine-addiction through tobacco smoking. Although the incidence of lung cancer among Dutch men has been decreasing since the 1980s, the decrease will likely reach a plateau in the beginning of the next century, because of a steady percentage of smokers since the end of the 1980s. The increase in the proportion of adenocarcinoma may be worrying, especially since the prognosis has also been decreasing. There is a need for studies on determinants of changes in the incidence and survival of adenocarcinoma. Furthermore, future studies should focus on the association between specific types of co-morbidity and determinants of prognosis, because the proportion of elderly patients who present with co-morbidity at diagnosis is rising.

Longkanker is de meest voorkomende vorm van kanker bij Nederlandse mannen en neemt een derde plaats in bij vrouwen. Sinds de Tweede Wereldoorlog zijn in Nederland ongeveer 250.000 mensen aan longkanker overleden. De incidentie van longkanker bij Nederlandse mannen is één van de hoogste in Europa. In de afgelopen 50 jaar is de incidentie van longkanker en van de histologische subtypen sterk veranderd. Over de trends in overleving voor ongeselecteerde patiënten is weinig bekend. In dit proefschrift werden veranderingen in incidentie en overleving van patiënten met de afzonderlijke histologische subtypen van longkanker bestudeerd en geïnterpreteerd tegen de achtergrond van veranderingen in rookgewoonten en therapie. Er werd gebruik gemaakt van gegevens van de kankerregistratie van het Integraal Kankercentrum Zuid (IKZ), die gegevens registreert in Zuidoost-Nederland, een gebied met ongeveer 2 miljoen inwoners sinds 1987. Voor de studie naar variatie in incidentie en overleving binnen Europa werden gegevens gebruikt van kankerregistraties die deelnemen aan EUROCIM en Eurocare.

De trends in incidentie werden geanalyseerd naar periode van diagnose en geboortecohort, omdat roken de belangrijkste risicofactor is voor het ontstaan van longkanker. Voor mannen steeg de voor leeftijd gestandaardiseerde incidentie van 30 per 100.000 persoonsjaren in 1960 naar 95 in 1983, waarna de incidentie daalde tot 70 per 100.000 in 1994. De daling trad het eerst op bij mannen van middelbare leeftijd, later ook bij oudere mannen. De incidentie steeg tot geboortecohort 1910-19, waarna een daling optrad. De incidentie voor vrouwen was veel lager dan voor mannen, maar steeg van 1 per 100.000 persoonsjaren in 1960 tot 13 in 1994. De trends in incidentie van longkanker voor mannen en vrouwen volgden die in rookgewoonten na 20-25 jaar. In Zuidoost-Nederland was het percentage mannelijke rokers erg hoog, maar daalde van 95% in 1960 tot 50% in 1981. Het percentage rooksters was relatief laag, maar steeg van 27% in 1960 tot 40% in 1967; na 1979 daalde dit percentage tot 36% in 1981.
In Zuidoost-Nederland heeft veel tabaksverwerkende industrie gestaan. Om het effect van rookgewoonten in steden, op het platteland en in gemeenten met tabaksverwerkende industrie te bestuderen, werden intraregionale verschillen in de incidentie van longkanker geanalyseerd. Voor mannen was de incidentie van longkanker in gemeenten met tabaksverwerkende industrie duidelijk hoger dan in andere gemeenten. Voor vrouwen was de incidentie van longkanker, in tegenstelling tot de mannen, in steden duidelijk hoger dan op het platteland, terwijl de aanwezigheid van tabaksverwerkende industrie geen verschil uitmaakte. De gemakkelijke toegang tot tabak in gemeenten met tabaksverwerkende industrie heeft waarschijnlijk geleid tot een stijging van het percentage mannelijke rokers en het aantal sigaretten dat per dag gerookt werd.

Een ander argument voor de rol van roken is het feit dat de piek in de incidentie van plaveiselcel- en kleincellig carcinoom, beide sterker samenhangend met roken dan adenocarcinoom, werd bereikt in 1978, terwijl die van adenocarcinoom pas in 1985 bereikt werd. Adenocarcinoom, als percentage van de niet-kleincellige longtumoren, steeg bij mannen van 10% in 1975-79 tot 18% in 1990-94 en steeg voor hen die geboren waren na 1920. Voor vrouwen steeg de incidentie van elk histologisch type van longkanker en het percentage adenocarcinoom bleef ongeveer 40%. In voorgaande studies werd de procentuele toename van adenocarcinoom gerelateerd aan de toename in het roken van filtersigaretten met een laag teergehalte sinds de zestiger jaren. De rook van deze sigaretten wordt vaak dieper geïnhaleerd om het lager nicotine-gehalte te compenseren. Zo penetreren carcinogenen dieper in de long en veroorzaken adenocarcinoom, dat meestal perifeer in de long onstaat.
Minder dan 1% van alle tumoren van de tractus respiratorius zijn zeldzame tumoren, zoals mesothelioom, carcinoïd tumor, carcinosarcoma en sarcoma. Deze verschillen in etiologie en prognose. De incidentie van mesothelioom en carcinoïd tumoren is gestegen gedurende de studieperiode, maar de incidentie is nog steeds erg laag.

Over de trends in lange-termijn overleving voor ongeselecteerde patiënten met longkanker is slechts weinig bekend. De korte-termijn overleving voor patiënten met een kleincellige longtumor in Zuidoost-Nederland is verbeterd sinds de introductie van chemotherapie in de jaren zeventig; de mediane overleving voor patiënten jonger dan 70 jaar steeg van 5 maanden in 1975-79 tot 10 maanden in 1985-89. De 2-jaars overleving bleef echter slechts 8%. De prognose voor patiënten met een niet-kleincellige longtumor veranderde niet in de loop van de tijd; echter, de trends waren niet gelijk voor elk histologisch subtype. De relatieve 1-jaars overleving voor patiënten met plaveiselcelcarcinoom verbeterde licht van 48% tot 51%, terwijl die voor patiënten met adenocarcinoom verslechterde van 59% in 1975-79 tot 45% in 1990-92; de verslechtering in overleving trad op bij patiënten die geboren waren na 1930. Bij jongere patiënten met adenocarcinoom steeg het percentage dat gediagnostiseerd werd met een tumor in een uitgebreid stadium; adenocarcinoom is dus mogelijk een agressievere tumor geworden. Het is onwaarschijnlijk dat veranderingen in detectie en classificatie een belangrijke rol hebben gespeeld in de verslechtering in prognose voor patiënten met adenocarcinoom. De toename in het roken van filtersigaretten met een laag teergehalte, hetgeen heeft geleid tot een hogere concentratie van carcinogenen in de perifere longdelen, is mogelijk verantwoordelijk voor de verslechtering in prognose. De relatieve overleving voor patiënten met een grootcellig ongedifferentieerd carcinoom was duidelijk lager dan de hierboven genoemde typen niet-kleincellig longcarcinoom en is niet veranderd in de loop van de tijd.
Eén van de prognostische factoren, co-morbiditeit, werd uitgebreid bestudeerd. Door de stijging van de gemiddelde leeftijd van longkanker-patiënten zal het percentage met

bijkomende ziekten op het moment van diagnose van kanker toenemen. Dus co-morbiditeit wordt steeds belangrijker voor therapie-keuze, vanwege per-operatieve en post-operatieve complicaties. De aanwezigheid van co-morbiditeit bij patiënten jonger dan 70 jaar met een lokale niet-kleincellige longtumor was inderdaad geassocieerd met een lager percentage resecties: 94% werd geopereerd in afwezigheid van co-morbiditeit vergeleken met 70% in geval van twee of meer bijkomende ziekten.

Variatie in de incidentie en overleving voor longkanker-patiënten binnen Europa werd gerelateerd aan verschillen in rookgewoonten en de toegang tot medische zorg. De incidentie voor mannen in Noord-Europa is gedaald sinds midden jaren tachtig, terwijl de piek in de incidentie voor mannen in Zuid- en Oost-Europa en voor vrouwen nog niet bereikt was in het begin van de jaren negentig. De trends in incidentie konden worden verklaard door de trends in rookgewoonten. De voor leeftijd gestandaardiseerde relatieve 1-jaars overleving varieerde van 24% in Denemarken, Engeland en Schotland tot 40% in Finland, Frankrijk, Nederland en Zwitserland. Het grootste deel van de variatie in overleving kan waarschijnlijk verklaard worden door verschillen in de toegang tot medische zorg.

Longkanker is een van de belangrijkste neveneffecten van nicotine-verslaving door het roken van tabak. De incidentie van longkanker bij mannen is sinds midden jaren tachtig gedaald, echter de daling zal waarschijnlijk een plateau bereiken in het begin van de volgende eeuw, omdat het percentage rokers sinds eind jaren tachtig niet meer gedaald is. De toename in het percentage adenocarcinoom verdient aandacht, omdat ook de prognose verslechterd is. Er is behoefte aan studies naar determinanten van de veranderingen in incidentie en overleving van adenocarcinoom. Verder zouden toekomstige studies zich moeten toespitsen op de relatie tussen bijkomende ziekten en determinanten van prognose, omdat het percentage oudere patiënten met bijkomende ziekten op het moment van diagnose van kanker toeneemt.

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Maryska Janssen-Heijnen

Maryska Janssen-Heijnen werd geboren in Steijl, Limburg, op tweede kerstdag 1968. In 1987 behaalde zij het VWO-diploma aan de Rijksscholengemeenschap "Den Hulster" te Venlo. In datzelfde jaar begon zij met de studie Geneeskunde aan de Katholieke Universiteit te Nijmegen. Na het behalen van het doctoraal examen in 1991 volgde zij een verkort doctoraal Gezondheidswetenschappen aan dezelfde universiteit. In 1993 studeerde zij af in de richting 'epidemiologie'. Haar afstudeeronderzoek voerde zij uit bij het Integraal Kankercentrum Zuid te Eindhoven, waar zij op 1 september 1993 werd aangesteld als wetenschappelijk onderzoeker en in de gelegenheid werd gesteld om onderzoek uit te voeren naar de trends in incidentie en overleving van kanker in Zuidoost-Nederland. In 1995 schreef zij samen met dr. J.W.W. Coebergh, L.H. van der Heijden en een aantal gast-auteurs het boek "Cancer incidence and survival in the southeast of the Netherlands, 1955-1994: a report from the Eindhoven Cancer Registry", ter gelegenheid van het 40-jarig bestaan van de kankerregistratie. In juni 1996 studeerde zij af als "Master-of-science in clinical epidemiology" bij het NIHES (Netherlands Institute of Health Sciences) aan de Erasmus Universiteit te Rotterdam. Sinds 1 april 1998 heeft zij de functie van senior-onderzoeker bij het Integraal Kankercentrum Zuid.