Multiple Primary Cancers in Patients with Breast and Skin Cancer

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Multiple Primary Cancers in Patients with Breast and Skin Cancer

Meervoudige tumoren in borst en huidkanker patiënten

Proefschrift

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Untuk mama, papa, Colette dan Pandji

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Contents

Part V General discussion and conclusion

PART I

Introduction

Chapter 1

Introduction

1.1. Multiple primary cancers

The extent of the problem

The number of cancer survivors has been increasing dramatically and is expected to keep growing in the near future. In the Netherlands, a 38% increase of cancer survivors is estimated from 2005 to 2015, representing an increase from 500,000 to 692,000 (ex-) patients in this period.[1] It is well known that individuals who suffered from cancer exhibit a 20% higher risk of subsequent primary malignancies.[2] Thus, as the number of cancer survivors increases, the number of patients with multiple primary cancers will increase as well. Because cancer is more frequent among the elderly, the ageing of the Dutch population will cause a further increase in the number of cases with multiple cancers: Only 5%-12% of cancer patients aged 50-64 were previously diagnosed with cancer, versus 12%-26% of those aged over 80[3]. Other forces, including increased awareness of (second) malignancies, the higher use and sensitivity of diagnostic/detection methods, and the recent improvements in cancer treatment and survival will further lead to higher prevalence of multiple cancers. Cancer survivors who develop a second malignancy have a higher risk of dying[4] and experience a worsening in their quality of life. Thus, increased interest in second cancer from the epidemiological and clinical perspective is highly relevant.

Breast cancer

The incidence of breast cancer among women has increased by 50% during the last 30 years. On the other hand, data from the Eindhoven cancer registry in the southwest of the Netherlands indicate that breast cancer mortality has been decreasing by 2% every year since 1995[5] due to earlier diagnosis and better treatment. These trends have led to a marked increase in the number of female cancer survivors who are at risk of developing another primary cancer. Breast cancer has been the most prevalent malignancy in women,[6] and also the most commonly occurring multiple malignancy.[7] Of all prevalent malignancies among women, 25% of them are breast cancer.[7]

Women with breast cancer do not only have an increased risk of second breast cancer. Studies indicate that these women also have an increased risk of developing other female genital, oesophageal, salivary gland and soft tissue cancers. On the other hand, women with a breast cancer have a lower risk compared to the general population, of developing cancer of the cervix, pancreas, lung, non-Hodgkin Lymphoma and chronic lymphocytic leukaemia[8].

Skin cancer

In industrialized countries, we have witnessed an increasing trend in the incidence of skin cancer over the last few decades.[9, 10] In 2005, there were 18,715 cases of newly diagnosed basal cell carcinoma (BCC) of the skin, 4,212 cases of squamous cell carcinoma (SCC) of the skin, and 3042 cases of cutaneous melanoma (CM) in the Netherlands[11], corresponding to 19%, 4% and 3% of the total number of incident cancers, respectively.[3] Due to the low case-specific mortality rates of skin cancer, the prevalence of skin cancer has increased dramatically, providing opportunities for the analysis on the incidence of multiple cancers (see chapter 10 of this thesis).

Recent studies have shown that although sun exposure increases the risk of skin cancer, it may have a protective effect against some major cancers including that of the breast as well as colorectal and prostate cancer, through the formation of vitamin D.[12-14] Patients with skin cancer constitute a good cohort to indirectly test this hypothesis. Examining the risk of second cancer among skin cancer patients can provide clues in this paradoxical effect of sun exposure: If more exposure to sunlight increases the risk of skin cancer but reduces the risk of breast, prostate and colorectal cancer, skin cancer patients should have a lower incidence of these cancers compared to the general population. Although cancer registry data do not provide individual information on sun exposure, examining the risk of a second cancer by various host and tumour characteristics may give further idea on the protective role of sun exposure (table 1.1). It is known that cumulative sun exposure is associated with an increased risk of SCC. The association of sun exposure is less strong for BCC, which has been hypothesized to be etiologically more similar to melanoma. Therefore a cohort of patients with SCC should show the highest protective effect against breast, prostate and colorectal cancer and cohort of patients with CM the lowest. Similarly, skin cancers occurring in the head and neck region and those diagnosed at older age are usually associated with chronic exposure and thus a lower risk of second breast, prostate and colorectal cancer skin cancers is expected in this group of patients.

Table 1.1. Associations between sun exposure pattern and skin cancer features[9, 15]

Host and tumour feature	**Sun Exposure**	
	Intermittent	Chronic
Skin cancer type		
Squamous Cell Carcinoma	+	+++
Basal Cell Carcinoma	++	++
Melanoma	+++	+
Age at diagnosis		
Young	+++	+
Old	+	+++
Subsite		
Head and neck	+	+++
Trunk and extremities	+++	+

In order to interpret the risk pattern of multiple cancers it is necessary to identify the factors that influence an individual's risk of developing a second cancer including: internal factors, e.g., genetic predisposition towards cancer; and external factors, e.g., lifestyle, treatment of the first cancer. Hereditary genetic predispositions may increase an individual risk of multiple malignancies.[16] Genetic factors have been more commonly related to an increased risk among those who were diagnosed with a first cancer at an early age. Other factors such as lifestyle should influence mainly the risk of second malignancy among the older age groups because of the long exposure time that is needed until such factors cause carcinogenic changes in a human body. Treatment of a first cancer may also be related to the occurrence of a second cancer. Comparing a group of patients who were exposed to a certain treatment to those who were spared from the treatment may further give light on this issue. Furthermore, increased monitoring may also elevate the risk of a second primary cancer.

Because the above mentioned factors have changed over time (except for genetic disorders), the risk of a second cancer among cancer patients also changes, thus continuous monitoring of second cancer risk is of utmost importance. Study of multiple cancers will provide information on the necessary guidelines to follow-up cancer patients.

Through such studies the patient group at high risk of developing a second cancer can be identified. In addition, the type of the second cancer with the highest risk and length of time where such risk is increased can be determined. Consequently, screening strategies for the early detection of a second cancer or lifestyle advise to reduce risk of developing a second cancer can be developed. Assessing the pattern of diseases has tremendously increased our knowledge on their causes, the same applies for multiple cancer studies.

1.2. Research questions

The study of multiple cancers is important from an etiological as well as from a clinical point of view. This thesis aims to explore both perspectives by assessing the risk of multiple cancers in breast and skin cancer patients, the two most prevalent cancers in the Netherlands. The specific study questions addressed in this thesis are:

1. What are the determinants of breast cancer incidence and survival?
2. What is the risk of second cancer among patients previously diagnosed with a primary breast cancer?
3. Is there a reduced risk of colorectal, breast and prostate cancers among skin cancer patients?

1.3. Methods

Study population

The studies in this thesis are performed using the data from the population-based cancer registry in Eindhoven (ECR). Cancer registries in the Netherlands receive lists of newly diagnosed cases on a regular basis from the pathology and haematology departments in the region (PALGA). In addition, lists of all hospitalised cancer patients based on data from the national Registry of Hospital Discharge Diagnosis were also used in the cancer registration process. Following the notification from these sources, the medical records of newly diagnosed patients (and tumours) are collected and abstracted by trained tumour registrars. Data of patients who live in the area of ECR, but are diagnosed in hospitals outside the ECR territory, are regularly retrieved from the other Dutch cancer registries since 1989. Before this year it was done directly through retrievals at all cancer centres particularly from Nijmegen, Rotterdam, Utrecht, and Amsterdam.

The following data were used in our studies: gender, date of birth, date of primary cancer diagnosis, order of cancer diagnosis, date of death, clinical and pathological staging, morphology, body site and initial treatment (i.e. treatment given or planned within the first 6 months after diagnosis, including surgery, radiotherapy, chemotherapy, and hormonal treatment). Topography and morphology are coded according to the International Classification of Diseases for Oncology (ICD-O). Staging of the tumours is done according to the most recent TNM classifications.[17] For coding of multiple tumours, the rules from the International Agency for Research on Cancer (IARC) were adopted.[18]

Methods of analysis

Incidence rates

Incidence rates are calculated by dividing the numbers of incident cases by the number of person-years at risk.[19] When we computed the incidence rate of second cancer, the person-years at risk extend from the date of the initial cancer diagnosis to the date of a second cancer, date of death, loss to follow-up, or end of the study, whichever occurred first. The role of changes in age structure over time was assessed by adjusting rates to the European Standard Population.[19]

Relative excess of cancer risk

In order to calculate the relative excess risk of a cancer (chapter 3), we assumed that the lowest incidence of a specific cancer in a certain country represents the baseline rate of a cancer or the achievable minimum rate,[20] presumably due to relatively low prevalence of risk factors.[21] The excess of cancers (proportion of relative excess risk= RER) in a country of interest was obtained by subtracting this baseline rate from the cancer incidence rate of the country of interest and dividing this to the cancer incidence rate of the country of interest.[20] We assumed that the excess cancer cases were caused by high prevalence of behavioral, occupational and/or environmental risk factors. The absolute number of excess cases was calculated by multiplying the rate difference to the size of the population of the country of interest in the same period and age group, divided by 100,000.

Measures used for multiple cancer studies

In order to determine whether cancer patients were at a higher or lower risk of developing a new primary cancers than the general population, the incidence rates of subsequent tumours among these patients (observed incidence) was compared to the incidence rates of the same tumours in the reference population. The expected incidence was calculated adjusting for gender, age (in 5-year age categories) and calendar time at first cancer diagnosis. Dividing the observed incidence by the expected incidence produced the standardized incidence ratio (SIR).[22] The 95% confidence intervals were calculated assuming a Poisson distribution.[19]

Absolute excess risk (AER) measures the excess number of subsequent malignancies per 10,000 patients per year.[22] The AER is obtained by subtracting the expected from the observed number of second cancer cases, and dividing it by the number of person-years and then multiplying it by 10,000. The AER gives crucial information for public health planning, particularly regarding the allocation of health-care resources according to the demands in the population.

Cumulative risk (CR) is the proportion of patients alive at time *t* who can be expected to develop a second cancer. The CR is estimated by using the life table method[23]. This method accounts for censoring in the data, allowing estimation of the proportion of patients that will develop a second cancer up to various time points during the follow up, conditional on surviving until that time point. The CR provides information on the average risk of multiple cancers among cancer patients.

1.4. Structure of the thesis

In the introduction we review the epidemiology of multiple primary cancers **(Part I, Chapters 1 and 2)**. Furthermore, this thesis is structured in five additional parts: **Part II (Chapter 3-5)** discusses general epidemiological aspects of breast cancer. In **Chapter 3** the correlation between average age of mothers at first childbirth, a major risk indicator of breast cancer, and current excess of breast cancer risk in 34 industrialized countries was assessed. **Chapter 4** briefly describes the trend of breast cancer in the Netherlands as compared to the USA and discusses the role of hormone replacement therapy on the observed trends. **Chapter 5** focuses on the prognostic factors of long-term breast cancer survivors. The current literature on determinants of breast cancer survival for 10 years or more was reviewed, and the influence of a second cancer on the prognosis of breast cancer patients is discussed.

Part III (Chapter 6-9) examines the risk pattern of multiple cancers among breast cancer patients in four chapters: **Chapter 6** assesses the incidence of breast cancer among female cancer survivors over the last decades. The following two chapters describe the risk pattern of second primary cancers among invasive **(Chapter 7)** as well as *in situ* **(Chapter 8)** breast cancer patients. **Chapter 9** assesses the risk of second breast and urogenital cancer after breast cancer. This chapter also aims to identify those with the highest risk of second primary cancer, by examining the role of age at diagnosis, treatment of first cancer, and time after first breast cancer.

Part IV (Chapter 10-12) focuses on the risk of second cancer among skin cancer patients, investigating the protective role of sun exposure on the occurrence of major cancers including breast, colorectal and prostate cancer. This section begins with a short description of the cohort of patients with skin cancer and of how examining the risk of multiple cancer among skin cancer patients can be used to explore hypotheses on the aetiology of cancer such as the role of sun exposure (**Chapter 10**). **Chapter 11** and **Chapter 12** assess the risk of colorectal, breast and prostate cancer in 3 groups of skin cancer patients (squamous cell carcinoma (SCC), basal cell carcinoma (BCC), and cutaneous malignant melanoma (CMM)). These chapters examine the relative risk of breast, colorectal and prostate cancer according to location of skin cancer, age at skin cancer diagnosis, and time since skin cancer diagnosis, as well as stage of breast, colorectal and prostate cancer at time of diagnosis.

Part V concludes with a general discussion of the findings, their policy implications and recommendations for future research **(Chapter 13)**.

References

1. Kanker in nederland. Trends, prognoses, en implicatie voor zorgvraag. 2004
2. Fraumeni JFJ, Curtis R, Edwards BK, Tucker MA. *Introduction*. Bethesda, MD: National Cancer Institute; 2006.
3. Janssen-Heijnen ML, Houterman S, Lemmens VE, Louwman MW, Maas HA, Coebergh JW. Prognostic impact of increasing age and co-morbidity in cancer patients: A population-based approach. *Crit Rev Oncol Hematol*. 2005;55:231-240
4. Soerjomataram I, Louwman MW, Ribot JG, Roukema JA, Coebergh JW. An overview of prognostic factors for long-term survivors of breast cancer. *Breast Cancer Res Treat*. 2007
5. Louwman M, Voogd AC, van Dijck JAAM, Nieuwenhuijzen GAP, Ribot JG, Pruijt JFM, Coebergh JW. On the rising trends of incidence and prognosis for breast cancer patients diagnosed 1975-2004: A long-term population-based study in southeastern netherlands. 2007:37-52
6. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. *CA Cancer J Clin*. 2005;55:74-108
7. Mariotto AB, Rowland JH, Ries LA, Scoppa S, Feuer EJ. Multiple cancer prevalence: A growing challenge in long-term survivorship. *Cancer Epidemiol Biomarkers Prev*. 2007;16:566-571
8. Curtis R, Ron E, Hankey BF, Hoover RN. New malignancies following breast cancer. In: Curtis R, Freedman DM, Ron E, Ries LAG, Hacker DG, Edwards BK, Tucker MA, Fraumeni JFJ, eds. *New malignancies among cancer survivors: Seer registries, 1973-2000*. Bethesda, MD: National Cancer Institute; 2006:181-205.
9. de Vries E, Louwman M, Bastiaens M, de Gruijl F, Coebergh JW. Rapid and continuous increases in incidence rates of basal cell carcinoma in the southeast netherlands since 1973. *J Invest Dermatol*. 2004;123:634-638
10. de Vries E, Schouten LJ, Visser O, Eggermont AM, Coebergh JW. Rising trends in the incidence of and mortality from cutaneous melanoma in the netherlands: A northwest to southeast gradient? *Eur J Cancer*. 2003;39:1439-1446
11. de Vries E, van de Poll-Franse LV, Louwman WJ, de Gruijl FR, Coebergh JW. Predictions of skin cancer incidence in the netherlands up to 2015. *Br J Dermatol*. 2005;152:481-488
12. van der Rhee HJ, de Vries E, Coebergh JW. Does sunlight prevent cancer? A systematic review. *Eur J Cancer*. 2006;42:2222-2232
13. Garland CF, Garland FC. Do sunlight and vitamin d reduce the likelihood of colon cancer? *Int J Epidemiol*. 1980;9:227-231
14. Grant WB. A meta-analysis of second cancers after a diagnosis of nonmelanoma skin cancer: Additional evidence that solar ultraviolet-b irradiance reduces the risk of internal cancers. *J Steroid Biochem Mol Biol*. 2007;103:668-674
15. Armstrong BK, Kricker A. The epidemiology of uv induced skin cancer. *J Photochem Photobiol B*. 2001;63:8-18
16. Fearon ER. Human cancer syndromes: Clues to the origin and nature of cancer. *Science*. 1997;278:1043-1050
17. Sobin LH, Fleming ID. Tnm classification of malignant tumors, fifth edition (1997). Union internationale contre le cancer and the american joint committee on cancer. *Cancer*. 1997;80:1803-1804
18. International rules for multiple primary cancers (icd-0 third edition). *Eur J Cancer Prev*. 2005;14:307-308
19. Breslow NE, Day NE. Statistical methods in cancer research. Volume ii--the design and analysis of cohort studies. *IARC Sci Publ*. 1987:1-406
20. Soerjomataram I, de Vries E, Pukkala E, Coebergh JW. Excess of cancers in europe: A study of eleven major cancers amenable to lifestyle change. *Int J Cancer*. 2007;120:1336-1343
21. Doll R, Peto R. The causes of cancer: Quantitative estimates of avoidable risks of cancer in the united states today. *J Natl Cancer Inst*. 1981;66:1191-1308
22. van Leeuwen FE, Travis LB. *Second cancers*. Philadelphia: Lippincott Williams and Wilkins; 2005.
23. Cutler SJ, Ederer F. Maximum utilization of the life table method in analyzing survival. *J Chronic Dis*. 1958;8:699-712

Chapter 2

Epidemiology of multiple primary cancers

Soerjomataram I, Coebergh JWW. Epidemiology of multiple primary cancers. In: Mukesh, V (ed.). Cancer Epidemiology. Humana Press: *In press*. December 2007.

Abstract

Cancer patients have a 20% higher risk of new primary cancer as compared to the general population. Approximately one third of cancer survivors aged more than 60 were diagnosed more than once with another cancer. As the number of cancer survivors and of older people increases, occurrence of multiple primary cancers is also likely to increase. An increasing interest from epidemiological and clinical perspectives seems logical. This chapter begins with the risk pattern of multiple cancers in the population of a developed country with high survival rates. Multiple cancers comprise two or more primary cancers occurring in an individual that originate in a primary site or tissue and are neither an extension, nor a recurrence or metastasis. Studies of multiple cancers have been mainly conducted in population-based settings, and more recently in clinical trials and case-control studies leading to further understanding of risk factors for the development of multiple primary cancers. These include an inherited predisposition to cancer, the usual carcinogenic or cancer promoting aspects of lifestyle, hormonal and environmental factors, treatment of the previous primary cancer, as well as increased surveillance of cancer survivors. Finally implication on research strategies and clinical practice are discussed: covering the whole range of epidemiological approach.

2.1. Introduction

The number of cancer survivors has been increasing with the rising survival, tripling between 1971 and in the United States. Individuals who were affected by cancer have a higher risk of subsequent primary cancers either in the same organ or in another one. Therefore the prevalence of patients with multiple cancers is expected to continue increasing. Accordingly, in the United States, an increased rate of new cancer diagnosis was observed among cancer survivors diagnosed in the most recent period (Relative risk (RR)=1.21 for those diagnosed from 1995 to 2000 vs. 1.14 for those diagnosed from 1990 to 1994).[1] Likewise, the overall risk of subsequent malignancies among cancer survivors in Finland increased 50% from the 1950s to the 1980s.[2]

Overall, about 8% of newly diagnosed cancers are in individuals who already have had a previous primary cancer.[3] Thus, annually we expect almost 900,000 new multiple cancer cases (8% out of 10.9 million[4] new cases) worldwide. This number tends to increase among others because the growing proportion of the elderly whose prevalence of multiple cancer is highest: only 5%-12% of cancer patients aged 50-64 were previously diagnosed with cancer, versus 12%-26% among those aged over 80.[5] Additionally, other forces increase the frequency of multiple cancers such as awareness of such cancers as well as use and sensitivity of screening and better treatment. Conversely, the diagnosis of a new primary cancer may confer to higher mortality[6] and reduce quality of life of cancer survivors. Therefore, the phenomenon of multiple cancers have become of increasing epidemiological and clinical interest.

Definitions

Multiple cancers are defined as two or more primary cancers occurring in an individual that originate in a primary site or tissue and are neither an extension, nor a recurrence, nor metastasis (IARC). They may occur in the same tissue or organ or affect different tissue or organs. Multiple cancers can be categorized into: (1) synchronous, in which the cancers occur at the same time (no common rule exists, it maybe 2, 3, 6 months or even 1 or 2 years); and (2) metachronous, the subsequent cancer occurs after the period covered for synchronous cancer.[7] Most cancer registries adopt either the criteria suggested by the International Agency for Research on Cancer or of the SEER Program, the former being more strict, resulting in fewer multiple cancer cases.[7-9] The term second (primary) cancer will be used often in the discussion of multiple malignancies and also in this chapter, because currently 75% of all multiple cancer cases were cancer survivors diagnosed with a second primary cancer.[3] To distinguish a new primary tumour from recurrent tumours or metastatic lesions can be sometimes problematic, and may lead to misclassification especially in paired organs such as the breast or in organs having the same morphology such head and neck cancers (squamous cell carcinoma) or urinary tract cancers[10, 11] (urothelial cell carcinoma). Distinguishing these entities is not only important to accurately assess the risk of multiple cancers, but also to determine appropriate treatment.[7, 12] Tumour characteristics i.e. histology, location, stage or molecular signature provide guidelines in their categorization.[12-14]

Epidemiology

Nowadays, about 1 in every 6 cancer-survivors had once breast cancer. Thus, women with breast cancer also represent the largest proportion (25%) of the total multiple cancer prevalence reported in the United States in 2002 (Figure 2.1).[3] The second and third largest group of multiple cancer cases were men and women whose first primary were colorectal cancer (15%) and men whose first primary were prostate cancers (13%).[3] Generally, women have a slightly higher relative risk of a second cancer as compared to men (17% higher for women vs.11% for men), probably because common female cancers confer much better survival chances as compared to that of the males.[1]

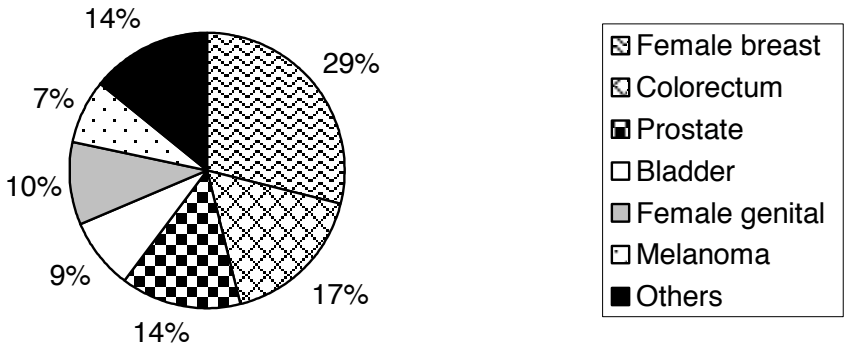

Figure 2.1. Multiple cancer cases according to first cancer types in the United States 1975-2001[3]

Data was based on 756,467 multiple primary cancer cases diagnosed among 9,606,460 first primary cancer patients in the United States in the last 27 years who were still alive at January 1, 2002. Subsequent cancers may be at the same site as the first primary cancer or at different site. Others include Hodgkin Disease, non-Hodgkin Lymphoma, kidney and renal pelvis and Leukaemia.

Adapted from Mariotto, A. B., Rowland, J. H., Ries, L. A., Scoppa, S., Feuer, E. J. (2007) Multiple cancer prevalence: a growing challenge in long-term survivorship. Cancer Epidemiol Biomarkers Prev. 16, 566-71. With permission from American Association for Cancer Research.

The absolute risk of multiple cancers is highest among the elderly, peaking among those aged 70-79 years i.e. 39% vs. 4%, 9%, 19% and 30% at 0-49, 50-59, 60-69 and 80+ years, respectively (Figure 2.2 a).[1] However, when such risk is compared to cancer risk in the population, a striking trend was observed from the youngest to the oldest age group. This ranges from a relative risk of 6 among those first diagnosed with a cancer at the age of 0-17 decreasing to 0.92 among those diagnosed with first cancer older than 80 years old (Figure 2.2 b). Underreporting of second cancers and a shorter life expectancy in the highest age group may cause the observed lower absolute and relative risk.

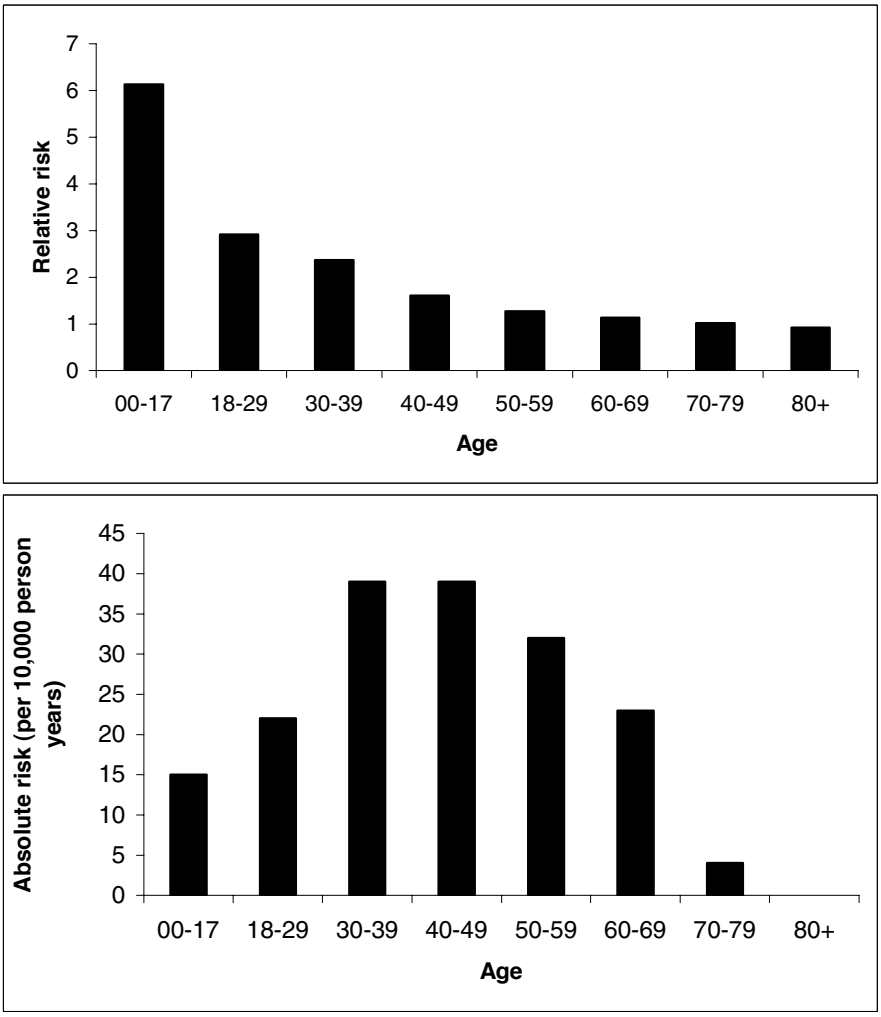

Figure 2.2. Relative and absolute risk of subsequent primary cancers according to age at first cancer diagnosis [1]

Panel a shows relative risk of subsequent primary cancers in both sexes by age in the Unites States 1973-2000.
Panel b shows absolute excess risk of subsequent primary cancers in both sexes by age in the Unites States 1973-2000.
Notes: Include all first primary cancer patients except non-melanoma skin. Subsequent primary cancers include 2nd, 3rd, and later cancers and encompass all cancer sites except non-melanoma skin and subsequent prostate cancers following first primary prostate cancer. The population at risk includes 2,036,597 patients who survived 2 or more months after initial cancer diagnosis during 1973 to 2000.
Adapted from Fraumeni, J. F. J., Curtis, R., Edwards, B. K., Tucker, M. A. (2006) Introduction. Bethesda, MD: National Cancer Institute, NIH Publ. No. 05-5302. 1-7.

Studies of geographic difference in incidence of multiple primaries have been hampered by the different registration methods used by various cancer registries.[15, 16] In an international context with common registration methods multiple cancer studies present a unique opportunity to assess the aetiology of cancer.[15, 17-20] Using the data of 13 worldwide cancer registries, the relative risk of second cancer was compared in patients with previous skin cancers in sunny countries compared to less sunny countries.[20] Skin cancers increased with higher sun exposure, whereas the UV of sunlight through the production of vitamin D might protect against some cancers.[21, 22] Concordantly, this study reported a significantly lower

relative risk of all second solid primary cancers (except skin and lip) after skin cancer in the sunny countries compared to the less sunny countries.

2.2. Study Design and Method of Analysis of Multiple Cancer Studies

Cohort Study

In a cohort study, also referred as longitudinal study, a large group of cancer patients is followed forward in time to ascertain the occurrence of another primary cancer. It can be done in two ways: (1) prospective cohort study, in which the cohort is identified in the present and followed into the future, or (2) historical cohort study (often denoted as retrospective cohort study), in which the cohort is identified in the present (some may already exhibit the outcome of interest, in this context another primary cancers) and by means of medical records the cancer experience is reconstructed between the defined time in the past and the present.[23-25] Data sources include population-based cancer registries, hospital-based cancer registries and clinical trial series. Population-based study gives large number of cases, allowing detection of even a small increase in risk as well of having determined reference population. However, detailed data on risk factors are usually lacking. Hospital-based studies may comprise large and extensive data, clinical trial databases even in more detail, but numbers of cases are usually smaller and occurrence of rare second cancer becomes much harder to ascertain.

In order to determine whether cancer patients are at a higher or lower risk of developing cancers than the general population, the incidence of subsequent cancers among these patients (observed incidence) is compared to the incidence of such cancers in the general population. The expected incidence derived from calculating person-years of follow-up in the cohort stratified by gender, age and calendar year. Dividing the observed incidence by the expected incidence results in the standardized incidence ratio (SIR).[23, 24, 26, 27] Examining SIR and its significance is a way to exclude the role of chance in assessing the risk of second primary cancer. Categorizing SIR in different follow-up time (after diagnosis of first cancers) may give clue to the excess cases due to heightened medical surveillance or to the role of cancer treatment. Excess risk only during the first years after first cancer diagnosis suggests a surveillance bias. Excess risk of solid second tumour occurs only after a latency time of 5-10 years. Whether a subsequent cancer has a large burden in a cohort, absolute excess risk (AER) provides the measure of the excess number of subsequent malignancies per 10,000 patients per year.[23, 25] It is estimated by subtracting the expected number of second cancers from the observed number, and dividing this by the number of person-years, usually per 10,000 cases. The last confers the cumulative risk, which is the proportion of patients who would develop a subsequent cancer conditional on survival. Cumulative risk can be calculated either using actuarial method [28] or cumulative incidence function.[29]

When time trend of multiple cancers is the main study interest, one should adjust for factors that increase the risk of subsequent cancers such as length of follow-up after the diagnosis of the first primary. A fixed inception cohort method where risk of second cancer in different cohorts with the same follow-time is compared may overcome this problem.[30] Multivariate regression adjusting for various factors may be employed to study determinants of interest corrected for confounding factors. [31]

Case-control Study

A nested case-control study within a cohort presents the opportunity to assess the role of risk factors in greater details, such as cancer therapy [23, 24, 32] or behavioural risk factors.[33] Detailed data could be ascertained through medical records or questionnaire to the therapist or patients themselves. Cases are patients with second cancer (or more). Controls are patients who do not develop the second cancer, randomly matched by age, gender, calendar year of diagnosis and naturally, length of follow-up time. Relative risk can then be calculated by comparing different exposures of interest among the cases and the cohort. Overmatching (of non-confounding factor(s)) would unnecessarily reduce statistical power and finally non-association of exposure and cases.[24]

2.3. Causes

Multiple cancers arise in the same individual due to several following causes: (i) host factors such as genetic or hormonal factors, (ii) lifestyle, (iii), first cancer treatment, and (iv) environment. In most patients, a combination of several factors likely contributes to the occurrence of multiple cancers (figure 2.3).[32, 34] Additionally, an elevated risk of multiple malignancies may also be caused by higher medical surveillance after a cancer diagnosis or merely due to chance (see study method to assess the role of risk factors).

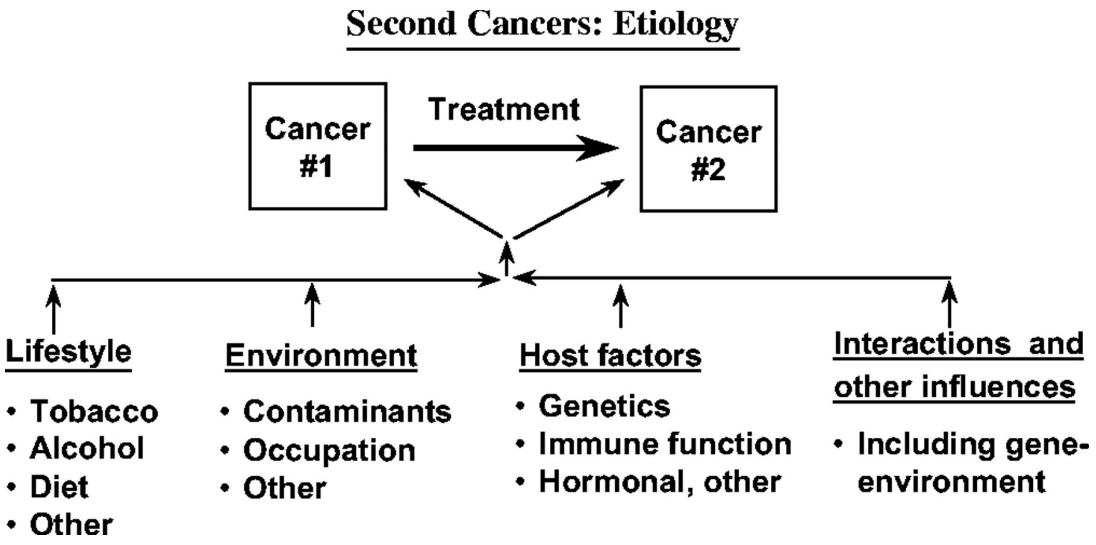

Figure 2.3. Factors related with risk of subsequent primary cancers [32]
Travis, L.B. Acta Oncologica 2002; 41:323-333, reprinted by permission of Taylor and Francis, Stockholm, Sweden.

Genetic Predisposition

About 5-10% of all cancers arise in individuals with an inherited genetic mutation conferring to heightened cancer-specific susceptibility.[35] A short list of selected cancer inherited syndromes, their gene mutations and penetrance based on comprehensive review in these area are listed in table 2.1.[35-37] Increased risk of multiple cancers have been consistently reported among patients with family history of cancer.[38-44] Cancer in patients with heritable cancer susceptibility generally presents at early ages.[42, 44] Among female breast cancer patients aged younger than 50 risk of ovarian cancer is fourfold among those with breast cancer diagnoses older than 50.[19, 45-47] This is consistent with the presence of germline mutation BRCA1/2 and possibly also other mutations. In 10 years after breast cancer diagnosis 20% [48] to 30% [49] of patients carrying this mutation would be diagnosed with ovarian or contralateral breast cancer, respectively. Breast cancer patients younger than 45 years may also carry a germline mutation in the TP53 (Li-Fraumeni syndrome), which is also related to higher incidence of soft tissue and sarcoma as well as brain tumours, adrenal cortical carcinoma and leukaemia.

Table 2.1. Selected inherited cancer syndromes, reported in various multiple cancer cases (modified table from Fearon et al[36] and Nagy R et al[37])

Syndrome	Affected sites	Penetrance	Gene(s)
Familial breast cancer	**Breast**, ovary, male breast, pancreas, prostate, melanoma	Up to 85%	BRCA1, BRCA2
Hereditary nonpolyposis colon cancer (HNPCC or Lynch syndrome)	**Colorectum**, corpus uteri, ovary, hepatobiliary and unrinary tract, brain. Also Muir-Torre and Turcot variant-related tumors.	90%	MLH1, MSH1, MSH2, PMS1, PMS2
Hereditary retinoblastoma	**Eyes**, bone and soft tissue sarcoma	90%	RB
Li-Fraumeni syndrome	**Sarcoma, breast**, brain, leukaemia and adrenocortical cancer	90-95%	TP53
Cowden syndrome	**Breast**, thyroid corpus uteri	~ 50%	PTEN (MMAC1)
Familial melanoma	**Melanoma**, pancreas	~ 90%	CDKN2A (p16)
Multiple endocrine neoplasia type 1	**Parathyroid**, entero-pancreas, pituitary	95%	MEN1
Familial adenomatous polyposis (FAP)	**Colorectum**, thyroid, pancreas, liver, central nervous system, and other benign conditions	~ 100%	APC

Bold refers to most affected sites (highest penetrance). More detailed table and overview please refer to [35-37, 50]
Adapted from Nagy, R., Sweet, K., Eng, C. (2004) Highly penetrant hereditary cancer syndromes. Oncogene. 23, 6445-70 with permission from Nature Publishing Group and from Fearon, E. R. (1997) Human cancer syndromes: clues to the origin and nature of cancer. Science. 278, 1043-50 with permission from AAAS.

Early-onset of colon cancer has also been associated to Lynch syndrome (hereditary nonpolyposis colorectal cancer [HNPCC]) or familial adenomatous polyposis (FAP). In addition, HNPCC patients have a heightened risk of endometrial, ovarian, stomach and kidney cancer[35, 50] and colorectal cancer patients may also have a higher breast cancer risk through inherited mutations of CHEK2.[51]

Beside the role of single gene mutation, the polygenic model may explain part of the increased risk of multiple cancers in an individual,[8, 52, 53] also interacting with other risk-enhancing factors such as smoking, alcohol or even cancer treatment such as radiation. A polygenic model would explain the occurrence of cases with familial clustering of cancers without (detectable) specific germline mutation, i.e. only 70% of all families meeting the criteria of Li-Fraumeni syndrome showed a germline mutation in TP53.[35, 42]

Common External Factors

Smoking and Alcohol

Smoking- and alcohol related second malignancies account for 35% of the total excess cases observed in the US cancer survivors.[1] Most multiple cancer studies have used population-based registry and data on behavioural risk factors such as smoking or alcohol intake is not readily available. The clustering of smoking or alcohol related cancer in an individual designates them as common risk factors. The pattern of multiple cancers risk that share common etiologic factors is a useful tool to give insight of their aetiology, and should generally comply to the following rules; (1) significant reciprocal increased risk (increased risk of cancer A after cancer B and vice versa) (2) persistent increased of relative risk since diagnosis of the index tumour (3) role of first cancer treatment could be excluded, i.e. similar risk pattern between those who received surgical and radio-therapy.[27] A consistent excess of subsequent primary smoking-related cancers (i.e. oral cavity, pharynx, pancreas, larynx, lung, kidney and bladder) has been reported among patients ever diagnosed with similar cancers.[18, 54-57] And for alcohol, it is likely to have contributed to the increased risk of liver and oesophageal cancer among laryngeal cancer patients.[57, 58]

Where individual behavioural history is available, cigarette smoking clearly increased risk of smoking-related second primary cancer (table 2.2).[58-63] Patients with Hodgkin's Disease (HD) who smoked exhibited an odds ratio of 6 to 13 for lung cancer as compared those who never smoked. Furthermore, studies indicated that smoking cessation following cancer diagnosis lowers the risk of new smoking-related malignancies.[60, 64] Breast cancer patients with the highest alcohol intake exhibited almost a 2-fold higher risk of colorectal cancer as compared to non-drinkers.[40] Likewise laryngeal and hypopharyngeal cancer survivors with the highest alcohol consumption (≥121 g/day) exhibited a 3-fold upper aero-digestive tract cancers compared to those with the lowest alcohol intake (0-40 g/day) (table 2.2).[58]

Table 2.2. Risk of lung and upper aerodigestive tract cancer following laryngeal/hypopharyngeal carcinoma, according to smoking and alcohol intake index[58]

Site of second primary/ Risk factor	Lung			UADT			
	Cases/total cohort	HR	95%CI		Cases/total cohort	HR	95%CI
Pack-years of cigarette smoking				Average alcohol drinking (g/day)			
0-20	3/115	1	-	0-40	4/197	1	-
21-40	26/362	3.3	0.9-11.0	41-80	4/227	0.8	0.2-3.3
41-60	15/264	2.4	0.7-8.6	81-120	12/206	3.0	0.9-9.5
≥ 61	10/128	3.9	1.0-14.6	≥ 121	17/246	3.5	1.1-11.2
Stratified log-rank test, *p* value			0.06				0.003

HR = Hazard ratio. 95%Ci = 95% confidence interval. UADT: upper aerodigestive tract including lip, tongue, oral cavity, oropharynx, nasopharynx, hypopharynx, larynx, esophagus (ICD9 140-150).

Data was based on 876 male primary larynx and hypopharynx cancer patients. Hazard ratio was adjusted for age, occupational group, alcohol drinking, cigarette smoking and site of first cancer (hypopharynx or larynx).[58] Cancer, Vol. 103, No. 11, 2326-33. Copyright @2005 American Cancer Society. This material is reproduced with permission of Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc.

Diet and Obesity

Dietary factors including obesity, diet low of fruit and vegetable as well as high in fat accompanied by low physical activity have been related to occurrence of a large number of cancers in the general population [65, 66] and also appear to account for multiple cancers involving the breast, female reproductive organs and lower and upper digestive tract.[19, 40, 45-47, 67] Obese breast cancer patients had approximately 2-fold greater hazard of contralateral breast tumors relative to underweight/normal-weight women (table 2.3).[40, 68, 69] Likewise, obesity and/or adult weight gain increased the risk of other second primary cancers including endometrial and colon cancer risk (table 2.3).[40, 41, 69] Furthermore, very obese colon cancer patients (BMI > or = 35 kg/m2) showed greater risk of a recurrence or second primary tumor of the colon; hazard ratio [HR] = 1.38, 95% confidence interval [CI] = 1.10 to 1.73) than normal weight patients (BMI = 18.5-24.9 kg/m2).[70] Finally, high citrus fruits and vegetable consumption may reduce lung cancer risk among patients previously diagnosed with laryngeal cancer by 10-60%.[58]

Table 2.3. Risk of primary breast, endometrial and colorectal cancer following breast cancer, according to body mass index before or at the diagnosis of first primary breast cancer

Site of second primary / Risk factor	**Breast** [a]		**Endometrial** [b]			**Colorectal** [b]	
	HR	95%CI		HR	95%CI	HR	95%CI
BMI (kg/m^2)			BMI (kg/m^2)				
≤ 24.9	1		< 22.5	1		1	
25.0-29.9	1.22	0.87-1.71	22.5-25.0	0.98	0.50-1.90	0.91	0.51-1.60
≥ 30.0	1.58	1.10-2.25	25.1-28.8	1.07	0.55-2.07	1.54	0.92-2.59
			≥ 28.9	2.23	1.23-4.05	1.67	0.99-2.82

BMI was defined weight in kilograms divided by height in meters squared. HR: Hazard Ratio. 95% CI: 95% Confidence Interval

a Data was based on 193 newly diagnosed patients with contralateral breast cancer among 3,385 primary (early stage) breast cancer patients. Hazard ratio was adjusted for treatment, age, menopausal status, race, tumor size, estrogen receptor level and progesterone receptor level. Risk of contralateral breast cancer was similarly elevated by increasing BMI in women who were premenopausal and postmenopausal at study entry. [68]
Adapted from Dignam, J. J., Wieand, K., Johnson, K. A., Fisher, B., Xu, L., Mamounas, E. P. (2003) Obesity, tamoxifen use, and outcomes in women with estrogen receptor-positive early-stage breast cancer. J Natl Cancer Inst. 95, 1467-76. With permission from Oxford University Press.

b Data was based on 90 primary endometrial cancer cases among 5,724 postmenopausal breast cancer patients and 127 primary colorectal cancer cases among 8,020 postmenopausal breast cancer patients. Regression models conditional on age and hazard ratio was adjusted for year of diagnosis, stage of breast cancer at initial diagnosis, family history of breast cancer, pack-years of cigarette smoking, recent alcohol intake, parity, postmenopausal hormone therapy. [40]
Adapted from Trentham-Dietz, A., Newcomb, P. A., Nichols, H. B., Hampton, J. M. (2006) Breast cancer risk factors and second primary malignancies among women with breast cancer. Breast Cancer Res Treat. With kind permission from Springer Netherlands.

Hormonal Factor

Hormonal and reproductive factors (age at birth of first child, at menarche and menopause, and parity, use of oral contraception and hormone-replacement therapy (HRT) are related to risk of several cancers such as breast, endometrial, ovarian and colon cancers. Cancer patients who had premature menopause i.e. due to chemotherapy exhibited a lower risk of second primary breast cancer.[71] Breast cancer survivors who were older age at menarche and have few children showed an increased risk of second primary breast cancer.[33, 40] Furthermore a reduced colorectal cancer risk is observed among those who were older at menarche, younger at menopause and used HRT.[40] The role of reproductive factors in relation did not seem to alter the effect of first cancer treatment.[38, 71, 72]

Infection and Immunosuppresion

Several infectious agents are considered to be causes of cancer in humans. Human Papillomavirus (HPV) infection is likely to play a role in case of multiple cancers of the tonsil, oropharynx, oesophagus, anus, cervix uteri, vagina and vulva. Among patients with cancer of the cervix, vulva and vagina a 3 to 5-fold increased risk of other HPV-related cancers was observed.[73-75] A similar excess of HPV-related cancers was reported in women diagnosed with in-situ cervical cancer.[74] Analysing the risk for in-situ and invasive cervical cancer patients separately gives the opportunity to assess and exclude the role cancer treatment i.e. radiation given to patients with invasive cervical cancer, provided the smoking patterns did or do not differ. Furthermore identical HPV DNA integration loci in tissue from the initial

cervical cancer and in the subsequent vaginal or vulvar cancers were detected, indicating common aetiology.[76]

Epstein-Bass virus (EBV) has been linked to multiple cancers of the nasopharynx, non-Hodgkin Lymphoma (NHL) as well as to Hodgkin's Disease.[18, 56, 77, 78] Among 1549 nasopharyngeal cancer patients, a 14-fold increased risk of second head and neck cancers was reported, and 9% of the patients with multiple head and neck cancers had positive EBV infection compared to only 4% among the control group of patients with only a primary head and neck cancer.[79]

Impairment of the immune system and thus lack of control of oncogenic viruses greatly elevates the risk of infection-related cancers.[80] Patients with HIV or with organ transplantation exhibited more than a hundred-fold increased risks of NHL or Kaposi Sarcoma (KS) and to a lesser extent of HD, cervical and skin cancer.[80, 81] Impaired immune function is supposed to explain the reciprocal increased risk multiple malignancies among patients NHL, HD, KS and melanoma.[1, 77, 82, 83]

Treatment

The etiologic role of cancer treatment for second primary malignancy has been extensively described by others.[23, 32, 84] Chemotherapy, radiotherapy, and hormonal therapy are largely responsible. Acute sequelae are generally associated to chemotherapy, second cancers arising from as little as a few months to 9 years post-therapy. As for radio- and hormonal therapy, chronic sequelae usually develop after a longer latency time of 5 to 10 years. The risk may remain elevated for long period of time, though a lowering of the observed risk as compared to an earlier follow-up period became visible after 25 years following the treatment of HD.[85, 86] Moreover, therapy-related second cancers may also arise due to combination of treatment modalities and genetic predisposition towards cancers or treatment and external factors such as lifestyle. Although a considerable proportion of second cancers can be therapy-related, one should always also consider the benefit of cancer treatment. Moreover, the knowledge on side-effects develops over time so that there is always a delay of at least a decade, before it affects the existing regimens and contributes to new ones that combine good survival chances with a lower risk of adverse effect.

Radiotherapy

Initiation and progression to cancer due to radiation induces cancer depend on several factors: (a) Dose of radiation, (b) sensitivity of the body tissue (c) exposure field (d) age at exposure and (e) interaction with other increasing- or decreasing-factor(s). Thyroid, breast and bone marrow are reported as the most radiosensitive tissue.[24, 87] The effect of radiation is often amplified when such tissue received radiation at an early age. For example risk of breast cancer following HD is highest for those who were treated before age 30 (RR: 6-8), whereas risk after age 30 is only minimally elevated.[59, 78, 86] Furthermore, the risk of lung cancer among HD survivors was significantly higher among smokers, based on a multiplicative relation between smoking and radiation (table 2.4).[62, 63] Finally, radiation also attenuated the risk of sarcoma among retinoblastoma patients [88] who were positive for Rb1 mutation (the cumulative risk at 50 years after diagnosis was 51%), whereas for those

without the mutation radiotherapy did not significantly affect their risk of second cancer (cumulative risk: 5%).[89]

Table 2.4. Relative risk of subsequent lung cancer by treatment and smoking habits in 19,046 patients treated for Hodgkin's Disease[63]

Treatment for Hodgkin's Disease	**Moderate-heavy smokers**	
	No. of Lung cancers	Relative risk (95% CI)
No	10	6 (1.9-20.4)
Radiation > 5 Gy	20	20.2 (6.8-68)
Chemotherapy	33	16.8 (6.2-53)
RT+CT	24	49.1 (15.1 -187)

Reference group was patients without radiation or chemotherapy who were non- or light smokers 5 years before lung cancer diagnosis. Moderate represents individuals who smoked one to two packs a day and heavy represents individuals who smoked two or more packs a day.

Adapted from . Travis, L. B., Gospodarowicz, M., Curtis, R. E., Clarke, E. A., Andersson, M., Glimelius, B., Joensuu, T., Lynch, C. F., van Leeuwen, F. E., Holowaty, E., Storm, H., Glimelius, I., Pukkala, E., Stovall, M., Fraumeni, J. F., Jr., Boice, J. D., Jr., Gilbert, E. (2002) Lung cancer following chemotherapy and radiotherapy for Hodgkin's disease. J Natl Cancer Inst. 94, 182-92. With permission from Oxford University Press.

Chemotherapy

Chemotherapy is commonly related to the increase occurrence of leukaemia, and its leukaemogenic effect is more potent than radiation (table 2.5). As for solid tumours, firm evidence has been established between the excess risk of bladder cancer among NHL patients treated with cyclophosphamide; 3-7 excess cancers in 100 NHL cases treated from moderate to high dose of cyclophosphamide.[90] There might also be an association between alkylating agents and bone sarcoma[91] and lung cancer[92], though not all could prove a dose-response (chemotherapy cycle) relationship.[93] Furthermore combination of chemotherapy with radiation may cause a higher risk of a second cancer than for the individual therapy alone.[93-95] Lung cancer risk after chemo- and radiotherapy among HD patients was as expected as excess risks were added together. On the other hand the combination with chemotherapy reduced the increased breast cancer risk among patients with HD who received radiotherapy (RR: 5.9 with Radiotherapy; RR: 4.2 with Chemotherapy; RR: 8.0 with radio- & chemotherapy) [63, 94] Similarly breast cancer patients who received chemotherapy in combination with radiation exhibited half of the second breast cancer as compared to those who only received radiotherapy.[46, 96] Chemotherapy induces early menopause, thus substantially reducing the risk of breast cancer.[71]

Table 2.5. Chemotherapy and related multiple cancers.*

Chemotherapeutic agents	Treatment for primary cancer	Therapy-related cancer
Alkylating agent (mechlorethamine, chlorambucil, cyclophosphamide, melphalan, semustine, lomustine, carmustine prednimustine, busulfan and dihydroxybusulfan.	Lymphomas[108] Breast[13, 109]	Leukemia [a b]
Platinating agents (cisplatin and carpboplatin)	Ovary[110, 111] Testis[112, 113]	Leukemia [a]
Topoisomerase II inhibitors (epipodophyllotoxins etoposide and teniposide)	Lung, Testis, Solid[114] and non-solid childhood cancers[115]	Leukemia [a c]
Intercalating topoisomerase II inhibitors (anthracycline, doxorubicin and 4-epidoxorubicin)	Lymphomas[108] Breast[13, 109]	Leukemia [a c]
Cyclophosphamide	NHL[90] Ovarian[116]	Bladder cancer
Alkylating agent MOPP regimen (mechloretamine, vincristine, procarbazine, prednisone)	HD[59, 62, 63]	Lung cancer
CHOP regimen (cyclophosphamide, doxorubicin, vincristine, prednisone)	NHL[92]	
Alkylating agent and anthracycline	Childhood cancers[91, 117]	Bone sarcoma

* Risk of second cancers due to a specific chemotherapeutic agent is difficult to separate because the common combination of several agents. Comprehensive review on the effect of these agents can be found in [23]

a Leukemia usually implies to acute myeloid leukaemia, so far only chronic lymphocytic leukaemia has not been linked to chemotherapy.[23]

b > 50% preceded by myelodysplastic syndrome (MDS). Peak 5-10 years after start of chemotherapy.

c Not preceded by MDS, peak 2-3 years after the start of chemotherapy.

Hormonal Therapy

Tamoxifen as breast cancer treatment has been consistently related to an elevated risk of endometrial cancer.[72, 97, 98] Endometrial cancer risk increased by 2-fold among 2 years tamoxifen users and by 4-8-fold among 5 or more years users. Most studies have found no difference in the effect of tamoxifen on endometrial cancer risk between HRT users and non-users or between obese and non-obese groups,[68, 72, 99] although one stated otherwise.[100] Risk of endometrial cancer is greater among breast cancer patients who received tamoxifen as treatment and used HRT or were obese as compared to non-HRT users and thinner patients who received tamoxifen.[72, 99]

On the other hand, hormonal therapy has demonstrated a protective effect against the normally increased risk of a second primary breast cancer among breast cancer patients.[46, 97] In the trials where patients took 1, 2, or about 5 years of adjuvant tamoxifen the 10-year proportional reductions in contralateral breast cancer were 13% (SD 13), 26% (SD 9), and 47% (SD 9), respectively.[101]

2.4. Conclusions and Future Research

Improvements in early detection, diagnosis and treatment of cancers have increased survival of patients with many types of cancer, however also carrying a significant increase in number of individuals with multiple malignancies. This problem is larger and will grow even larger in industrialized societies with increasing proportion of elderly persons. Study of occurrence and course of multiple malignancies will improve our insight in etiology and the genesis of cancer in general. Furthermore, human behaviour is and will be constantly changing, cancer treatment continuously improving either or not through emerging new therapies, therefore the need for continuous surveillance. Their effect on the risk of multiple cancers needs a certain period of time till it surfaces and is clarified unequivocally. Population-based data can serve very well for early warning and verification of 'loose' notifications.

The agenda of guideline development for and research of multiple cancers might cover the following 6 major areas,[34] including additional issues beyond what have been laid-out earlier:

1. Development of a(n) (inter)national research infrastructure for studies of cancer survivorship; similar registration method is needed to facilitate international collaborative efforts.[15-18, 55]
2. Creation of a coordinated system of tumour banking for biospecimen collection;[102]
3. Development of new technology, bioinformatics and biomarkers to assess risk and etiologic pathway of multiple cancers; e.g. distinguishing second primary cancers from recurrent or metastatic lesions is important to determine therapy; advances in tumour molecular analysis will certainly improve classification.[103-105]
4. Design of new epidemiologic method and studies; accurate projections of new primary cancer risk among cancers survivors are important to facilitate the surveillance recommendations and are now available for second cancers after childhood leukaemia and HD.[106, 107]
5. Clinical studies assessing the impact of early detection and treatment of a second or higher order malignancy on cause of death and patients' survival as well as quality of life.
6. Development of evidence-based clinical practice guidelines: including intervention strategies such as behaviour modification to prevent occurrence of a new primary cancer; follow-up of cancer survivors; and tailored-therapy for the second, third or higher order primary cancer, which usually involved the elderly who are more fragile to cancer treatment.

References

1. Fraumeni JFJ, Curtis R, Edwards BK, Tucker MA. *Introduction*. Bethesda, MD: National Cancer Institute; 2006.
2. Sankila R, Pukkala E, Teppo L. Risk of subsequent malignant neoplasms among 470,000 cancer patients in finland, 1953-1991. *Int J Cancer*. 1995;60:464-470
3. Mariotto AB, Rowland JH, Ries LA, Scoppa S, Feuer EJ. Multiple cancer prevalence: A growing challenge in long-term survivorship. *Cancer Epidemiol Biomarkers Prev*. 2007;16:566-571
4. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. *CA Cancer J Clin*. 2005;55:74-108
5. Janssen-Heijnen ML, Houterman S, Lemmens VE, Louwman MW, Maas HA, Coebergh JW. Prognostic impact of increasing age and co-morbidity in cancer patients: A population-based approach. *Crit Rev Oncol Hematol*. 2005;55:231-240
6. Soerjomataram I, Louwman MW, Ribot JG, Roukema JA, Coebergh JW. An overview of prognostic factors for long-term survivors of breast cancer. *Breast Cancer Res Treat*. 2007
7. Howe HL. A review of the definition for multiple primary cancers in the united states. Workshop proceedings from december 4-6, 2002, in princeton, new jersey. 2003
8. Johnson CH, Adamo M. *Seer program coding and staging manual 2007*. Bethesda, MD: National Cancer Institute; 2007.
9. International rules for multiple primary cancers (icd-0 third edition). *Eur J Cancer Prev*. 2005;14:307-308
10. Vriesema JL, Aben KK, Witjes JA, Kiemeney LA, Schalken JA. Superficial and metachronous invasive bladder carcinomas are clonally related. *Int J Cancer*. 2001;93:699-702
11. Aben KK, Witjes JA, van Dijck JA, Schalken JA, Verbeek AL, Kiemeney LA. Lower incidence of urothelial cell carcinoma due to the concept of a clonal origin. *Eur J Cancer*. 2000;36:2385-2389
12. Harari PM. Re: Distinguishing second primary tumors from lung metastases in patients with head and neck squamous cell carcinoma. *J Natl Cancer Inst*. 1998;90:1571
13. Smith RE, Bryant J, DeCillis A, Anderson S. Acute myeloid leukemia and myelodysplastic syndrome after doxorubicin-cyclophosphamide adjuvant therapy for operable breast cancer: The national surgical adjuvant breast and bowel project experience. *J Clin Oncol*. 2003;21:1195-1204
14. Huang E, Buchholz TA, Meric F, Krishnamurthy S, Mirza NQ, Ames FC, Feig BW, Kuerer HM, Ross MI, Singletary SE, McNeese MD, Strom EA, Hunt KK. Classifying local disease recurrences after breast conservation therapy based on location and histology: New primary tumors have more favorable outcomes than true local disease recurrences. *Cancer*. 2002;95:2059-2067
15. Crocetti E, Lecker S, Buiatti E, Storm HH. Problems related to the coding of multiple primary cancers. *Eur J Cancer*. 1996;32A:1366-1370
16. Hotes JL, Ellison LF, Howe HL, Friesen I, Kohler B. Variation in breast cancer counts using seer and iarc multiple primary coding rules. *Cancer Causes Control*. 2004;15:185-191
17. Scelo G, Boffetta P, Autier P, Hemminki K, Pukkala E, Olsen JH, Weiderpass E, Tracey E, Brewster DH, McBride ML, Kliewer EV, Tonita JM, Pompe-Kirn V, Chia KS, Jonasson JG, Martos C, Giblin M, Brennan P. Associations between ocular melanoma and other primary cancers: An international population-based study. *Int J Cancer*. 2007;120:152-159
18. Scelo G, Boffetta P, Corbex M, Chia KS, Hemminki K, Friis S, Pukkala E, Weiderpass E, McBride ML, Tracey E, Brewster DH, Pompe-Kirn V, Kliewer EV, Tonita JM, Martos C, Jonasson JG, Brennan P. Second primary cancers in patients with nasopharyngeal carcinoma: A pooled analysis of 13 cancer registries. *Cancer Causes Control*. 2007;18:269-278
19. Mellemkjaer L, Friis S, Olsen JH, Scelo G, Hemminki K, Tracey E, Andersen A, Brewster DH, Pukkala E, McBride ML, Kliewer EV, Tonita JM, Kee-Seng C, Pompe-Kirn V, Martos C, Jonasson JG, Boffetta P, Brennan P. Risk of second cancer among women with breast cancer. *Int J Cancer*. 2006;118:2285-2292
20. Tuohimaa P, Pukkala E, Scelo G, Olsen JH, Brewster DH, Hemminki K, Tracey E, Weiderpass E, Kliewer EV, Pompe-Kirn V, McBride ML, Martos C, Chia KS, Tonita JM, Jonasson JG, Boffetta P, Brennan P. Does solar exposure, as indicated by the non-melanoma skin cancers, protect from solid cancers: Vitamin d as a possible explanation. *Eur J Cancer*. 2007
21. Grant WB. A meta-analysis of second cancers after a diagnosis of nonmelanoma skin cancer: Additional evidence that solar ultraviolet-b irradiance reduces the risk of internal cancers. *J Steroid Biochem Mol Biol*. 2007;103:668-674

22. de Vries E, Soerjomataram I, Houterman S, Louwman MW, Coebergh JW. Decreased risk of prostate cancer after skin cancer diagnosis: A protective role of ultraviolet radiation? *Am J Epidemiol*. 2007;165:966-972
23. van Leeuwen FE, Travis LB. *Second cancers*. Philadelphia: Lippincott Williams and Wilkins; 2005.
24. Travis LB. The epidemiology of second primary cancers. *Cancer Epidemiol Biomarkers Prev*. 2006;15:2020-2026
25. Curtis R, Ries LAG. *Methods*. Bethesda, MD: National Cancer Institute; 2006.
26. Schoenberg BS, Myers MH. Statistical methods for studying multiple primary malignant neoplasms. *Cancer*. 1977;40:1892-1898
27. Begg CB, Zhang ZF, Sun M, Herr HW, Schantz SP. Methodology for evaluating the incidence of second primary cancers with application to smoking-related cancers from the surveillance, epidemiology, and end results (seer) program. *Am J Epidemiol*. 1995;142:653-665
28. Cutler SJ, Ederer F. Maximum utilization of the life table method in analyzing survival. *J Chronic Dis*. 1958;8:699-712
29. Gooley TA, Leisenring W, Crowley J, Storer BE. Estimation of failure probabilities in the presence of competing risks: New representations of old estimators. *Stat Med*. 1999;18:695-706
30. Yu GP, Schantz SP, Neugut AI, Zhang ZF. Incidences and trends of second cancers in female breast cancer patients: A fixed inception cohort-based analysis (united states). *Cancer Causes Control*. 2006;17:411-420
31. Yasui Y, Liu Y, Neglia JP, Friedman DL, Bhatia S, Meadows AT, Diller LR, Mertens AC, Whitton J, Robison LL. A methodological issue in the analysis of second-primary cancer incidence in long-term survivors of childhood cancers. *Am J Epidemiol*. 2003;158:1108-1113
32. Travis LB. Therapy-associated solid tumors. *Acta Oncol*. 2002;41:323-333
33. Largent JA, Capanu M, Bernstein L, Langholz B, Mellemkjaer L, Malone KE, Begg CB, Haile RW, Lynch CF, Anton-Culver H, Wolitzer A, Bernstein JL. Reproductive history and risk of second primary breast cancer: The wecare study. *Cancer Epidemiol Biomarkers Prev*. 2007;16:906-911
34. Travis LB, Rabkin CS, Brown LM, Allan JM, Alter BP, Ambrosone CB, Begg CB, Caporaso N, Chanock S, DeMichele A, Figg WD, Gospodarowicz MK, Hall EJ, Hisada M, Inskip P, Kleinerman R, Little JB, Malkin D, Ng AK, Offit K, Pui CH, Robison LL, Rothman N, Shields PG, Strong L, Taniguchi T, Tucker MA, Greene MH. Cancer survivorship--genetic susceptibility and second primary cancers: Research strategies and recommendations. *J Natl Cancer Inst*. 2006;98:15-25
35. Garber JE, Offit K. Hereditary cancer predisposition syndromes. *J Clin Oncol*. 2005;23:276-292
36. Fearon ER. Human cancer syndromes: Clues to the origin and nature of cancer. *Science*. 1997;278:1043-1050
37. Nagy R, Sweet K, Eng C. Highly penetrant hereditary cancer syndromes. *Oncogene*. 2004;23:6445-6470
38. Hill DA, Gilbert E, Dores GM, Gospodarowicz M, van Leeuwen FE, Holowaty E, Glimelius B, Andersson M, Wiklund T, Lynch CF, Van't Veer M, Storm H, Pukkala E, Stovall M, Curtis RE, Allan JM, Boice JD, Travis LB. Breast cancer risk following radiotherapy for hodgkin lymphoma: Modification by other risk factors. *Blood*. 2005;106:3358-3365
39. Landgren O, Pfeiffer RM, Stewart L, Gridley G, Mellemkjaer L, Hemminki K, Goldin LR, Travis LB. Risk of second malignant neoplasms among lymphoma patients with a family history of cancer. *Int J Cancer*. 2007;120:1099-1102
40. Trentham-Dietz A, Newcomb PA, Nichols HB, Hampton JM. Breast cancer risk factors and second primary malignancies among women with breast cancer. *Breast Cancer Res Treat*. 2006
41. Kmet LM, Cook LS, Weiss NS, Schwartz SM, White E. Risk factors for colorectal cancer following breast cancer. *Breast Cancer Res Treat*. 2003;79:143-147
42. Hisada M, Garber JE, Fung CY, Fraumeni JF, Jr., Li FP. Multiple primary cancers in families with li-fraumeni syndrome. *J Natl Cancer Inst*. 1998;90:606-611
43. Hemminki K, Ji J, Forsti A. Risks for familial and contralateral breast cancer interact multiplicatively and cause a high risk. *Cancer Res*. 2007;67:868-870
44. Hemminki K, Li X. Familial risk for lung cancer by histology and age of onset: Evidence for recessive inheritance. *Exp Lung Res*. 2005;31:205-215
45. Soerjomataram I, Louwman WJ, de Vries E, Lemmens VE, Klokman WJ, Coebergh JW. Primary malignancy after primary female breast cancer in the south of the netherlands, 1972-2001. *Breast Cancer Res Treat*. 2005;93:91-95

46. Soerjomataram I, Louwman WJ, Lemmens VE, de Vries E, Klokman WJ, Coebergh JW. Risks of second primary breast and urogenital cancer following female breast cancer in the south of the netherlands, 1972-2001. *Eur J Cancer*. 2005;41:2331-2337
47. Raymond JS, Hogue CJ. Multiple primary tumours in women following breast cancer, 1973-2000. *Br J Cancer*. 2006;94:1745-1750
48. Metcalfe KA, Lynch HT, Ghadirian P, Tung N, Olivotto IA, Foulkes WD, Warner E, Olopade O, Eisen A, Weber B, McLennan J, Sun P, Narod SA. The risk of ovarian cancer after breast cancer in brca1 and brca2 carriers. *Gynecol Oncol*. 2005;96:222-226
49. Metcalfe K, Lynch HT, Ghadirian P, Tung N, Olivotto I, Warner E, Olopade OI, Eisen A, Weber B, McLennan J, Sun P, Foulkes WD, Narod SA. Contralateral breast cancer in brca1 and brca2 mutation carriers. *J Clin Oncol*. 2004;22:2328-2335
50. Lynch HT, Shaw TG, Lynch JF. Inherited predisposition to cancer: A historical overview. *Am J Med Genet C Semin Med Genet*. 2004;129:5-22
51. Meijers-Heijboer H, Wijnen J, Vasen H, Wasielewski M, Wagner A, Hollestelle A, Elstrodt F, van den Bos R, de Snoo A, Fat GT, Brekelmans C, Jagmohan S, Franken P, Verkuijlen P, van den Ouweland A, Chapman P, Tops C, Moslein G, Burn J, Lynch H, Klijn J, Fodde R, Schutte M. The chek2 1100delc mutation identifies families with a hereditary breast and colorectal cancer phenotype. *Am J Hum Genet*. 2003;72:1308-1314
52. Dong C, Hemminki K. Multiple primary cancers of the colon, breast and skin (melanoma) as models for polygenic cancers. *Int J Cancer*. 2001;92:883-887
53. Balmain A, Gray J, Ponder B. The genetics and genomics of cancer. *Nat Genet*. 2003;33 Suppl:238-244
54. Levi F, Randimbison L, Maspoli M, Te VC, La Vecchia C. Second neoplasms after oesophageal cancer. *Int J Cancer*. 2007;121:694-697
55. Shen M, Boffetta P, Olsen JH, Andersen A, Hemminki K, Pukkala E, Tracey E, Brewster DH, McBride ML, Pompe-Kirn V, Kliewer EV, Tonita JM, Chia KS, Martos C, Jonasson JG, Colin D, Scelo G, Brennan P. A pooled analysis of second primary pancreatic cancer. *Am J Epidemiol*. 2006;163:502-511
56. Brown LM, McCarron P, Freedman DM. *New malignancies following cancer of the buccal cavity and pharynx*. Bethesda, MD: National Cancer Institute; 2006.
57. Caporaso N, Dodd KW, Tucker MA. *New malignancies following cancer of the respiratory tract*. Bethesda, MD: National Cancer Institute; 2006.
58. Dikshit RP, Boffetta P, Bouchardy C, Merletti F, Crosignani P, Cuchi T, Ardanaz E, Brennan P. Risk factors for the development of second primary tumors among men after laryngeal and hypopharyngeal carcinoma. *Cancer*. 2005;103:2326-2333
59. Swerdlow AJ, Barber JA, Hudson GV, Cunningham D, Gupta RK, Hancock BW, Horwich A, Lister TA, Linch DC. Risk of second malignancy after hodgkin's disease in a collaborative british cohort: The relation to age at treatment. *J Clin Oncol*. 2000;18:498-509
60. Tucker MA, Murray N, Shaw EG, Ettinger DS, Mabry M, Huber MH, Feld R, Shepherd FA, Johnson DH, Grant SC, Aisner J, Johnson BE. Second primary cancers related to smoking and treatment of small-cell lung cancer. Lung cancer working cadre. *J Natl Cancer Inst*. 1997;89:1782-1788
61. Khuri FR, Kim ES, Lee JJ, Winn RJ, Benner SE, Lippman SM, Fu KK, Cooper JS, Vokes EE, Chamberlain RM, Williams B, Pajak TF, Goepfert H, Hong WK. The impact of smoking status, disease stage, and index tumor site on second primary tumor incidence and tumor recurrence in the head and neck retinoid chemoprevention trial. *Cancer Epidemiol Biomarkers Prev*. 2001;10:823-829
62. Gilbert ES, Stovall M, Gospodarowicz M, Van Leeuwen FE, Andersson M, Glimelius B, Joensuu T, Lynch CF, Curtis RE, Holowaty E, Storm H, Pukkala E, van't Veer MB, Fraumeni JF, Boice JD, Jr., Clarke EA, Travis LB. Lung cancer after treatment for hodgkin's disease: Focus on radiation effects. *Radiat Res*. 2003;159:161-173
63. Travis LB, Gospodarowicz M, Curtis RE, Clarke EA, Andersson M, Glimelius B, Joensuu T, Lynch CF, van Leeuwen FE, Holowaty E, Storm H, Glimelius I, Pukkala E, Stovall M, Fraumeni JF, Jr., Boice JD, Jr., Gilbert E. Lung cancer following chemotherapy and radiotherapy for hodgkin's disease. *J Natl Cancer Inst*. 2002;94:182-192
64. Do KA, Johnson MM, Lee JJ, Wu XF, Dong Q, Hong WK, Khuri FR, Spitz MR. Longitudinal study of smoking patterns in relation to the development of smoking-related secondary primary tumors in patients with upper aerodigestive tract malignancies. *Cancer*. 2004;101:2837-2842
65. Pike MC, Pearce CL, Wu AH. Prevention of cancers of the breast, endometrium and ovary. *Oncogene*. 2004;23:6379-6391

66. Samanic C, Chow WH, Gridley G, Jarvholm B, Fraumeni JF, Jr. Relation of body mass index to cancer risk in 362,552 swedish men. *Cancer Causes Control*. 2006;17:901-909
67. Mysliwiec PA, Cronin KA, Schatzkin A. *New malignancies following cancer of the colon, rectum, and anus*. Bethesda, MD: National Cancer Institute; 2006.
68. Dignam JJ, Wieand K, Johnson KA, Fisher B, Xu L, Mamounas EP. Obesity, tamoxifen use, and outcomes in women with estrogen receptor-positive early-stage breast cancer. *J Natl Cancer Inst*. 2003;95:1467-1476
69. Dignam JJ, Wieand K, Johnson KA, Raich P, Anderson SJ, Somkin C, Wickerham DL. Effects of obesity and race on prognosis in lymph node-negative, estrogen receptor-negative breast cancer. *Breast Cancer Res Treat*. 2006;97:245-254
70. Dignam JJ, Polite BN, Yothers G, Raich P, Colangelo L, O'Connell MJ, Wolmark N. Body mass index and outcomes in patients who receive adjuvant chemotherapy for colon cancer. *J Natl Cancer Inst*. 2006;98:1647-1654
71. van Leeuwen FE, Klokman WJ, Stovall M, Dahler EC, van't Veer MB, Noordijk EM, Crommelin MA, Aleman BM, Broeks A, Gospodarowicz M, Travis LB, Russell NS. Roles of radiation dose, chemotherapy, and hormonal factors in breast cancer following hodgkin's disease. *J Natl Cancer Inst*. 2003;95:971-980
72. Swerdlow AJ, Jones ME. Tamoxifen treatment for breast cancer and risk of endometrial cancer: A case-control study. *J Natl Cancer Inst*. 2005;97:375-384
73. Kleinerman RA, Kosary C, Hildesheim A. *New malignancies following cancer of the cervix uteri, vagina, and vulva*. Bethesda, MD: National Cancer Institute; 2006.
74. Hemminki K, Dong C, Vaittinen P. Second primary cancer after in situ and invasive cervical cancer. *Epidemiology*. 2000;11:457-461
75. Levi F, Te VC, Randimbison L, La Vecchia C. Second primary cancers after in situ and invasive cervical cancer. *Epidemiology*. 2001;12:281-282
76. Vinokurova S, Wentzensen N, Einenkel J, Klaes R, Ziegert C, Melsheimer P, Sartor H, Horn LC, Hockel M, von Knebel Doeberitz M. Clonal history of papillomavirus-induced dysplasia in the female lower genital tract. *J Natl Cancer Inst*. 2005;97:1816-1821
77. Brennan P, Scelo G, Hemminki K, Mellemkjaer L, Tracey E, Andersen A, Brewster DH, Pukkala E, McBride ML, Kliewer EV, Tonita JM, Seow A, Pompe-Kirn V, Martos C, Jonasson JG, Colin D, Boffetta P. Second primary cancers among 109 000 cases of non-hodgkin's lymphoma. *Br J Cancer*. 2005;93:159-166
78. Dores GM, Cote TR, Travis LB. *New malignancies following hodgkin lymphoma, non-hodgkin lymphoma, and myeloma*. Bethesda, MD: National Cancer Institute; 2006.
79. Wang CC, Chen ML, Hsu KH, Lee SP, Chen TC, Chang YS, Tsang NM, Hong JH. Second malignant tumors in patients with nasopharyngeal carcinoma and their association with epstein-barr virus. *Int J Cancer*. 2000;87:228-231
80. Schwartz RS. Immunodeficiency, immunosuppression, and susceptibility to neoplasms. *J Natl Cancer Inst Monogr*. 2001:5-9
81. Clifford GM, Polesel J, Rickenbach M, Dal Maso L, Keiser O, Kofler A, Rapiti E, Levi F, Jundt G, Fisch T, Bordoni A, De Weck D, Franceschi S. Cancer risk in the swiss hiv cohort study: Associations with immunodeficiency, smoking, and highly active antiretroviral therapy. *J Natl Cancer Inst*. 2005;97:425-432
82. Hemminki K, Jiang Y, Steineck G. Skin cancer and non-hodgkin's lymphoma as second malignancies. Markers of impaired immune function? *Eur J Cancer*. 2003;39:223-229
83. Metayer C, Lynch CF, Clarke EA, Glimelius B, Storm H, Pukkala E, Joensuu T, van Leeuwen FE, van't Veer MB, Curtis RE, Holowaty EJ, Andersson M, Wiklund T, Gospodarowicz M, Travis LB. Second cancers among long-term survivors of hodgkin's disease diagnosed in childhood and adolescence. *J Clin Oncol*. 2000;18:2435-2443
84. Allan JM, Travis LB. Mechanisms of therapy-related carcinogenesis. *Nat Rev Cancer*. 2005;5:943-955
85. Dores GM, Metayer C, Curtis RE, Lynch CF, Clarke EA, Glimelius B, Storm H, Pukkala E, van Leeuwen FE, Holowaty EJ, Andersson M, Wiklund T, Joensuu T, van't Veer MB, Stovall M, Gospodarowicz M, Travis LB. Second malignant neoplasms among long-term survivors of hodgkin's disease: A population-based evaluation over 25 years. *J Clin Oncol*. 2002;20:3484-3494

86. van Leeuwen FE, Klokman WJ, Veer MB, Hagenbeek A, Krol AD, Vetter UA, Schaapveld M, van Heerde P, Burgers JM, Somers R, Aleman BM. Long-term risk of second malignancy in survivors of hodgkin's disease treated during adolescence or young adulthood. *J Clin Oncol*. 2000;18:487-497
87. Boice JD. *Ionizing radiation*. New York: Oxford University Press.
88. Kleinerman RA, Tucker MA, Abramson DH, Seddon JM, Tarone RE, Fraumeni JF, Jr. Risk of soft tissue sarcomas by individual subtype in survivors of hereditary retinoblastoma. *J Natl Cancer Inst*. 2007;99:24-31
89. Wong FL, Boice JD, Jr., Abramson DH, Tarone RE, Kleinerman RA, Stovall M, Goldman MB, Seddon JM, Tarbell N, Fraumeni JF, Jr., Li FP. Cancer incidence after retinoblastoma. Radiation dose and sarcoma risk. *Jama*. 1997;278:1262-1267
90. Travis LB, Curtis RE, Glimelius B, Holowaty EJ, Van Leeuwen FE, Lynch CF, Hagenbeek A, Stovall M, Banks PM, Adami J, et al. Bladder and kidney cancer following cyclophosphamide therapy for non-hodgkin's lymphoma. *J Natl Cancer Inst*. 1995;87:524-530
91. Henderson TO, Whitton J, Stovall M, Mertens AC, Mitby P, Friedman D, Strong LC, Hammond S, Neglia JP, Meadows AT, Robison L, Diller L. Secondary sarcomas in childhood cancer survivors: A report from the childhood cancer survivor study. *J Natl Cancer Inst*. 2007;99:300-308
92. Mudie NY, Swerdlow AJ, Higgins CD, Smith P, Qiao Z, Hancock BW, Hoskin PJ, Linch DC. Risk of second malignancy after non-hodgkin's lymphoma: A british cohort study. *J Clin Oncol*. 2006;24:1568-1574
93. Garwicz S, Anderson H, Olsen JH, Dollner H, Hertz H, Jonmundsson G, Langmark F, Lanning M, Moller T, Sankila R, Tulinius H. Second malignant neoplasms after cancer in childhood and adolescence: A population-based case-control study in the 5 nordic countries. The nordic society for pediatric hematology and oncology. The association of the nordic cancer registries. *Int J Cancer*. 2000;88:672-678
94. Travis LB, Hill DA, Dores GM, Gospodarowicz M, van Leeuwen FE, Holowaty E, Glimelius B, Andersson M, Wiklund T, Lynch CF, Van't Veer MB, Glimelius I, Storm H, Pukkala E, Stovall M, Curtis R, Boice JD, Jr., Gilbert E. Breast cancer following radiotherapy and chemotherapy among young women with hodgkin disease. *Jama*. 2003;290:465-475
95. Guerin S, Guibout C, Shamsaldin A, Dondon MG, Diallo I, Hawkins M, Oberlin O, Hartmann O, Michon J, Le Deley MC, de Vathaire F. Concomitant chemo-radiotherapy and local dose of radiation as risk factors for second malignant neoplasms after solid cancer in childhood: A case-control study. *Int J Cancer*. 2007;120:96-102
96. Rubino C, de Vathaire F, Shamsaldin A, Labbe M, Le MG. Radiation dose, chemotherapy, hormonal treatment and risk of second cancer after breast cancer treatment. *Br J Cancer*. 2003;89:840-846
97. Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: An overview of the randomised trials. *Lancet*. 2005;365:1687-1717
98. Fisher B, Costantino JP, Wickerham DL, Redmond CK, Kavanah M, Cronin WM, Vogel V, Robidoux A, Dimitrov N, Atkins J, Daly M, Wieand S, Tan-Chiu E, Ford L, Wolmark N. Tamoxifen for prevention of breast cancer: Report of the national surgical adjuvant breast and bowel project p-1 study. *J Natl Cancer Inst*. 1998;90:1371-1388
99. Bergman L, Beelen ML, Gallee MP, Hollema H, Benraadt J, van Leeuwen FE. Risk and prognosis of endometrial cancer after tamoxifen for breast cancer. Comprehensive cancer centres' alert group. Assessment of liver and endometrial cancer risk following tamoxifen. *Lancet*. 2000;356:881-887
100. Bernstein JL, Thompson WD, Risch N, Holford TR. Risk factors predicting the incidence of second primary breast cancer among women diagnosed with a first primary breast cancer. *Am J Epidemiol*. 1992;136:925-936
101. Tamoxifen for early breast cancer: An overview of the randomised trials. Early breast cancer trialists' collaborative group. *Lancet*. 1998;351:1451-1467
102. Teodorovic I, Isabelle M, Carbone A, Passioukov A, Lejeune S, Jamine D, Therasse P, Gloghini A, Dinjens WN, Lam KH, Oomen MH, Spatz A, Ratcliffe C, Knox K, Mager R, Kerr D, Pezzella F, van Damme B, van de Vijver M, van Boven H, Morente MM, Alonso S, Kerjaschki D, Pammer J, Lopez-Guerrero JA, Llombart Bosch A, van Veen EB, Oosterhuis JW, Riegman PH. Tubafrost 6: Virtual microscopy in virtual tumour banking. *Eur J Cancer*. 2006;42:3110-3116
103. Leong PP, Rezai B, Koch WM, Reed A, Eisele D, Lee DJ, Sidransky D, Jen J, Westra WH. Distinguishing second primary tumors from lung metastases in patients with head and neck squamous cell carcinoma. *J Natl Cancer Inst*. 1998;90:972-977

104. Blokx WA, Lesterhuis JJ, Andriessen MP, Verdijk MA, Punt KJ, Ligtenberg MJ. Cdkn2a (ink4a-arf) mutation analysis to distinguish cutaneous melanoma metastasis from a second primary melanoma. *Am J Surg Pathol*. 2007;31:637-641
105. Geurts TW, Nederlof PM, van den Brekel MW, van't Veer LJ, de Jong D, Hart AA, van Zandwijk N, Klomp H, Balm AJ, van Velthuysen ML. Pulmonary squamous cell carcinoma following head and neck squamous cell carcinoma: Metastasis or second primary? *Clin Cancer Res*. 2005;11:6608-6614
106. Travis LB, Hill D, Dores GM, Gospodarowicz M, van Leeuwen FE, Holowaty E, Glimelius B, Andersson M, Pukkala E, Lynch CF, Pee D, Smith SA, Van't Veer MB, Joensuu T, Storm H, Stovall M, Boice JD, Jr., Gilbert E, Gail MH. Cumulative absolute breast cancer risk for young women treated for hodgkin lymphoma. *J Natl Cancer Inst*. 2005;97:1428-1437
107. Hijiya N, Hudson MM, Lensing S, Zacher M, Onciu M, Behm FG, Razzouk BI, Ribeiro RC, Rubnitz JE, Sandlund JT, Rivera GK, Evans WE, Relling MV, Pui CH. Cumulative incidence of secondary neoplasms as a first event after childhood acute lymphoblastic leukemia. *Jama*. 2007;297:1207-1215
108. Schonfeld SJ, Gilbert ES, Dores GM, Lynch CF, Hodgson DC, Hall P, Storm H, Andersen A, Pukkala E, Holowaty E, Kaijser M, Andersson M, Joensuu H, Fossa SD, Allan JM, Travis LB. Acute myeloid leukemia following hodgkin lymphoma: A population-based study of 35,511 patients. *J Natl Cancer Inst*. 2006;98:215-218
109. Howard RA, Gilbert ES, Chen BE, Hall P, Storm H, Pukkala E, Langmark F, Kaijser M, Andersson M, Joensuu H, Fossa SD, Travis LB. Leukemia following breast cancer: An international population-based study of 376,825 women. *Breast Cancer Res Treat*. 2007
110. Travis LB, Holowaty EJ, Bergfeldt K, Lynch CF, Kohler BA, Wiklund T, Curtis RE, Hall P, Andersson M, Pukkala E, Sturgeon J, Stovall M. Risk of leukemia after platinum-based chemotherapy for ovarian cancer. *N Engl J Med*. 1999;340:351-357
111. Kaldor JM, Day NE, Pettersson F, Clarke EA, Pedersen D, Mehnert W, Bell J, Host H, Prior P, Karjalainen S, et al. Leukemia following chemotherapy for ovarian cancer. *N Engl J Med*. 1990;322:1-6
112. Robinson D, Moller H, Horwich A. Mortality and incidence of second cancers following treatment for testicular cancer. *Br J Cancer*. 2007;96:529-533
113. Travis LB, Andersson M, Gospodarowicz M, van Leeuwen FE, Bergfeldt K, Lynch CF, Curtis RE, Kohler BA, Wiklund T, Storm H, Holowaty E, Hall P, Pukkala E, Sleijfer DT, Clarke EA, Boice JD, Jr., Stovall M, Gilbert E. Treatment-associated leukemia following testicular cancer. *J Natl Cancer Inst*. 2000;92:1165-1171
114. Le Deley MC, Leblanc T, Shamsaldin A, Raquin MA, Lacour B, Sommelet D, Chompret A, Cayuela JM, Bayle C, Bernheim A, de Vathaire F, Vassal G, Hill C. Risk of secondary leukemia after a solid tumor in childhood according to the dose of epipodophyllotoxins and anthracyclines: A case-control study by the societe francaise d'oncologie pediatrique. *J Clin Oncol*. 2003;21:1074-1081
115. Neglia JP, Friedman DL, Yasui Y, Mertens AC, Hammond S, Stovall M, Donaldson SS, Meadows AT, Robison LL. Second malignant neoplasms in five-year survivors of childhood cancer: Childhood cancer survivor study. *J Natl Cancer Inst*. 2001;93:618-629
116. Kaldor JM, Day NE, Kittelmann B, Pettersson F, Langmark F, Pedersen D, Prior P, Neal F, Karjalainen S, Bell J, et al. Bladder tumours following chemotherapy and radiotherapy for ovarian cancer: A case-control study. *Int J Cancer*. 1995;63:1-6
117. Hawkins MM, Wilson LM, Burton HS, Potok MH, Winter DL, Marsden HB, Stovall MA. Radiotherapy, alkylating agents, and risk of bone cancer after childhood cancer. *J Natl Cancer Inst*. 1996;88:270-278

PART II

The epidemiology of breast cancer

Chapter 3

On the avoidability of breast cancer in industrialized societies: Older mean age at first birth as an indicator of excess breast cancer risk

Soerjomataram I, Pukkala E, Brenner H, Coebergh JWW. On the avoidability of breast cancer in industrialized societies: Older mean age at first birth as an indicator of excess breast cancer risk. Breast Cancer Res Treat. 2007.

Abstract

Background and objectives: Breast cancer incidence continuous to increase. We examined at population level the association between the relative excess risk of breast cancer and previous age of mother at first birth.

Methods: Incidence of breast cancer in 34 industrialized countries was obtained from the GLOBOCAN 2002 and SEER databases. Data on age of mother at first birth was collected through national statistics offices. National relative excess risk (RER) was calculated by subtracting the lowest age-specific incidence rate from the rate in each population, and dividing the difference by the latter.

Results: The national RER in 2002 correlated closely with a higher average age at first birth in 1972, 1982, 1992 and also 2002, Pearson correlation [r] being 0.83, 0.79, 0.72 and 0.61, respectively; $p<0.0001$. RER of breast cancer in 2002 for those aged 15-44 years correlated closely with the mean age at first birth in 1982 and 1992 (r: 0.81 and 0.75; $p<0.0001$), whereas RER for those aged 45-54 years correlated strongly with age at first birth in 1972 and 1982 (r: 0.81 and 0.76; $p<0.0001$), and for those aged 55-64 years with age at first birth in 1972 (r: 0.77; $p<0.0001$).

Conclusions: The rising age at first childbirth of mothers has been followed by marked increases in breast cancer incidence. Later age at first birth seems to characterize secular diffusion of 'modern' lifestyles with a potentially large impact on increased breast cancer risk, and hence should be accompanied by greater opportunities for prevention through modifiable risk factors.

3.1. Introduction

Global trends in breast cancer incidence have been attributed to various factors including reproductive history and hormonal factors, female body composition and nutritional factors, also alcohol consumption.[1-3] Higher socioeconomic status has also been associated with a higher risk of breast cancer.[4] Furthermore, increased use of mammography has increased the detection rate leading to a higher observed breast cancer incidence.[5] Reproductive-related factors including age at birth of first child and number of children has been suggested as one of the major determinants of breast cancer incidence,[2] and has been attributed to 28% of its incidence.[6] Women who had their first birth at age 35 or older exhibit a 60% higher risk of breast cancer than women who had their first child at age 20-21.[7] There are large differences between countries in the age of the mother at first birth[8], as well as in the incidence of breast cancer[9]. Recent and historical data on national fertility patterns are available and comparable for most western populations. However the role of mother's age at first birth in the past, marking current breast cancer risk has not yet been examined. Thus, we assessed the association between age at first birth and the excess risk of breast cancer a few decades later using data from 34 industrialized countries.

3.2. Methods

Materials

We performed this study within the framework of the European collaborative project Eurocadet which estimates the future potential of cancer prevention based on recent trend in cancer incidence and its related risk factors.[10] Incidence data was obtained from GLOBOCAN 2002[11] and the SEER database for white non-Hispanic Americans.[12] We included European countries (Austria, Belgium, Bulgaria, Croatia, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Former Yugoslavic Republic of Macedonia, the Netherlands, Norway, Poland, Portugal, Romania, Serbia and Montenegro, Slovakia, Slovenia, Spain, Sweden, Switzerland and United Kingdom) as well as Australia, Canada, Israel, New Zealand and the USA. In GLOBOCAN 2002 incidence rates were estimated based on the best available data from national or regional cancer registries. Methods of estimation and correction for suspected under-recording have been described elsewhere.[11] We included only countries with more than 1 million inhabitants. Data on mother's average age at first birth in 1972, 1982, 1992 and 2002 or approximately the same period were retrieved from EUROSTAT[8] or National Statistics Institutes for non-European countries (table 3.1). In the United States, we only included data of non-Hispanic whites.

Table 3.1. Fertility pattern and relative excess risk of breast cancer by period

Countries	Average age at first birth (years)				Relative excess risk in 2002 (%)			
	1972	1982	1992	2002	All ages	Age group 15-44	Age group 45-54	Age group 55-64
Australia [a]	n.a.	25.5	28.0	30.2	49.9	46.9	50.4	59.5
Austria	n.a.	24.1 [c]	25.0	27.4	45.9	47.0	36.7	48.9
Belgium	24.3	24.9	26.7	27.6 [i]	59.1	59.8	58.9	59.3
Bulgaria	22.1	21.9	21.9	23.9	21.1	25.2	11.7	18.3
Canada	n.a.	24.9	26.0	27.7	48.0	43.7	47.8	57.5
Croatia	n.a.	23.5 [d]	24.7 [g]	25.9	37.5	37.1	34.7	40.5
Czech Republic	22.6	22.4	22.5	25.6	14.0	ref	27.6	37.4
Denmark	24.0	25.0	26.9	28.5 [j]	48.8	43.2	51.3	63.0
Estonia	23.9	23.3	22.8	24.6	19.4	19.2	21.5	17.8
Finland	24.6	25.4	26.7	27.6	48.2	42.7	59.6	56.6
France	24.3	25.3	27.4	27.9 [k]	57.4	56.7	58.8	61.2
Germany	24.1	25.4	26.9	28.6	49.6	47.7	50.2	54.5
Greece	n.a.	24.2	26.0	27.9	22.0	19.1	27.4	21.6
Hungary	22.7	22.6	23.3	25.6	29.3	21.9	36.2	41.6
Ireland	25.8	25.6	26.7	28.0	41.5	35.6	49.9	54.7
Italy	24.9	25.3	27.3	28.6 [l]	50.0	51.5	47.2	45.2
Israel	n.a.	n.a.	24.4 [h]	25.8	46.5	38.1	55.5	62.9
Latvia	n.a.	22.9	22.8	24.9	16.6	20.6	8.7	ref
Lithuania	n.a.	24.2	23.1	24.3	0.9	1.4	ref	0.1
Macedonia	n.a.	na	23.5	24.7	26.7	27.4	22.5	24.9
New Zealand	n.a.	25.6	28.4	30.4	55.3	53.7	52.2	66.4
Norway	n.a.	24.8 [e]	25.9	27.2	40.8	34.5	48.3	53.7
Poland	23.0	23.4	23.4	25.0	17.5	12.0	30.4	22.7
Portugal	n.a.	24.0	25.2	26.8	33.3	35.5	35.1	26.2
Romania	22.5	22.5	22.6	24.1	9.2	5.4	18.5	14.2
Serbia & Montenegro	n.a.	23.5 [f]	24.2	25.5	37.0	39.6	37.0	30.5
Slovakia	22.7	22.7	22.6	24.7	17.1	15.1	18.2	13.7
Slovenia	23.3	23.1	24.1	27.2	30.5	27.4	30.6	33.7
Spain	22.5	25.4	27.5	29.2	25.1	25.4	28.4	23.3
Sweden	26.0	25.6	26.7	28.3	47.6	41.3	51.8	64.6
Switzerland	25.4	26.5	27.8	29.0	51.1	50.4	44.3	57.4
The Netherlands	24.8	26.0	28.0	28.7	54.5	53.3	57.1	53.2
United Kingdom	24.1	25.4	27.8	29.3	52.7	50.1	54.2	58.5
United States [b]	n.a.	n.a.	25.1	26.1	52.9	48.1	51.3	64.6

n.a.: not available; ref: reference group; [a] median age at first birth within marriage; [b] data was not categorized by non-Hispanic white and Hispanic white before 1989; [c] data in 1984; [d] 1983; [e] median age at first birth within marriage in 1976-1980; [f] data in 1983; [g] data in 1993; [h] data in 1994; [i] data in 1997; [j] data in 2001; [k] data in 2000; [l] data in 1998

Statistical analysis

Incidence rates for breast cancer were calculated by five-year age groups and age-adjusted (world standard population) for truncated age categories (15-44, 45-54, 55-64 and 65+). Excess incidence was calculated by subtracting the lowest rate age-specific observed in the selected countries from the respective national rate. Incidence rate was lowest in Czech Republic for age group 15-44, in Lithuania for age groups 45-54 and 65+, and in Latvia for age group 55-64. Absolute numbers of excess cases were calculated by multiplying the excess incidence rates by the size of the population of the country of interest in the same period and age group.[13] Relative excess risk (RER) was calculated as the ratio of excess incidence and observed incidence in a country. We used the Pearson correlation coefficient to quantify the relationship between national RER and current as well as past average age of the mother at first birth. We also examined the correlation of age at first childbirth in 1972 and 1982, and 1992 with RER for those aged 45-54 and 15-44 years, respectively. We assumed that most women of 45-54 years in 2002 had their first childbirth between the 1970s and the 1980s. The age group 15-44 years mostly comprised breast cancer cases older than 35 years, who typically had their first childbirth in between the 1980s and the

1990s. In addition, we correlated RER for those aged 55-64 years in 2002 to average age at first child in 1972. These women most likely had their first child between 1965 and 1975. Correlation analysis was performed only with the year 1972, because data of the 60s were scarce. In order to take the large variation of population sizes of the included countries into account, correlation coefficients were weighted by population sizes in the respective age groups.

3.3. Results

The highest overall age-adjusted relative excess risk of breast cancer was found for Belgium, France, New Zealand and the Netherlands (59%, 57%, 55% and 54%), whereas the lowest was in Romania and Czech Republic (9% and 14%) (Table 3.1). Incidence rates for two age groups (45-54 and 65+ years) were lowest in Lithuania, which explains the low RER for this population (1%). In countries with the highest RER in 2002, the average age at first birth was 24-25 years in 1972, 25-26 years in 1982, 27-28 years in 1992 and 28-29 years in 2002. In contrast, mothers in countries with the lowest RER in 2002 had their first child at 23 years in 1972, 22-24 years both in 1982 and 1992 and 24-26 years in 2002 (Table 3.1). Figure 3.1 illustrates the correlations between RER in 2002 for 15-44 years, 45-54 years and 55-64 years with mean age at first child in 1972, 1982 and 1992. Mean age at first childbirth in 1982 and 1992 correlated closely with RER of breast cancer in 2002 for those aged 15 to 44 years (r: 0.81 and 0.75; p-value < 0.0001). Among 45 to 54 year old breast cancer cases, the corresponding correlations were 0.81 for 1972, and 0.76 for 1982. The correlation for average age at birth of first child in 1972 and RER for those aged 55 to 64 in 2002 was 0.77 (p-value < 0.0001). Finally, we found a decreasing magnitude of the correlation between RER in 2002 for 15+ years with increasing calendar year of mean age at first child (figure not shown); Pearson correlation coefficients (r) were 0.83 for 1972, 0.79 for 1982, 0.72 for 1992 and 0.61 for 2002 (p-value < 0.0001).

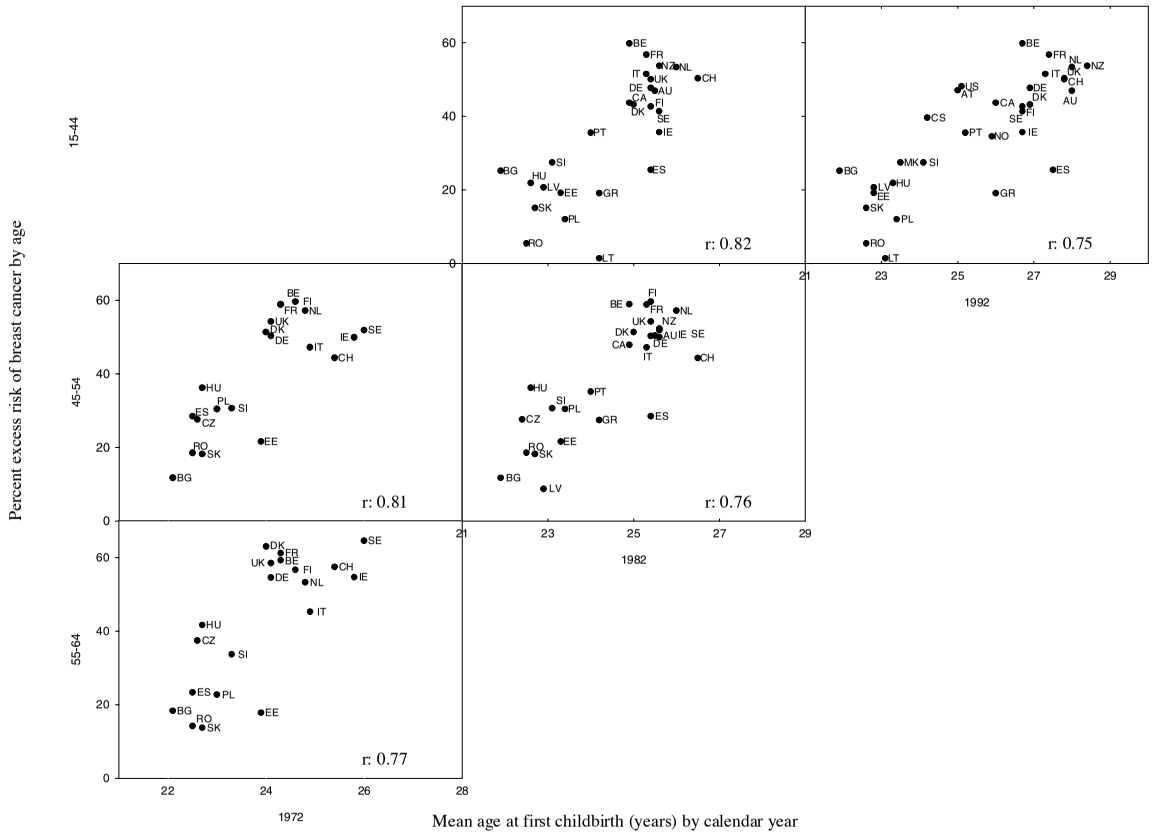

Figure 3.1. Plot of mother's average age at first birth and the percent excess risk of breast cancer among women in 2002, by age groups and calendar years.
AU: Australia, AT: Austria, BE: Belgium, BG: Bulgaria, HR: Croatia, CA: Canada, CZ: Czech Republic, DK: Denmark, EE: Estonia, FI: Finland, FR: France, DE: Germany, GR: Greece, HU: Hungary, IE: Ireland, IT: Italy, LV: Latvia, LT: Lithuania, MK: Macedonia, NZ: New Zealand, NO: Norway, PL: Poland, PT: Portugal, RO: Romania, CS: Serbia and Montenegro, SK: Slovakia, SL: Slovenia, ES: Spain, SE: Sweden, CH: Switzerland, NL: The Netherlands, UK: United Kingdom and US: United States of America

3.4. Discussion

We observed a strong correlation between the overall excess incidence of breast cancer in 2002 and the average age of the mother at first birth in 1972-2002. Both current and past average age at first childbirth were related with recent excess risk of breast cancer. The earliest period of exposure assessment correlated best with the current excess risk of breast cancer. For those aged about 40 at breast cancer diagnosis in 2002, mean age at first childbirth in 1982 and 1992 correlated closely with their excess risk. For those aged about 50 years at diagnosis, age at first birth in 1972 and in 1982 correlated with their current excess risk. Finally, for those aged about 60 years at diagnosis, age at first birth in 1972 strongly correlated with their current excess risk.

We determined excess breast cancer incidence as the difference between national incidence rates and the lowest observed rate. Hence, the relative excess in 2002 is supposed to be largely due to variations in external risk factors across populations, such as age at birth of first child, and hardly to genetic differences.[13] Though the latter may have played a interactive role, the prevalence of predisposing breast cancer genes is too low to explain these inter-population differences.[14] Our results are consistent with previous studies[15-17] and supported by biological evidence of the role of pregnancy in the pathogenesis of breast cancer.[18]

In affluent countries, the higher excess risk of breast cancer may be caused by practices of early detection and screening programs, especially among women over 50.[5] In such populations, age at first birth also tends to be higher. However, increasing breast cancer rates have also been observed in countries without national screening programs (e.g. Czech republic, Slovenia, Slovakia, Estonia and Norway).[5] Moreover, in countries where organized screening is present such as in the Netherlands and in Finland, increasing rates of breast cancer have been observed before the screening period.[5] Thus, it is unlikely that higher breast cancer rates in industrialized societies are entirely attributable to screening.

The excess of cases of breast cancer in 2002 reflects past exposure to multiple risk factors. Availability of comparable data on other risk factors is limited for most countries, and we were therefore unable to adjust for possible confounders, such as parity or duration of hormonal contraception use, which are also related to breast cancer risk.[19] Moreover as with any correlation study, observed correlations may be due to these other factors.[20] However, studies have shown that after correcting for other breast cancer risk factors such as oral contraceptive use and number of children, age at first birth remained an independent indicator of higher breast cancer risk among women who were older at birth of their first child.[17, 19]

We correlated average age of mother at first birth to breast cancer risk, hence our finding might not sufficiently apply to the increasing proportion of childless women with an even higher breast cancer risk.[21] The proportion of women still childless at age 40 might therefore be an indicator for the proportion of nulliparous and be used in the analysis to adjust for it. However historical data for this indicator is limited and when available (e.g. in 2002), [22] we found a very high correlation with average age at first birth (r: 0.90, data not shown). The observed correlation in this study thus partly reflects the risk of childless women; nations in

which women were older at delivery of their first child also comprise a higher proportion of childless women and a higher excess breast cancer risk.

We found the largest increase in age at first birth in countries with the highest relative risk of breast cancer between 1982-2002, being 3 to 4 years in the UK, the Netherlands, France Spain and Australia. By contrast, average age at first birth in countries like Bulgaria, Slovakia, Lithuania, Latvia and Poland hardly changed between 1982 and 1992, but increased by an average of 2 years between 1992 and 2002. Overall, the trend in postponing children seems to be continuing.[22] Despite some flattening in the Netherlands, postponement of childbearing is likely to be resumed, and mean age at first birth is predicted to increase up to 33 years.[23] A further increase of breast cancer incidence might be the result.

We observed a marked relationship between average age at first birth in 1972, 1982, and 1992 and excess risk among women diagnosed in 2002 with breast cancer aged 55-64, 45-54 and 15-44. Most women diagnosed with breast cancer at age 45 to 54 in 2002 probably had their first child 20-30 years before 2002, thus mostly around 1980. For age groups 15-44 and 55-64 years, year of first childbirth was mostly around 1990 and 1970, respectively. The correlation between RER in 2002 and age at first delivery is thus equally seen among pre-menopausal and post-menopausal breast cancer.[16] Furthermore, we observed the correlation to decrease with shorter time since exposure (age at first birth): the correlation between RER in 2002 for all age groups (15+) and mean age at first birth in 1972 was 0.83, continuously decreasing to 0.61 in 2002. Findings were similar across all age groups, suggesting a lag time of 20-30 years until variation in age at first birth is projected on the risk of breast cancer in the population.

What about the association between age at first birth in 1992 and 2002 and excess breast cancer risk in 2002? Most women who gave birth to their first child in 1992 or 2002 were too young to account for the association with breast cancer risk in 2002. However, risk factors for breast cancer are generally clustered more in countries with a high incidence of breast cancer.[16] For example; younger age at menarche (by 1.1 year) has been reported in countries with a high breast cancer risk, such as United States and Wales as opposed to Taiwan and Japan with a lower risk.[16] Similarly, lower parity and higher prevalence of nulliparity was observed in high breast cancer risk countries.[16] Furthermore, in countries with a higher risk of breast cancer higher body mass index was also observed,[16] possibly also reflecting the combination of a diet high in calories and lack of exercise. Finally, wider use of alcohol among women[24] and post-menopausal hormonal therapy[25, 26] are generally observed in more affluent regions, thus also in populations with a higher incidence of breast cancer. To summarize, older age at first child delivery probably is also a risk indicator of clustering of risk factors in western populations. This implies that a part of excess cases might be preventable by other means.

Basically, opportunities appear to be small of modifying some of the known risk factors for breast cancer, especially the timing of conceiving children. Delayed childbirth represents increasing educational opportunities and career choices for most women.[22] As a consequence, enhancing the potential for altering modifiable risk factors becomes even

more important: minimizing alcohol intake[27], avoiding weight gain by the combination of a balanced diet and enough physical activity[28] and promoting breast-feeding[29] should, to a certain extent, reduce the risk of breast cancer.

Acknowledgement

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References

1. Familial breast cancer: Collaborative reanalysis of individual data from 52 epidemiological studies including 58,209 women with breast cancer and 101,986 women without the disease. *Lancet*. 2001;358:1389-1399
2. Colditz GA, Rosner B. Cumulative risk of breast cancer to age 70 years according to risk factor status: Data from the nurses' health study. *Am J Epidemiol*. 2000;152:950-964
3. Ravdin PM, Cronin KA, Howlader N, Berg CD, Chlebowski RT, Feuer EJ, Edwards BK, Berry DA. The decrease in breast-cancer incidence in 2003 in the united states. *N Engl J Med*. 2007;356:1670-1674
4. Dano H, Hansen KD, Jensen P, Petersen JH, Jacobsen R, Ewertz M, Lynge E. Fertility pattern does not explain social gradient in breast cancer in denmark. *Int J Cancer*. 2004;111:451-456
5. Botha JL, Bray F, Sankila R, Parkin DM. Breast cancer incidence and mortality trends in 16 european countries. *Eur J Cancer*. 2003;39:1718-1729
6. Pisani P. Avoidable cancer in europe: Estimating etiologic fractions. Final report to the european commission. 2000
7. Layde PM, Webster LA, Baughman AL, Wingo PA, Rubin GL, Ory HW. The independent associations of parity, age at first full term pregnancy, and duration of breastfeeding with the risk of breast cancer. Cancer and steroid hormone study group. *J Clin Epidemiol*. 1989;42:963-973
8. Statistical office of the European Communities. 1995-2006. http://epp.eurostat.ec.europa.eu/portal/page?_pageid=1090,30070682,1090_33076576&_dad=portal&_schema=PORTAL
9. Althuis MD, Dozier JM, Anderson WF, Devesa SS, Brinton LA. Global trends in breast cancer incidence and mortality 1973-1997. *Int J Epidemiol*. 2005;34:405-412
10. Eurocadet: Towards less cancer in europe. http://www.eurocadet.org 2005
11. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. *CA Cancer J Clin*. 2005;55:74-108
12. National Cancer Institute. Seer*stat software, version 5.3.1. Surveillance research program.;2006
13. Soerjomataram I, de Vries E, Pukkala E, Coebergh JW. Excess of cancers in europe: A study of eleven major cancers amenable to lifestyle change. *Int J Cancer*. 2006
14. Narod SA. Modifiers of risk of hereditary breast cancer. *Oncogene*. 2006;25:5832-5836
15. Pisani P. Breast cancer: Geographic variation and risk factors. *J Environ Pathol Toxicol Oncol*. 1992;11:313-316
16. Pathak DR, Whittemore AS. Combined effects of body size, parity, and menstrual events on breast cancer incidence in seven countries. *Am J Epidemiol*. 1992;135:153-168
17. Chie WC, Hsieh C, Newcomb PA, Longnecker MP, Mittendorf R, Greenberg ER, Clapp RW, Burke KP, Titus-Ernstoff L, Trentham-Dietz A, MacMahon B. Age at any full-term pregnancy and breast cancer risk. *Am J Epidemiol*. 2000;151:715-722
18. Russo J, Mailo D, Hu YF, Balogh G, Sheriff F, Russo IH. Breast differentiation and its implication in cancer prevention. *Clin Cancer Res*. 2005;11:931s-936s
19. Breast cancer and hormonal contraceptives: Collaborative reanalysis of individual data on 53 297 women with breast cancer and 100 239 women without breast cancer from 54 epidemiological studies. Collaborative group on hormonal factors in breast cancer. *Lancet*. 1996;347:1713-1727
20. Morgenstern H. Uses of ecologic analysis in epidemiologic research. *Am J Public Health*. 1982;72:1336-1344
21. Anderson WF, Matsuno RK, Sherman ME, Lissowska J, Gail MH, Brinton LA, Yang XR, Peplonska B, Chen BE, Rosenberg PS, Chatterjee N, Szeszenia-Dabrowska N, Bardin-Mikolajczak A, Zatonski W, Devesa SS, Garcia-Closas M. Estimating age-specific breast cancer risks: A descriptive tool to identify age interactions. *Cancer Causes Control*. 2007;18:439-447
22. Billari FC, Liefbroer AC, Philipov D. The postponement of childbearing in europe: Driving forces and implications. *Vienna Yearbook of population Research 2006*. 2006:1-17
23. Goldstein JR. How late can first births be postponed? Some illustrative population-level calculations. *Vienna Yearbook of Population Research*. 2006:153-165
24. Sieri S, Agudo A, Kesse E, Klipstein-Grobusch K, San-Jose B, Welch AA, Krogh V, Luben R, Allen N, Overvad K, Tjonneland A, Clavel-Chapelon F, Thiebaut A, Miller AB, Boeing H, Kolyva M, Saieva C, Celentano E, Ocke MC, Peeters PH, Brustad M, Kumle M, Dorronsoro M, Fernandez Feito A, Mattisson I, Weinehall L, Riboli E, Slimani N. Patterns of alcohol consumption in 10 european countries

participating in the european prospective investigation into cancer and nutrition (epic) project. *Public Health Nutr*. 2002;5:1287-1296

25. Keating NL, Cleary PD, Rossi AS, Zaslavsky AM, Ayanian JZ. Use of hormone replacement therapy by postmenopausal women in the united states. *Ann Intern Med*. 1999;130:545-553
26. Bernstein L, Allen M, Anton-Culver H, Deapen D, Horn-Ross PL, Peel D, Pinder R, Reynolds P, Sullivan-Halley J, West D, Wright W, Ziogas A, Ross RK. High breast cancer incidence rates among california teachers: Results from the california teachers study (united states). *Cancer Causes Control*. 2002;13:625-635
27. Hamajima N, Hirose K, Tajima K, Rohan T, Calle EE, Heath CW, Jr., Coates RJ, Liff JM, Talamini R, Chantarakul N, Koetsawang S, Rachawat D, Morabia A, Schuman L, Stewart W, Szklo M, Bain C, Schofield F, Siskind V, Band P, Coldman AJ, Gallagher RP, Hislop TG, Yang P, Kolonel LM, Nomura AM, Hu J, Johnson KC, Mao Y, De Sanjose S, Lee N, Marchbanks P, Ory HW, Peterson HB, Wilson HG, Wingo PA, Ebeling K, Kunde D, Nishan P, Hopper JL, Colditz G, Gajalanski V, Martin N, Pardthaisong T, Silpisornkosol S, Theetranont C, Boosiri B, Chutivongse S, Jimakorn P, Virutamasen P, Wongsrichanalai C, Ewertz M, Adami HO, Bergkvist L, Magnusson C, Persson I, Chang-Claude J, Paul C, Skegg DC, Spears GF, Boyle P, Evstifeeva T, Daling JR, Hutchinson WB, Malone K, Noonan EA, Stanford JL, Thomas DB, Weiss NS, White E, Andrieu N, Bremond A, Clavel F, Gairard B, Lansac J, Piana L, Renaud R, Izquierdo A, Viladiu P, Cuevas HR, Ontiveros P, Palet A, Salazar SB, Aristizabel N, Cuadros A, Tryggvadottir L, Tulinius H, Bachelot A, Le MG, Peto J, Franceschi S, Lubin F, Modan B, Ron E, Wax Y, Friedman GD, Hiatt RA, Levi F, Bishop T, Kosmelj K, Primic-Zakelj M, Ravnihar B, Stare J, Beeson WL, Fraser G, Bullbrook RD, Cuzick J, Duffy SW, Fentiman IS, Hayward JL, Wang DY, McMichael AJ, McPherson K, Hanson RL, Leske MC, Mahoney MC, Nasca PC, Varma AO, Weinstein AL, Moller TR, Olsson H, Ranstam J, Goldbohm RA, van den Brandt PA, Apelo RA, Baens J, de la Cruz JR, Javier B, Lacaya LB, Ngelangel CA, La Vecchia C, Negri E, Marubini E, Ferraroni M, Gerber M, Richardson S, Segala C, Gatei D, Kenya P, Kungu A, Mati JG, Brinton LA, Hoover R, Schairer C, Spirtas R, Lee HP, Rookus MA, van Leeuwen FE, Schoenberg JA, McCredie M, Gammon MD, Clarke EA, Jones L, Neil A, Vessey M, Yeates D, Appleby P, Banks E, Beral V, Bull D, Crossley B, Goodill A, Green J, Hermon C, Key T, Langston N, Lewis C, Reeves G, Collins R, Doll R, Peto R, Mabuchi K, Preston D, Hannaford P, Kay C, Rosero-Bixby L, Gao YT, Jin F, Yuan JM, Wei HY, Yun T, Zhiheng C, Berry G, Cooper Booth J, Jelihovsky T, MacLennan R, Shearman R, Wang QS, Baines CJ, Miller AB, Wall C, Lund E, Stalsberg H, Shu XO, Zheng W, Katsouyanni K, Trichopoulou A, Trichopoulos D, Dabancens A, Martinez L, Molina R, Salas O, Alexander FE, Anderson K, Folsom AR, Hulka BS, Bernstein L, Enger S, Haile RW, Paganini-Hill A, Pike MC, Ross RK, Ursin G, Yu MC, Longnecker MP, Newcomb P, Kalache A, Farley TM, Holck S, Meirik O. Alcohol, tobacco and breast cancer--collaborative reanalysis of individual data from 53 epidemiological studies, including 58,515 women with breast cancer and 95,067 women without the disease. *Br J Cancer*. 2002;87:1234-1245
28. Lahmann PH, Friedenreich C, Schuit AJ, Salvini S, Allen NE, Key TJ, Khaw KT, Bingham S, Peeters PH, Monninkhof E, Bueno-de-Mesquita HB, Wirfalt E, Manjer J, Gonzales CA, Ardanaz E, Amiano P, Quiros JR, Navarro C, Martinez C, Berrino F, Palli D, Tumino R, Panico S, Vineis P, Trichopoulou A, Bamia C, Trichopoulos D, Boeing H, Schulz M, Linseisen J, Chang-Claude J, Chapelon FC, Fournier A, Boutron-Ruault MC, Tjonneland A, Fons Johnson N, Overvad K, Kaaks R, Riboli E. Physical activity and breast cancer risk: The european prospective investigation into cancer and nutrition. *Cancer Epidemiol Biomarkers Prev*. 2007;16:36-42
29. Shantakumar S, Terry MB, Teitelbaum SL, Britton JA, Millikan RC, Moorman PG, Neugut AI, Gammon MD. Reproductive factors and breast cancer risk among older women. *Breast Cancer Res Treat*. 2007;102:365-374

Chapter 4

Does the decrease in hormone-replacement therapy also affect breast cancer risk in the Netherlands?

Soerjomataram I, Louwman M, Visser O, van Leeuwen FE, Coebergh JWW. Does the decrease in hormone-replacement therapy also affect breast cancer risk in the Netherlands? Journal of Clinical Oncology (*in press*)

Recently Robbins and Clarke reported a sharp decrease in the incidence rate of first primary breast cancer in women over 50 years in the United States, which was attributed to a decrease in hormone-replacement therapy (HRT) since 2001[1], consistent to an earlier study that was also done in the United States.[2] Although there was a similar decrease in HRT across Europe, such a remarkable decline in breast cancer rates has only been reported in Germany.[3] Generally, women in Europe have shown a different pattern of HRT use than the USA, mostly less frequent use and of shorter durations.[4, 5] Only 13% of women aged 49-70 years used HRT in the Netherlands between 1993 and 1997,[5] versus 38% in the USA.[4] In the Netherlands HRT use decreased by 12 % between 2002 and 2003, followed by another 26% between 2003 and 2004. By the end of 2005 there was a decrease of 42% as compared to 2001 of combined estrogen-progesterone and natural and semi-organic estrogen use. However the rate of first primary breast cancer among women aged 50-69 in the northwestern and southeastern Netherlands has not changed up till 2005 (figure 4.1). The impact of the sudden fall of HRT use would account for about a 6% fall of breast cancer incidence in the US versus only 0.4% in the Netherlands, using the following formula (p-p*)(RR-1)/(p(RR-1)+1)[6] (p=past prevalence, p*=current prevalence and RR=relative risk:1.07 for the Netherlands for duration of use <5 years and 1.25 for the USA for duration of use ≥5 years[7]). A similar small impact of decrease in HRT use on the breast cancer incidence is expected in Spain or Italy with a low use (5%-8%), contrasting countries with a high use such as Belgium or France (32%-38%).[4] There is however another pitfall, HRT use has been related to increased breast density, thus reducing the specificity of mammography and delaying detection of 20% of breast cancer cases.[8] The maximum benefit of HRT reduction should be evident within the next 2 years (data until 2007) in the Netherlands where biannual mass screening with more than 80% attendance rate is being practiced since the early 90's, and might take longer in the USA having only opportunistic screening with lower coverage/attendance rate.

The two cancer registries involved have proven to be a valuable source of data.[9] Currently, only a flattening of the 40-year rising trend in breast cancer incidence following the decrease of HRT use has been observed, warranting more years of observation.

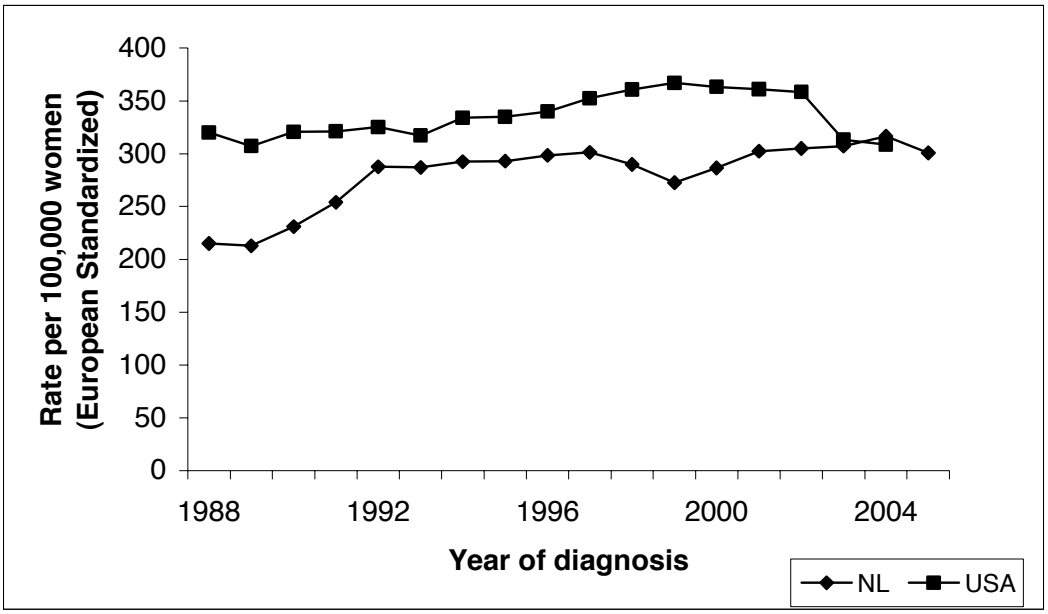

Figure 4.1. Annual Incidence of Female Breast cancer between the Ages of 50 and 69 Years in the Netherlands and in the United States.
US data are from nine of the SEER registries and Netherlands data are from two registries (northwest and southeast Netherlands). Data of the Netherlands for 2004-2005 (northwest) and 2003-2005 (southeast) are corrected for extra regional cases by adding the average number of extra regional cases in preceding years. Rates were age adjusted to the European standard population.

Acknowledgements

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References

1. Robbins AS, Clarke CA. Regional changes in hormone therapy use and breast cancer incidence in california from 2001 to 2004. *J Clin Oncol*. 2007
2. Ravdin PM, Cronin KA, Howlader N, Berg CD, Chlebowski RT, Feuer EJ, Edwards BK, Berry DA. The decrease in breast-cancer incidence in 2003 in the united states. *N Engl J Med*. 2007;356:1670-1674
3. Katalinic A, Rawal R. Decline in breast cancer incidence after decrease in utilisation of hormone replacement therapy. *Breast Cancer Res Treat*. 2007
4. Lundberg V, Tolonen H, Stegmayr B, Kuulasmaa K, Asplund K. Use of oral contraceptives and hormone replacement therapy in the who monica project. *Maturitas*. 2004;48:39-49
5. van Duijnhoven FJ, van Gils CH, Bezemer ID, Peeters PH, van der Schouw YT, Grobbee DE. Use of hormones in the menopausal transition period in the netherlands between 1993 and 1997. *Maturitas*. 2006;53:462-475
6. Murray CJ, Ezzati M, Lopez AD, Rodgers A, Vander Hoorn S. Comparative quantification of health risks conceptual framework and methodological issues. *Popul Health Metr*. 2003;1:1
7. Breast cancer and hormone replacement therapy: Collaborative reanalysis of data from 51 epidemiological studies of 52,705 women with breast cancer and 108,411 women without breast cancer. Collaborative group on hormonal factors in breast cancer. *Lancet*. 1997;350:1047-1059
8. Kavanagh AM, Mitchell H, Giles GG. Hormone replacement therapy and accuracy of mammographic screening. *Lancet*. 2000;355:270-274
9. Comprehensive Cancer Centres. http://www.ikcnet.nl. Accessed June 2007.

Chapter 5

An overview of prognostic factors for long-term survivors of breast cancer

Soerjomataram I, Louwman MW, Ribot JG, Roukema JA, Coebergh JWW. An overview of prognostic factors for long-term survivors of breast cancer. *Breast Cancer Res Treat.* 2007.

Abstract

Background and objectives: Numerous studies have examined prognostic factors for survival of breast cancer patients, but relatively few have dealt specifically with 10+-year survivors.

Methods: A review of the PubMed database from 1995 to 2006 was undertaken with the following inclusion criteria: median/mean follow-up time at least 10 years; overall survival and/or disease-specific survival known; and relative risk and statistical probability values reported. In addition, we used data from the long-standing Eindhoven cancer registry to illustrate survival probability as indicated by various prognostic factors.

Results: 10-year breast cancer survivors showed 90% 5-year relative survival. Tumor size, nodal status and grade remained the most important prognostic factors for long-term survival, although their role decreased over time. Most studies agreed on the long-term prognostic values of MI (mitotic index), LVI (lymphovascular invasion), Her2-positivity, gene profiling and comorbidity for either all or a subgroup of breast cancer patients (node-positive or negative). The roles of age, socioeconomic status, histological type, BRCA and p53 mutation were mixed, often decreasing after correction for stronger prognosticators, thus limiting their clinical value. Local and regional recurrence, metastases and second cancer may substantially impair long-term survival. Healthy lifestyle was consistently related to lower overall mortality.

Conclusions: Effects of traditional prognostic factors persist in the long term and more recent factors need further follow-up. The prognosis for breast cancer patients who have survived at least 10 years is favorable and increases over time. Improved long-term survival can be achieved by earlier detection, more effective modern therapy and healthier lifestyle.

5.1. Introduction

Breast cancer (BC) is the most common cancer among women, with a lifetime risk of up to 12% and a risk of death of up to 5%.[1] Its incidence has been increasing but after a period of continuous rise in many industrialized countries BC mortality has been stable or has even decreased in the last 10-15 years.[2, 3] The introduction of mass mammographic screening programmes also resulted in earlier detection and diagnosis of small and less aggressive tumours. This, in combination with therapeutic improvements, has led to a substantial increase in breast cancer survivors over the last few decades (figure 5.1). A long-term survivor is commonly defined as a person who is still alive 5 years after cancer diagnosis.[4] For breast cancer, the relative survival at five and ten years after diagnosis is 88% and 77%, respectively, both substantially higher than the 5-year relative survival of all cancers together (64%).[4] Thus, it seems logical to consider factors known to play an important role in predicting 5-year survival of BC patients and to question their importance in survival 10 years after diagnosis and even longer. Furthermore, in recent years major advances in the prognostic value of several molecular markers have been achieved, hence the need to incorporate this data into our current knowledge. Therefore, we have summarized available knowledge on the determinants of survival 10 years or more after breast cancer diagnosis. We supported our analyses and considerations with data from the population-based, long-standing Eindhoven cancer registry in the Netherlands.

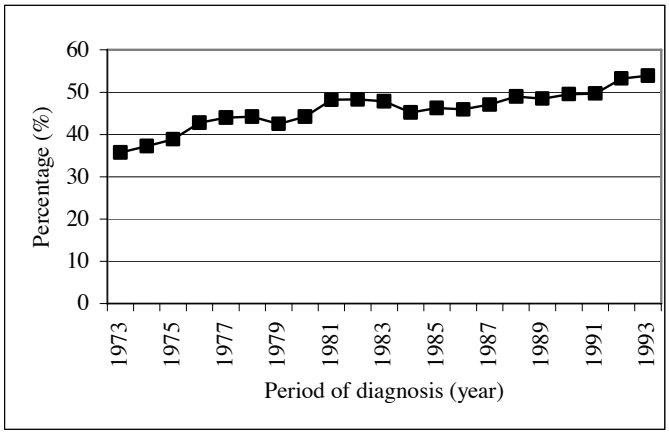

Fig. 5.1. Proportion of breast cancer patients (3-year moving average) diagnosed between 1973 and 1993 who survived 10 years or longer in Southeastern Netherlands

5.2. Methods

We initially searched PubMed, using the search MESH term for 'breast neoplasms' AND 'prognoses' AND 'long-term'. Only papers published in English between 1995 and 2006 (September) which researched female adults (19+ years) were included. We retrieved 528 articles and studied the abstracts (sometimes also the methods section). We selected only articles that assess or show the results for those surviving 10 years or longer with cohorts having a mean/median follow-up of 10 years or longer. If mean/median follow-up time was not reported, we examined the proportion of patients who survived 10 years after diagnosis, and this ought to be larger than 50%. If, for a specific topic of interest, no relevant studies with a follow-up of at least 10 years were found (such as BRCA mutation or gene profiling, which have been studied only during the last decade), then studies with the longest available follow-up were chosen. Furthermore, the following inclusion criteria were used: overall and/or breast cancer-specific survival was reported; relative risk or hazard rate and statistical probability values were given; at least 250 BC patients included at the beginning of study. We also searched the reference lists collected by this search strategy and selected those that were relevant to both our study question and inclusion criteria (list of studies, table 5.1). Reviews and books that gave general overviews were also included in the reference list.

We present data from the Eindhoven Cancer Registry (ECR) to illustrate the role of factors such as age, tumour size, lymph node involvement and time since diagnosis. Within the Netherlands, ECR is unique because it has collected follow-up data since 1970, including clinical aspects of cancer patients. This is a population-based cancer registry covering a population of almost 2.4 million people in 2004.[5] Cumulative survival proportion was calculated using the Kaplan Meier method. Relative survival was calculated by comparing the survival of breast cancer patients to the general population.

Throughout the text the term long-term and/or survival will frequently be mentioned; this corresponds to at least 10-year survival unless otherwise indicated.

5.3. Results and discussions

5.3.1. Determinants of survival breast cancer 10 years or longer

Patient characteristics

Age at diagnosis

Very young women, i.e. younger than 30/35 years,[6, 7] exhibited a particularly poor survival as do those older than 70 (figure 5.2).[8, 9] Young BC patients were more likely to have a more negative clinical presentation, such as affected lymph nodes, negative for oestrogen receptors, and have large tumour with a high fraction of p53 nuclei and overexpression of c-erb-2 oncoprotein.[6, 10, 11] However, current adjuvant treatment seems to diminish the poor prognostic value of young age;[6] young women who did not receive adjuvant treatment had a significantly increased risk of dying; those diagnosed at 35-39 years and <35 years had a 1.4 and 2.2 higher risk of death, respectively, compared to those of 45-49 years.[6] Older patients exhibited higher mortality rates,[12] probably because of less extensive treatment (either related to advanced age itself or the presence of serious concomitant diseases (comorbidity)).[13]

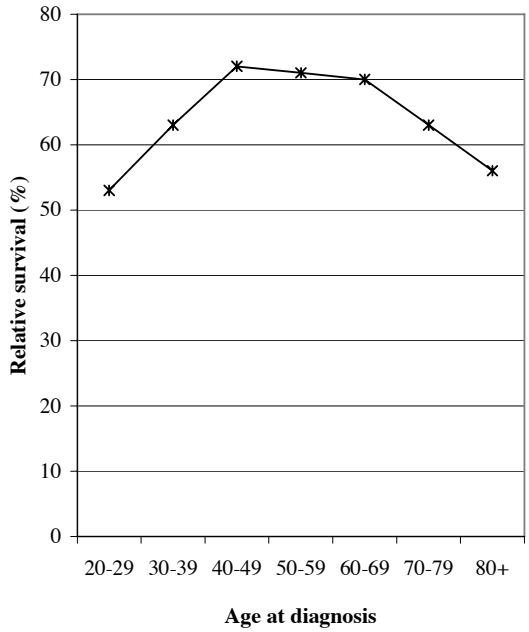

Fig. 5.2. Relative survival of breast cancer patients (n: 13,279) diagnosed in 1990–2002 and followed until 2004, according to age at diagnosis in southeastern Netherlands

Comorbidity

Concurrent health conditions (comorbidity) at the time of BC diagnosis have a significant impact on early[13] as well as long-term survival of BC patients.[12] The most prevalent conditions were cardiovascular disease (7%), previous cancer (7%) and diabetes mellitus (6%), all becoming more common with increasing age.[13] Compared to those without comorbidity whose 5-year relative survival was 87%, those with diabetes mellitus or cardiovascular disease represented 78% and 83% of the respective survival estimates.[13] Patients with severe comorbidity exhibited a 2.7-3.4 higher risk of death in 10 years compared to those without comorbidity.[12, 14]

Period of diagnosis

Access to care and treatment of BC has improved over time in most industrialized countries, which is reflected in the higher long-term survival of BC cases across all age groups and the tumour characteristics of those diagnosed more recently.[15-18] In Finland, relative survival 10 years after diagnosis among patients younger than 50 years increased from 49% for those diagnosed in 1953-1959 to 68% for the 1983-1989 cohort.[15] Furthermore, 60% of node-positive BC patients diagnosed in 1978–1979 in Italy survived 10 years or longer compared to the 50% probability 10-year survival for those diagnosed in 1968–1969.[17] In addition, changes in BC diagnosis, e.g. screening[19, 20] and better staging[17], may partly be responsible for the observed increase in the proportion of survivors.

Time after diagnosis

The longer a woman survives BC the more the prognosis improves, illustrated by conditional survival.[16, 21] Probably the subgroup of patients who survived longer had less aggressive tumours due to a different genetic make-up or better life-style. In Australia, 79% of women with localized BC survived 10 years after diagnosis, yet among those still alive 5 years after diagnosis 84% had a 10-year survival.[16] The respective values for regional vs. advanced BC were 53% and 68%.[16] Unlike other cancers, relative conditional survival remained stable below 100% after 12 years of survival and decreased again after about 19 years (figure 5.3).[5] This may be a consequence of late recurrences and metastases, second cancers or late side-effects of treatment.[23]

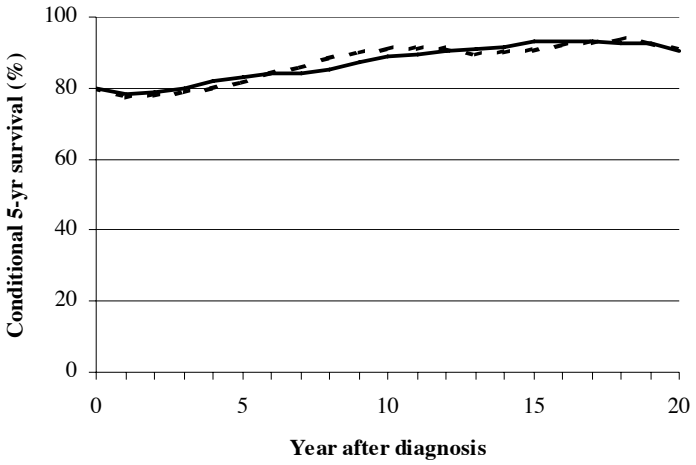

Fig. 5.3. Conditional 5-year relative survival (calculated using period analysis [22] of breast cancer patients diagnosed in southern Netherlands in 1985–2002 and followed until 2004, according to age. (Dashed line): diagnosed at 25–49 years, (solid line): diagnosed at 50–74 years

Socioeconomic status (SES) and race

A population-based study of breast cancer patients diagnosed in 1968-1999 in France showed a diminishing role of SES on excess mortality among women with BC over these periods.[24] Long-term follow-up studies reported that women with BC from low social classes had a 20-50% poorer survival compared to patients from higher social classes,[25, 26] although others contradicted this.[27] Low SES patients were more likely to be diagnosed at a later stage, had more aggressive tumour characteristics and might have received sub-optimal treatment. However, differences in these prognostic factors did not fully explain the variation in survival according to social class.[25] This is also the case when breast cancer survival is studied according to race/ethnicity. Ten years after treatment 58% of African Americans were still alive compared to 66% of the white Americans. After adjusting for other prognostic factors, 41% excess mortality from all causes was still observed among African Americans compared to caucasians.[28] This suggests other residual factors such as lifestyle (higher body weight was observed among African Americans), comorbidity,[14] genetics or variation in the delivery of treatment, which influence outcome beyond variation in tumour aggressiveness.[29]

Tumour-related characteristics

Tumour size

Tumour size is one of the strongest prognostic indicators (figure 5.4),[7, 30] even after 20 years of follow-up.[8, 31] A larger tumour has been related to more positive lymph nodes,[32] thus their interaction further influences the survival from BC. Nonetheless, the independence of survival by node status is shown by the lower 10-year overall survival rate found for node-negative patients with a tumour of 2-5 cm compared to those with a tumour smaller than 1 cm, 66% vs. 79%, respectively.[33]

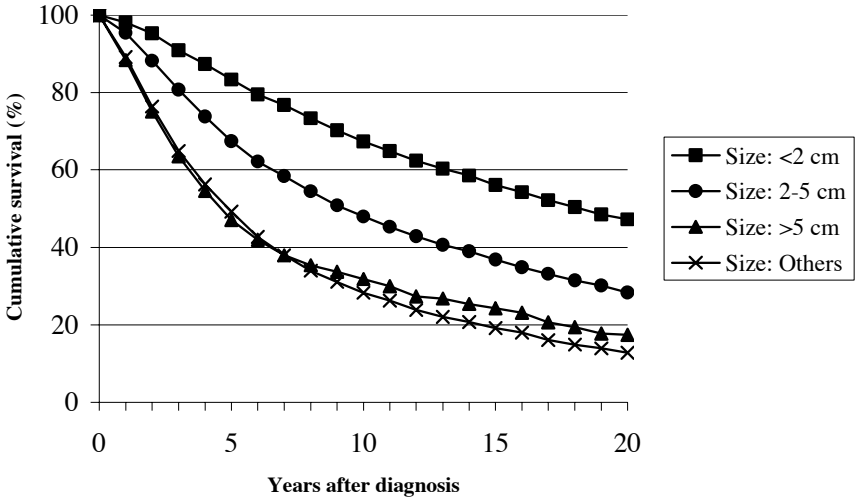

Fig. 5.4. Cumulative survival proportion of breast cancer patients diagnosed in southern Netherlands in 1970–1994 and followed until 2004, according to tumor size (based on pathological diagnosis). ■ tumor size: <2 cm (n: 3263) • tumor size: 2–5 cm (n: 3420) □ tumor size: >5 cm (n: 474) x tumor size: involvement of skin (n: 1133) and unknown/not applicable tumor size: 1410

Histological type

The prognostic value of histological type can be grouped into four: excellent, good, poor and very poor prognosis.[34] BC with an excellent prognosis, such as invasive cribriform, tubular[35], tubulo-lobular and mucinous [36, 37] showed >80% survival at 10 years.[9] Tubular mixed, mixed ductal with special type, atypical medullary[38] and alveolar lobular carcinoma have a good prognosis with a 60-80% 10-year survival. Those with invasive papillary, classic lobular and medullary cancers have a worse prognosis. Finally, 10-year survival among those with ductal, solid lobular, mixed ductal and lobular carcinoma is below 50%.[34] In most populations infiltrating ductal carcinoma covers about 70% of all diagnoses.[36, 39] Inflammatory BC has a particularly poor prognosis: about 30% survived 10 years.[40]

Histological grade

The most widely used grading systems are Scarff-Bloom-Richardson classification, Fisher grading nuclear system and Nottingham Combined Histologic Grade (NCHG).[41] The validity of grading has been subjected to inter-observer reproducibility and subjectivity.[42] However, higher grades have been quite consistently associated with lower long-term survival.[7, 8, 31, 43-45] Depending on other prognostic factors, such as nodal status or tumour size,[46, 47] cumulative survival among patients with the lowest score was 90-94% 10 years after diagnosis and 30-78% among those with the highest score.[37, 48]

Regional lymph node involvement

Lymph node involvement is a valuable indicator of long-term survival (figure 5.5).[8, 32] Node- positive patients have about a 4-8 times higher mortality than those without nodal involvement.[8, 9, 49] The more nodes involved the worse the prognosis. Prognosis for patients with 10 or more involved axillary nodes showed 70% more deaths at 10 years than for those with 1-3 involved nodes.[32] The survival of node-positive patients improved due to better staging procedures and application of systemic treatment.[7, 31, 50]

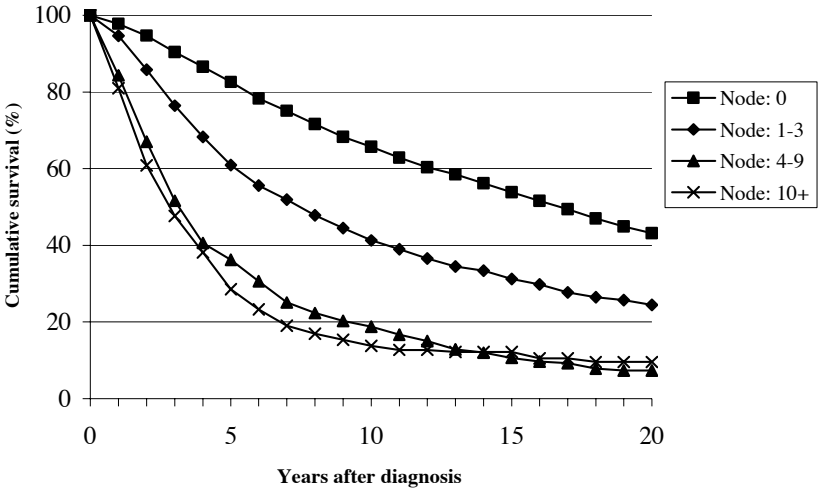

Fig. 5.5. Cumulative survival proportion of breast cancer patients diagnosed in southern Netherlands in 1970–1994 and followed until 2004, according to nodal status (based on pathological diagnosis). ■ node negative (n: 4452) • node status: 1–3 positive nodes (n: 3266) □ node status: 4–9 positive nodes (n: 255) x node status: 10+ positive nodes (n: 189), unknown/not applicable node status: 1538

Lymphovascular invasion (LVI) and molecular markers of tumours angiogenesis

At the St. Gallen meeting in 2005, LVI was added to the prognostics for node-negative patients.[51] Compared to patients having no LVI, a 60% higher breast cancer mortality was observed for node-negative BC patients having positive LVI,[52, 53] although others did not observe the independent role of LVI.[46, 50] In this line of research, studies have also focused on the value of microvessel density,[44] blood invasion (BVI)[54] and markers of angiogenesis (VEGFR (vascular endothelial growth factor receptor), CD105, Tie-2)[55, 56] in predicting long-term survival of BC patients, although the results are still conflicting.

Grouped prognostic factors

Some of the prognostic factors have been combined into a prognostic index, such as the TNM classification, as shown by the data of the ECR (figure 5.6), and also the more current Nottingham Prognostic Index (NPI), both highly predictive for estimating long-term survival.[41] TNM staging consists of information on primary tumour size, involvement of the regional lymph node and the presence of distant metastasis. Only 53% of patients with regional or locally advanced BC had survived 10 years after diagnosis compared to79% of those with localised BC[16]. Patients with metastasis (stage: M1) at diagnosis exhibited very poor 10-year survival (3.4%).[57]

Tumour size, grade and lymph node status make up the NPI.[11, 46, 49] In a large series of 2879 BC patients, 10-year survival proportion was 85% for those with the lowest NPI score and 19% for those with the highest score.[11]

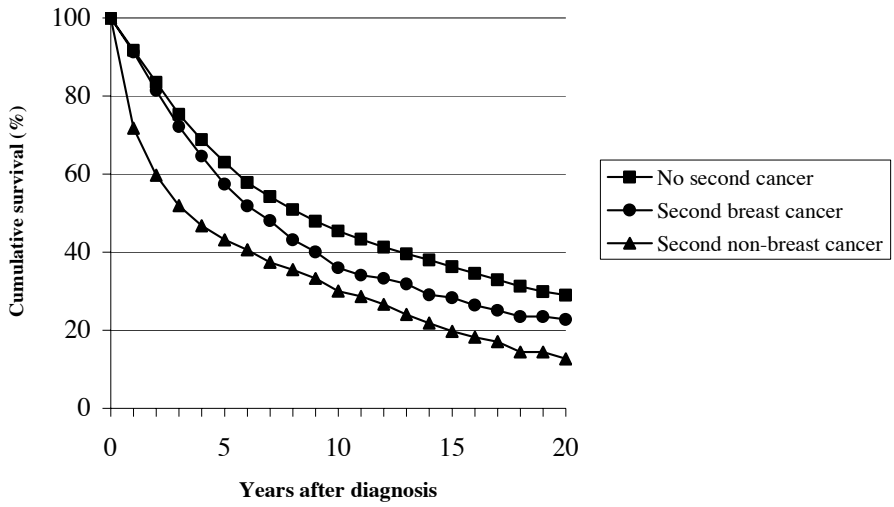

Fig. 5.6. Cumulative survival of breast cancer patients diagnosed in southern Netherlands in 1970–1994 and followed-up until 2004, according to second cancer. Follow-up for patients with second cancer begins at the date of second cancer diagnosis. ■ no second cancer (n: 8137) • second breast cancer (n: 744) □ second non-breast cancer (n: 819)

Recurrence, metastasis and second cancer

Patients with recurrent, metastasized or second cancer generally exhibited lower long-term survival than those without.[9, 21, 58-61] Ten years after surgery, the probability for survival for another 10 years, thus 20 years after diagnosis, for node-negative patients aged ≥45 years, tumour ≤1 cm, grade 1 and without a recurrence or metastasis was 0.89. If a recurrence occurred, the probability of being alive at 20 years dropped to 0.72. If a metastasis was observed the probability of survival was only 0.18.[21] The prognosis decreases with larger primary tumour size, nodal involvement,[62] higher grade,[21] early recurrence (within 5 years of surgery)[63], location of recurrence (regional rather than local ipsilateral)[59] and inadequate primary cancer treatment.[9, 64] In the dataset of the ECR, overall survival was better for women without second primary tumours than for women who developed a new primary cancer (figure 5.6). Only 68% of early BC patients with second malignancies had survived 10 years of follow-up compared to 78% of those without multiple cancers.[65] Younger breast cancer patients are reported to have poorer survival and a higher risk of second cancer.[59] Corrected for race and grade, women in the 20-29 year old category who had a second breast cancer had a probability of 10-year survival probability of only 23% compared to 57% for those without multiple cancers.

Other tumour markers

Hormone Receptors

The presence of hormone receptors such as oestrogen (ER) and progesterone (PR) receptors predicts the long-term outcome of hormonal therapy,[66] thus they have been more commonly used as a predictive marker rather than as a prognostic marker. Thus given a particular treatment, e.g. tamoxifen, ER-positive patients have a considerably better prognosis than ER-negative patients. The prognostic value is weak[30, 43] or negligible,[37] particularly in the early years after diagnosis.[67]

HER-2 expression

Node-positive patients with BC cells showing amplification of the gene for human epidermal growth factor receptor type 2 (HER2), and/or overexpression of its product had a lower 10-year overall survival proportion, 50% versus 65% for those without HER2 amplification.[17, 68] After 10 years the difference in survival persisted, although it became somewhat smaller.[17] Tumours that overexpress HER2 are more likely to contain p53 abnormalities, to be hormone receptor- and bcl-2-negative and to have lymphoid infiltration and a high mitotic index, all known to be markers of poor prognosis for breast cancer.[17, 69, 70] As for patients with node- negative tumours, HER2 did not seem to affect long-term survival significantly.[17, 37, 69] HER-2 expression has been valuable in predicting treatment responses to trastuzumab, certain endocrine therapies and chemotherapy, adding to it's role as a predictive marker.[68]

MAI (Mitotic Activity Index)

MAI is an indicator of tumour proliferative activity that represents the mitotic activity in a given area of the tumour. Combined with another prognostic factor (NCHG), MAI has proven to be an accurate tool for assessment of long-term survival.[48] In a population-based study women with node-negative tumours < 5 cm and a MAI ≥ 10 exhibited 80% survival at 10 years compared to 90% for an MAI <10.[71]

Gene expression profile

A very promising new finding is the microarrays method, in which a set of intrinsic genes is clustered and segregated into major subgroups; BC with a good and poor prognosis profile is correlated to the probability of distant metastases[72] or a tumour with basal or luminal characteristics which are strongly associated with ER status.[73] In a study of 295 patients diagnosed with stage I or II breast cancer, those classified as having a good prognosis profile had a 95% overall 10-year survival rate compared to 55% for those with a poor profile.[74] This classification predicted outcome regardless of the nodal status, implying that more accurate criteria have become available for administering adjuvant systemic treatment.

Various molecular markers

BRCA1 & 2 mutations were first identified in 1994 and are BC risk factors for some specific groups.[75] Their role as prognostic indicator for long-term (more than 10-year) survival has not yet been established. A study of 496 women (median follow-up: 116 months), 56 of whom (11%) carried a BRCA1/BRCA2 mutation, showed worse

breast cancer-specific survival for women with BRCA1 mutations than for those without (62% at 10 years versus 86%; P < 0.0001), but not for women with the BRCA2 mutation.[76] However, another study which compared patients from BRCA1, BRCA2 and non-BRCA1/2 families as well as sporadic cases did not confirm the prognostic role of BRCA1/2.[77]

Long-term follow-up studies have not demonstrated an independent effect of p53 mutations on long-term survival. The P53 mutation was related to a poor clinical profile for patients, hence in multivariate analysis its role on survival diminished.[10, 69, 78, 79]

A high level of tissue urokinase-type plasminogen activator (uPA) and its inhibitors has been correlated with poor outcome for node-negative and node-positive patients. Those having the highest level of uPA have a 5 times greater risk of dying from breast cancer compared to those with the lowest level.[69] Other factors such as Ki67 (MIB-1), cathepsin-D, DNA ploidy and S-phase have been suggested as prognosticators of survival, with conflicting results, particularly among long-term survivors. Their use in general clinical settings is therefore not recommended.[80, 81]

Miscellaneous

Lifestyle

Generally, increased death rates due to BC (13-20%), other causes (49-86%) and all causes (14-70%) have been observed among obese patients.[82-85] Normal body weight tended be more beneficial in death from other causes than from BC:[83, 84] 9.5% of obese patients died from non breast cancer causes compared to 6.4% and 5.8%, respectively, of the normal or intermediate groups.[82] Obesity was also related to a 2-fold increased risk of postmenopausal contralateral BC and a 60% higher occurrence of second other cancers.[84] Therefore, normal weight may reduce the risk of second post-menopausal BC, second other cancers and overall mortality.[83, 84, 86]

Compared with women who engaged in less than 9 MET (metabolic equivalent task)-hours per week of activity, women who engaged in 9 or more MET-hours per week had a 40% lower risk of death from all causes, translating into a 6% absolute (unadjusted) reduction in mortality,[87] which emphasizes the need to advise physical activity.

So far, although studies have not convincingly shown the positive influence of eating fruit, vegetables and soy bean on long-term BC survival,[85, 88] diets high in fruits, vegetables, legumes, poultry, and fish and a low intake of red meat, desserts and high fat dairy products are likely to protect against mortality from non-BC causes.[89]

5.3.2. Modification of BC's prognostic factors

Various studies have questioned the role of breast cancer risk factors in determining the biological tumour features as mentioned above. Indeed, breast cancer risk factors seem to differ according to histological type, grade, size, nodal status and ER/PR receptor status.[90-93] For example, excessive alcohol intake and obesity increased the risk for the development of ER-positive tumours.[92, 93] As for late age at first full-term birth and obesity are related to an increased risk of large tumours.[91] Hence, risk factors for breast cancer may also affect breast biology and clinical behaviour, thus also BC prognosis.

5.3.3. Changing importance of prognostic factors over time after diagnosis

Commonly, the value of prognostic factors decreases depending on the length of the follow-up period.[31, 94] Survival curves according to prognostic factors usually show a large drop in survival for all stages during the first 5 years; afterwards the curve stabilizes. Studies agreed on the long-lasting influence of tumour size at diagnosis on survival, albeit attenuating over time.[31, 94, 95] Grade, nodal status and metastases were also valuable in predicting survival up to 20 years after diagnosis.[31, 95] Although, others have reported that 10 years after diagnosis only tumour size[94] or nodal status[8] or old age[8] remained as an independent predictor of long-term survival. Similarly, ER/PR status and MAI only had a significant prognostic role in the first 5-10 years after diagnosis.[67, 71, 96] Because even 10 years after BC diagnosis the probability of survival for BC patients does not seem to reach that of the general population, the role of other prognostic factors in determining survival for long-term survivors still needs to be determined.

5.3.4. The role of early detection

Increased awareness among women and improvement in diagnostic procedures have enabled earlier and better detection of BC. Trials on population screening have reported 21%-29% reduction in BC mortality for women invited for screening within 14-16 years of follow-up.[19, 97] Screening identified tumours at an early stage consequently, survival improved.[98, 99] Screening also identified patients with slowly growing tumours who might receive unnecessarily aggressive cancer treatment. Thus, Joensuu et al[100] examined recurrence rates among patients detected by screening compared to those detected outside screening. After adjusting for tumour aggressiveness (tumour size, nodal status, grade, age, treatment, PR status, HER-2), hence eliminating bias towards detection of indolent cancers (length bias), the benefit of screening for the prognosis for BC patients remained evident.[100] This suggests that other factors explain the indolent behaviour of BC detected by screening. Hence, until this factor is established, detection mode should probably be considered as a prognostic factor and thus be taken into account in patient management.

5.3.5. The role of treatment

Improvement in BC treatment has undoubtedly also increased the long-term survival of BC patients,[101] as reflected by the improved overall survival across all BC stages.[16] Using historical data from population-based studies in periods when effective

treatment was not available, it was estimated that without treatment only 4% of BC patients would survive 10 years or longer.[102] BC treatment guidelines have been modified continuously in the last 28 years, tailored to most of the prognosticators mentioned earlier.[51] Effectiveness of various treatment modalities has been summarized by others who conclude that radiation, chemotherapy and hormonal therapy may reduce long-term mortality by up to 57%.[66, 103-105] Emerging new therapeutic approaches using a monoclonal antibody directed against HER-2 have yielded improved short-term survival for advanced stage[106] as well as operable BC patients.[107] Quality of treatment as indicated by loco-regional failure[108], surgeon workload[109] or hospital volume[110], may affect survival although its role on long-term survival still needs confirmation. In conclusion, on the one hand we have observed a shift in stage towards less aggressive cancers; on the other hand, better and more (systemic) treatment has become available, leading to improved survival for breast cancer patients.

Table 5.1. Overview of studies reporting long-term prognostic factors for breast cancer (BC) patients

No.	Author, year	No. of patients	Mean/median follow-up (yrs)	Univariate (UV) analysis significant	Multivariate (UV) analysis significant	Not significant	Remarks
1	Haerslev & Jacobsen 1995[70] *	490	10.6	MS, T, N, Htyp, MI, G, PR, Her2	All patients: N & PR. In N+: MI & PR. In N-: MS & G.	Her2	Overall survival was measured. P53 was related to absence of tubular formation, high G, ER-negative, high PCNA (proliferating cell nuclear antigen) score.
2	Pietilainen 1995[10]	392	11.1	P53, N, T, Htyp, tubular formation, intraductal growth, margin formation, necrosis, DNA ploidy, S-phase fraction	All patients: N, T, MI In N+: T, MI In N-: T, p53, G		Overall survival was measured. P53 is related to younger age, MI, AI, G, nuclear pleomorphism
3	Haerslev 1995[79] *	490	11	PCNA	T, G, PR	Her2 & PCNA (Proliferating cell nuclear antigen)	Overall survival was measured. PR was only an independent factor in N-positive pts. Her2 & PCNA were related to more positive N, higher G, ER-/PR-negative.
4	Gamel 1996[39]	163,808	NR. Range 1mos-19yrs.	Histological type by stage (localized & regional BC)			Breast cancer specific survival was measured.
5	West 1996[12]	1196	NR. Diagnosed: 1973-1986. End FU: 1994.	Comorbidity	Level of comorbidity	Adjusted for age, race, stage, N, therapy. Values for these factors were not shown	Overall survival was measured. Charlson comorbidity index was used. There is no difference in the significance of comorbidity on survival of Caucasians and African American (AA)
6	Haerslev 1996[112] *	487	>10	Ki-67, PCNA	T, G, PR	Ki-67 & PCNA.	Overall survival was measured. PR only an independent factor for N+ patients. Ki-67 was related to T, MI, G.
7	Northridge 1997[36]	Mucinous BC: 4082. Infiltrating duct BC: 139,154	NR. Diagnosed: 1973-1990.		HTyp, period of diagnosis, Stage, G	Age	Breast cancer specific survival was measured.
8	Kollias 1997[11] *	2879 age≤70, T<5cm	>10	Age<35, NPI	T, G, N	Age	Overall survival was measured. Younger than 35 yrs had higher grade, more LVI and worse NPI group. After 10yrs NPI did not change OS.

Table 5.1. Continued.

9	Zahl & Tretli 1997[95]	8802 age< 70	Diagnosed: 1965-74. End FU: 1991	Survival categorized by age, stage and follow-up time			Excess hazard from breast cancer was measured. After 8 yrs being younger than 35 does not influence survival. Stage was an important prognosticator up to 20 years.
10	Pinder 1998[47]	465	12	N by grade, Treatment by grade			Overall survival was measured. The study aimed to confirm value of Nottingham grading system for survival. N+G3 patients benefited from prolonged chemotherapy.
11	Gaffney 1998[113]	BRCA1: 30. BRCA2: 20 Control: 18278 BC pts	BRCA1: 9.8 BRCA2: 7.5 Control: NR			BRCA1 vs. BRCA2 vs. control	Overall survival was measured. Case and control were matched for date of birth, date of diagnosis and tumour size. Patients with BRCA+ were younger. Patients with BRCA1 had higher grade.
12	Wojcik 1998[28]	6577 patients. Whites: 5879. African American (AA): 698	At 10 years 59-67% patients were alive	Race, G, N, T, stage, waiting time, smoking, being a widow, having other family as dependent	Race, age, stage	UV: alcohol, family history	Overall survival was measured. AA is more likely to be younger at diagnosis, have larger tumour, higher stage and more lymph nodes.
13	Mansi 1999[114]	350	12.5	Bone marrow micrometastases	N, T	Bone marrow micrometastases, LVI	Overall and breast cancer-specific survival was measured. Bone marrow metastases may be useful as prognostic factor for BC pts without information on T and N.
14	Kollias 1999[46] *	319 T≤1cm	>10	G, N, LVI, NPI	G, N	LVI	Overall survival was measured.
15	Tabar 1999[45]	2468	NR. Diagnosed: 1977-85. End FU: 1996	T, N, G, detection mode, HTyp	TXN, age*N, Htyp*N, T*N*G.		Overall survival was measured. Screening arrests disease progression. Tumour progression is more rapid in BC patients <50yrs. OS of T1a(1-5mm) vs. T1b(6-10mm) NS.

Table 5.1. continued.

16	Holmes 1999[85]	1982	13.1	BMI ≥ 30	3rd to 5th quintile of protein protein intake after diagnosis, N, T, G	BMI, protein intake prior diagnosis, alcohol intake.	All cause mortality was measured. MV for BMI was corrected for age, diet interval, oral contraceptive use, hormone replacement therapy, MS, age at menarche, aget at birth and parity, smoking, T, G, N, ER, PR. BMI < 21 and 1st quintile of protein intake were reference. Significant trend of higher mortality from lowest to highest quintiles of fiber, lutein &zeaxanthin, calcium & protein intake, with 13-35% lowest mortality in the lowest quintile.
17	Nomura 1999[58]	1857 <80yrs stage I-III	12	Second cancer and recurrence	Age, ER, N, recurrence, second cancer		Overall survival was measured. Recurrence is related to higher stage, younger age at diagnosis, Htyp, and therapy. Second cancer is related to younger age. Death related to recurrence and second cancer is increased 12 yrs after diagnosis.
18	Reed 1999[37]	613 T1-2N0	15.5	Age >50, T, G	G, T, treatment	UV: treatment, ER, PR, Her2, P53	Overall survival was measured. Her2 was related to PR-, ER-negative, P53, G. P53 was related to PR-. Treatment was ovarian & locoregional irradiation that had lower mortality rate
19	Aebi 2000[7]	3700 pre- & perimenopausal	12	Age <35 vs. ≥35	N, T, G, age<35*ER+	Age, ER	Overall survival was measured. Younger patients with ER+ who were not amenorrhoea had a significantly shorter survival.
20	Ferrero 2000[78]	297 N-	11	T, ER, P53	T, ER	Age, PR, G	Breast cancer-specific survival was measured. P53 was related to grade, T, ER-negative. P53 was continuous variable
21	Kroman 2000[6]	10,356 age<50	NR. Diagnosed: 1978-96.		Age, T, N, G	Period of treatment and surgery	Relative survival was measured for excess mortality due to BC. When chemotherapy was given BC at young age does have worse prognosis.
22	Ferrero-Pous 2000[69]	488	10	ER, uPA, G, N, PR, P53 by Her2	All patients: uPA, N, T, Her2, age. In N-: uPA, T. In N+: N: uPA, T, age, Her2.		Overall survival was measured. For patients who received chemotherapy uPA, T & N determined OS. For patients who received hormonal therapy uPA, Her2 & N determined OS.

Table 5.1. continued

23	Kato 2001[44] *	377	10	T, N, G	AMC, T, N, G	Necrosis	Overall survival was measured. AMC is a good prognostic factor for N- and T2-3 patients.
24	Liu 2001[96]	791	16.3	T, N, G, ER, Her2, p53, MIB-1, MAI, AI	All patients: N, T, G, ER, Her-2. In N-: G. In N+: N, age, ER, Her2	UV: age. MV All patients: AI, MI, MIB-1, ER, G MV in N- & N+: AI, MI, ER, G.	Breast cancer-specific mortality was measured. When patient FU was truncated at 5 years, MI was prognostic factor for N+ and N-.
25	Page 2001[115]	311 no adjuvant therapy.	11.6	High risk group (ER- or T≥3cm) vs. low risk (ER+ and T<2cm)	T, risk group (high vs. low)	G, MI	Overall survival was measured. MI was only significant when FU was truncated at 5 years. Grade was significant prognostic factor for short- and long-term survival.
26	Frkovic-Grazio & Bracko 2001[48]	270 T1N0M0	12.5	G, Tubular score, MI	Tubular score and MI		Breast cancer-specific survival was measured. This study confirmed the use of Nottingham grading system in their cohort.
27	D'Eredita 2001[49]	402	≥16	T, N, Htyp, G, LVI, NPI	T, N, G	UV: Age, MS, ER, type of surgery. MV: LVI & Htyp	Overall survival was measured. NPI gives similar survival prognosis as T, N, G.
28	Thomson 2001[26]	23786	At 10 years about 50% patients were alive	Age stratified by SES	Intermediate vs. high SES group corrected for age, ER, N, T, stage	Deprived vs. high SES group corrected for age, ER, N, T, stage	Deprived women have more ER- tumours. ER distribution and treatment method accounted for 20% of disparities in survival.
29	Vorgias 2001[30]	269 stage II	12	NR	T, N, age, ER/PR	MS, therapy	Overall survival was measured.
30	Vincent-Salomon 2001[43]	685 T≤3 cm	10.8	G, N, ER, necrosis	N, necrosis, G	UV: Vascular density, LVI, age, PR	Overall survival was measured. Intratumoral vascular density was related to larger tumour size and higher grade.
31	Eerola 2001[77]	Familial BC: 359. Sporadic BC: 59517.	NR. Diagnosed: 1953-1995. End FU: 1997		Stage, age, period of BC diagnosis, FU time (after 2 and 3 yrs of diagnosis)	BRCA1, BRCA2	5-year relative survival was measured for excess mortality due to BC.

Table 5.1. continued

32	Kitchen 2001[35]	9520	12		Tubular BC type vs. other type, by nodal status and chemotherapy		**Overall survival was measured.** Tubular BC type had better prognosis than other type. This type was more likely to have low G & ER+.
33	Kato 2002[50]*	422	10	P53, MI, necrosis, T, N, LVI	MI, T, N	UV: AI	**Overall survival was measured.** In MV P53 & MI were independent prognostic factors for N- patients only. P53 was related to MI, AI, necrosis, G, T, N, ER/PR
34	Kato 2002[54]*	398	10	BVI, T, N, G, chemotherapy	BVI, T, N, G, chemotherapy	UV: necrosis	Overall survival was measured.
35	Costa 2002[67]	670	11.4	N, T, age, ER/PR	N, T, age	MS, ER/PR	Breast cancer-specific survival was measured. After 5 years of FU ER and PR were not independent prognostic factors.
36	Menard 2002[17]	1928	Diagnosed in 1968-69 and 1978-79.	Her2, N, T, MS, lymphoid infiltration, PR-	G, T, N, lymphoid infiltration		Overall survival was measured. HER-2 was related to large tumours, higher G, lymphoid infiltration, higher mitotic index, PR-.
37	Van de Vijver 2002[74]	295 age<53, stage I-II	6.7	Gene profile (Good vs. bad prognosis) for all patients, N+, N-	Gene profile, T, N, chemotherapy	VI, G, age, hormonal therapy	Overall survival was measured.
38	Van't veer 2002[72]	117 age <55	NR.				Better classification of patients with high risk of metastasis and in need of chemotherapy.
39	Hatteville 2002[21]	3180	15.8		OS<5yr: N, G, recurrence or metastasis OS≥5 yr: G and recurrence or metastasis	Age, T	If patient remains without recurrence or metastasis, effect of prognostic factors decreases over time. With metastases, this effect increases.
40	Sotiriou 2003[73]	99	6.1	Gene profile (luminal 1-3 vs. basal 1-2 & Her2 type)			Luminal-like 1-3 was predominantly ER+. Basal-like 1-2 and Her2 was predominantly ER-

Table 5.1. continued

41	Dignam 2003[83]	3385 N-, ER+	13.8		BMI <18.5 & BMI ≥ 30 higher total mortality and other deaths.	BMI on deaths after BC events.	Total mortality, death after BC events and other deaths as well as recurrence rate and occurrence of a second cancer was were measured. MV was adjusted for treatment, age, MS, race, T, ER and PR. Reference group was BMI 18.5-24.9.
42	Olivotto 2003[57]	620 stage IIIB-M1	>20	Supraclavicular BC, Stage IIIB and M1			Overall and breast cancer specific survival were measured. Patients with supraclavicular metastases had significantly better survival than patients with M1. Survival of these patients resembles that of BC stage IIB. (FU for living patients 20 yrs, for all patients 4.5 yrs)
43	Weiss 2003[32]	905 N+ Chemotherapy+	22.6	N+ (N1-3 vs. N4-9 vs. N>10), also by treatment and follow-up time	N, T, MS	MV: NXT, MSXT, additional vincristine and prednison	Overall survival was measured. N was related to T. MS was related to receptor status.
44	Taylor 2003[16]	54,228	At 10 years 65% patients were alive	Period of diagnosis, stage by age, FU time by stage			Relative survival was measured for excess mortality due to BC. The longer the survival the better the prognosis. Improvement in relative survival for all patients and all stages since 1972.
45	Dales 2004[56]	905 aged 25-81	11.7	In N- : CD105+ vessels. In all pts: CD31, Tie-2/Tek	In all pts: G, CD105 vessels, ER. In N-: G, CD105 vessels, PR.	In all pts: T, Htyp, CD31, PR, age. In N-: T, CD31 vessels, ER, age.	Overall survival was measured. MV: Tie-2/Tek showed significant role for predicting OS in all patients and N- patients.
46	Brenner & Hakulinen 2004[15]	18,578 age< 50	NR. Diagnosed: 1953-1999.	Period of diagnosis, stage, stage*period, time after diagnosis			Improvement of prognosis for BC patients younger than 50 over the past decades. Relative survival remains lowered even 40 yrs after diagnosis.
47	Robson 2004[76]	584 Ashkenazi Jewish	116	BRCA1, T, N, ER, age, chemotherapy	BRCA1, T, N, Age	Tamoksifen, BRCA2	Breast cancer-specific survival was measured. No effect of BRCA on non-BC death. BRCA1 only predicted BC death in patients without chemotherapy
48	Chia 2004[33]	1187 LVI-, N-, Adjuvant systemic therapy-	10.4	T, G	TXG		Overall and breast cancer specific survival were measured. Patients with higher grade and size have greater chance to die from other & those with low risk disease greater chance of death from BC.

Table 5.1. continued

49	Yoshimoto 2004[18]	15,416	NR. Diagnosed 1946-2001.	Period of diagnosis.			Over the decades, there were less extensive surgery and lymph node examination, less radiotherapy, more chemo- and hormonal therapy.
50	Houterman 2004[116]	527 age≥40	4.7	Comorbidity, N, Therapy, age≥70, comorbidity*N	In age<70: comorbidity, N In age≥70: comorbidity, age	In age <70: therapy In pts age≥70: N, therapy	Relative survival was measured for excess mortality due to BC. Older patients with comorbidity were not treated differently but had a worse prognosis.
51	Schoppmann 2004[53]	374	22.4	LVI, G, N, Therapy	LVI, G, N	LMVD (Lymphatic Microvessel Density), T, Htyp, ER, age, MS	**Overall survival was measured.** LVI is related to young premenopausal BC, lower G, N+
52	Warwick 2004[31]	2299	>10	G, N, T, Metastases	G, N, T, Metastases		Breast cancer specific survival was measured. All studied factors predicted long-term survival, but their value decreased over time.
53	Berclaz 2004[82]	6792	14	BMI 25-29, BMI ≥30 lower overall survival.	BMI ≥30	BMI 25-29.	Overall survival and also disease free survival were measured. Reference group was BMI ≤ 24.9. MV adjusted for ER, T, N, MS, treatment, chemotherapy, hormonal- in combination with chemotherapy.
54	Dignam 2005[84]	4077 N-, ER-	NR		BMI ≥35 and AA had higher overall mortality and non-BC death.	BMI and race on death after BC events.	Total mortality, death after BC events and other deaths as well as recurrence rate and occurrence of a second cancer were measured. MV was adjusted for treatment, age, MS, race, T, ER and PR. Reference group was BMI ≤ 24.9.
55	Holmes 2005[87]	2987	96 months		Physical activity after diagnosis (MET ≥ 9) on BC and total mortality.		Breast cancer and total mortality were measured. MV corrected for age, interval between diagnosis and physical activity assessment, smoking, BMI, MS, hormone therapy use, age at first birth, parity, energy intake, stage and treatment. MET: metabolic equivalent task hours per week. Patients with BMI ≥25 & more physical activity before diagnosis there was a significant trend for less breast cancer death.
56	Robsahm & Tretli 2005[27]	5042	NR. Diagnosed: 1964-92. End FU: 1992	NR	Location of home, age at first child, physical activity at work	MV corrected for: age, period of diagnosis, birth cohort, educational level	Breast cancer-specific survival was measured. Incidence of BC increases with higher educational level, and case fatality decreases by increasing education level.

Table 5.1. continued

57	Vu-Nishino 2005[38]	1490 received breast-conserving treatment	13.9			Medullary BC vs other BC type	Overall survival was measured. Medullary BC type had better prognosis than other type. This type was more likely to have ER+, PR+ & less BRCA1/2 mutation. Medullary type was only a prognostic factor for the first 5 years.
58	Galper 2005[63]	2102 stage I-II, 314 with local recurrence (LR)	13.1	NR	No LR treatment, Invasive LR, time (yrs) to local recurrence, age at initial BC diagnosis	T, detection method, number of nodes sampled, ER/PR, histological type, G, LVI, margins	Measure of survival: distant failure, second malignancy, or death. Patients with a longer time to recurrence have prolonged survival.
59	Voogd 2005[62]	266 BC with LR	11.2 after LR for living pts	NR	Location of LR, size of LR, skin involvement of LR, N+ for primary tumour		Overall survival was measured. Early detection of local recurrence may improve the treatment outcome.
60	Louwman 2005[13]	8966	Diagnosed 1995-2001. End FU: 2004	2 or more comorbidities, diabetes mellitus and previous cancer	Previous cancer, CVD, DM, cerebrovascular disease, dementia, 2 or more comorbidities, stage, treatment (RT, ST, age)		Overall as well as relative survival was measured for excess mortality due to BC. Primary treatment of BC patients with serious comorbidity was less extensive than treatment of those without comorbidity.
61	Tammemagi 2005[14]	906	10	Number of severe comorbidities, race, type of comorbidity	All patients: 3 or more comorbidities adjusted for stage, age, ER, surgery, chemotherapy, radiotherapy		Overall survival was measured. AA had more diabetes and hypertension. After adjustment for these 2 comorbidities disparity disappeared.
62	Meunier-Carpentier 2005[55]	909/918 age: 25-81	11.3	Tie2	-	UV: VEGFR-2, VEGFR-2	Overall survival was measured. VEGFR-1 and Tie2 were reported as independent prognostic factors corrected for T, G, Htyp, in all patients and N-.
63	Tai 2005[40]	6184 Inflammatory BC	NR. Diagnosed 1973-1995. End FU: 2000.	Period of diagnosis			Breast cancer-specific survival was measured. Prognosis has improved over the decades due to more aggressive therapy.

Table 5.1. continued

64	Louwman 2005[71]	492 T1-2 N0	>10 yrs	MAI	OS: age, T BCS: MAI	OS: HTyp, therapy, period of diagnosis. BCS: therapy, period of diagnosis, age, T, Htyp	Overall (OS) as well as relative survival (BCS) was measured for excess mortality due to BC. Higher MAI was a significant prognostic factor for N- and N+, but only during the first 10 yrs of FU.
65	Arrigada 2006[8]	2410 T≤7cm N1-2	19	T, skin fixation, muscle fixation, G, N, age.	**Total FU: T, N, G, age<35, age≥55.** FU 0-5yrs: T, N, G, age≥55. FU 5-10yrs: N, G, age <35, age≥55. FU 10-15yrs: N>10, age>55. FU 15-20yrs: age≥65.		Overall survival was measured. Long-term effect of prognostic factors vanishing.
66	Newman 2006[29]	90,124. White American: 76,111. AA: 14,013			Age, stage, SES		Meta-analysis. African American is an independent predictor of poor outcome for overall survival and breast cancer specific mortality
62	Menvielle 2006[24]	407,435 women followed for BC death (N:1408)	Women who died of BC in 1968-96.	Level of education by period of diagnosis			Breast cancer death among women with the highest education compared to women with the lowest education in 1968-74 was 0.43; and in 1990-96: 1.17 (NS)
67	Bouchardy 2006[25]	3920 age<70	NR. Diagnosed in 1980-2000.	SES	SES corrected for age, period of diagnosis, marital status, country of birth, Htyp, ER, detection method, stage, sector of care, therapy		Overall survival was measured. Lowest SES had less frequently screen-detected cancers, less stage I, less lobular BC, less BCT, less lymph node dissection.

Table 5.1. continued

68	Siegelmann-Danieli 2006[117]	992, age≥70	6.9	Being in wheelchair, renal insufficiency, dementia, CHF, cardiac arrhythmia, DM, IHD, osteoporosis, PVD, cerebrovascular disease, COPD, Parkinson's disease, valvular heart disease.	In stage 1A-2A: age, CHF, DM, PVD, stage, cardiac arrhythmia, Parkinson's disease, renal insufficiency. In stage 2B-4: G, stage, N, wheelchair-bound, renal insufficiency, COPD, age, DM	Systemic therapy	Overall survival was measured. CHF: Cardiac Heart Failure. DM: Diabetes Mellitus. IHD: Ischemic Heart Disease. PVD: Peripheral Heart Disease. COPD: Chronic Obstructive Pulmonary Disease. Role of comorbidity varies by age.
69	Pritchard 2006[68]	639 premenopausal N+	10	Her2 amplification	Her2 corrected for age, N, ER, type of surgery		Overall survival was measured. Those with amplified Her2 have improved survival with CEF.
70	Lee 2006[52]	(A) Adjuvant therapy - : 990. (B) Adjuvant treatment + : 1765	Group A: 13. Group B: 6.8.	LVI	Group A: T, G, LVI, Htyp. Group B: T, G, LVI, chemotherapy, hormonal therapy	B: ER, age, Htyp	Breast cancer-specific survival was measured. For patients without adjuvant treatment, role of G in survival was higher in the first 5 years. Role of Htyp was not significant for the first 5 years of FU.

indicates the overlapping patients used by the same author to answer another research question; yrs: years; UV: Univariate analysis. MV: Multivariate analysis. MS: Menopausal Status; T: Tumour size; N: Nodal involvement; Htyp: Histological type; MI: Mitotic Index; G: Grade; PR: Progesterone Receptor status; ER: Oestrogen Receptor status; PCNA: proliferating cell nuclear antigen; mos: months; NR: Not Reported; AA: African American; age: is in year and indicate age at primary breast cancer unless otherwise state; NPI: Nottingham Prognostic Index; LVI: Lymphovascular Invasion; (Prognostic factor)(Prognostic factor): interaction between 2 factors; BMI: Body Mass Index; AMC: Average Microvessel Count; MAI: Mitotic Activity Index; AI: Apoptosis Index; FU: Follow-up; SES: Socioeconomic Status; BVI: Blood vessel Invasion; LMVD: Lymphatic Microvessel Density; LR: local recurrence; CVD: Cardiovascular Disease; DM: Diabetes Mellitus; RT: radiotherapy; ST: Systemic therapy; VEGFR: Vascular Endothelial Growth Factor Receptor; OS: Overall survival; BCS: Breast Cancer Specific Survival; NS: not significant; CHF: Cardiac Heart Failure; IHD: Ischemic Heart Disease. PVD: Peripheral Heart Disease. COPD: Chronic Obstructive Pulmonary. CEF: cyclophosphamide, epirubicin and fluorouracil

5.4. Conclusion

The prognosis of breast cancer has become relatively good, with current 10-year relative survival about 70% in most western populations,[16, 111] especially if up-to-date statistical method such as the period analyses is used.[111] Even better, the longer patients survive their breast cancer the higher their survival chance.[16] Our review shows conventional prognostic factors of survival, such as tumour size, lymph node status and grade, remain the most important determinants of 10-year survival for BC patients (table 5.2). Most studies agreed on the value of MAI and LVI for prediction of long-term survival. The influence of host factors including age, race/ethnicity or socio-economic factors and tumor-related factors such as histological type and angiogenesis diminishes after correction for other factors. For most recent markers such as Her2, gene profiling, p53 mutation and uPA level longer follow-up is needed. Recurrence, metastases and a second cancer double the burden of disease thus increase risk of mortality. Similarly, co-occurrence with other diseases is in no doubt decrease survival.

Healthier lifestyle generally increases long-term survival. Modifiable risk factors (such as alcohol consumption and obesity) not only affect incidence but also tumour' clinical behaviour and thus survival.

Although a lot is known about the prognosis for breast cancer patients, effect of traditional prognostic factors appears to attenuate over time, leaving room for studies on the role of other and newer factors for long-term survival.

Table 5.2. Selected prognostic factors for long-term overall mortality of breast cancer (BC) patients

Patient groups based	Hazard ratio (HR) for overall follow-up or Survival probability (S) 10 years after diagnosis	Morphology based	Hazard ratio (HR) for overall follow-up or Survival probability (S) 10 years after diagnosis	Molecular based	Hazard ratio (HR) for overall follow-up or Survival probability (S) 10 years after diagnosis
Age at diagnosis [8]	HR:	Lymph node status [31]	HR:	HER2[69]	HR:
<35 vs. 35-44	1.4 (p: 0.07)	N≥1 vs. N0	2.4 (1.9-3.9)	> 500 vs. ≤ 500	1.82 (1.1-2.9)
45-54 vs. 35-44	1.1 (ns)				Only in node-positive
55-64 vs. 35-44	2.0 (p: 0.000)	Metastases vs. N0	22.73 (16.1-32.2)		patients
65-75 vs. 35-44	2.5 (p: 0.000)				
Period of diagnosis [16]	Relative Survival [b]:	Tumour size (mm) [31]	HR:	Cell proliferation index	HR:
1972-1976	59%	T10-14 vs. T1-9	1.2 (0.8-1.9)	(MAI)	
1977-1986	64%	T15-19 vs. T1-9	1.7 (1.1-2.6)	>10 vs. ≤10 [10]	1.02 (1.00-1.03)
1987-1991	70%	T20-29 vs. T1-9	2.5 (1.6-3.9)		Only in node-positive
		T30-49 vs. T1-9	3.8 (2.4-6.0)		patients
		T≥50 vs. T1-9	4.6 (2.9-7.6)		
Time after diagnosis [16]	Relative Survival:	Tumour grade [44]	HR:	Gene expression profile[74]	
0 vs. 5 yrs after diagnosis		II vs. I	2.5 (1.0-6.1)	Poor vs. good signature [f]	S:
Regional BC	79% vs. 84%	III vs. I	5.7 (2.6-12.4)		55% vs. 95%
Locally advanced BC	53% vs. 68%				
Socioeconomic status [26]	HR:	Tumour type[34]	S:	ER/PR status [30]	HR:
Intermediate vs. affluent	1.2 (1.0-1.4)	Poor vs. excellent [d,e]	<50% vs. >80%	Positive vs. negative	0.38 (0.02-1.06)
Deprived vs. affluent	1.2 (0.99-1.53)				
Lifestyle	HR:				
Body Mass Index					
<21 vs. 29+ kg/m^2	1.4 (0.97-2.00)[85] [c]				
Physical activity					
<3 vs. 23.9 MET-h/wk[a]	0.56 (0.4-0.8)[87]				

HR: Hazard ratio calculated within multivariate analysis of breast cancer patients followed for a median/mean of 10 years or longer

[a] Metabolic equivalent task hours per week; [b] Estimates taken from graph; [c] Higher alcohol intake no significant effect on mortality. Significant trend of higher mortality for lowest compared to highest quintiles of fiber, lutein & zeaxanthin, calcium & protein intake; [d] Becomes larger as numbers of involved lymph nodes increases [8]; [e] Excellent prognosis: tubular, invasive cribriform, mucinous, tubulolobular. Poor prognosis: mixed lobular, solid lobular, ductal and mixed ductal lobular; [f] unadjusted estimates

References

1. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. *CA Cancer J Clin*. 2005;55:74-108
2. Sant M, Aareleid T, Berrino F, Bielska Lasota M, Carli PM, Faivre J, Grosclaude P, Hedelin G, Matsuda T, Moller H, Moller T, Verdecchia A, Capocaccia R, Gatta G, Micheli A, Santaquilani M, Roazzi P, Lisi D. Eurocare-3: Survival of cancer patients diagnosed 1990-94--results and commentary. *Ann Oncol*. 2003;14 Suppl 5:v61-118
3. Botha JL, Bray F, Sankila R, Parkin DM. Breast cancer incidence and mortality trends in 16 european countries. *Eur J Cancer*. 2003;39:1718-1729
4. ACS. Cancer facts and figures 2005. 2005
5. Janssen-Heijnen MLG, Louwman WJ, van de Poll-Franse LV, Coebergh JWW. Van meten naar weten. 50 jaar kankerregistratie. 2005:104
6. Kroman N, Jensen MB, Wohlfahrt J, Mouridsen HT, Andersen PK, Melbye M. Factors influencing the effect of age on prognosis in breast cancer: Population based study. *Bmj*. 2000;320:474-478
7. Aebi S, Gelber S, Castiglione-Gertsch M, Gelber RD, Collins J, Thurlimann B, Rudenstam CM, Lindtner J, Crivellari D, Cortes-Funes H, Simoncini E, Werner ID, Coates AS, Goldhirsch A. Is chemotherapy alone adequate for young women with oestrogen-receptor-positive breast cancer? *Lancet*. 2000;355:1869-1874
8. Arriagada R, Le MG, Dunant A, Tubiana M, Contesso G. Twenty-five years of follow-up in patients with operable breast carcinoma: Correlation between clinicopathologic factors and the risk of death in each 5-year period. *Cancer*. 2006;106:743-750
9. Fisher ER, Anderson S, Tan-Chiu E, Fisher B, Eaton L, Wolmark N. Fifteen-year prognostic discriminants for invasive breast carcinoma: National surgical adjuvant breast and bowel project protocol-06. *Cancer*. 2001;91:1679-1687
10. Pietilainen T, Lipponen P, Aaltomaa S, Eskelinen M, Kosma VM, Syrjanen K. Expression of p53 protein has no independent prognostic value in breast cancer. *J Pathol*. 1995;177:225-232
11. Kollias J, Elston CW, Ellis IO, Robertson JF, Blamey RW. Early-onset breast cancer--histopathological and prognostic considerations. *Br J Cancer*. 1997;75:1318-1323
12. West DW, Satariano WA, Ragland DR, Hiatt RA. Comorbidity and breast cancer survival: A comparison between black and white women. *Ann Epidemiol*. 1996;6:413-419
13. Louwman WJ, Janssen-Heijnen ML, Houterman S, Voogd AC, van der Sangen MJ, Nieuwenhuijzen GA, Coebergh JW. Less extensive treatment and inferior prognosis for breast cancer patient with comorbidity: A population-based study. *Eur J Cancer*. 2005;41:779-785
14. Tammemagi CM, Nerenz D, Neslund-Dudas C, Feldkamp C, Nathanson D. Comorbidity and survival disparities among black and white patients with breast cancer. *Jama*. 2005;294:1765-1772
15. Brenner H, Hakulinen T. Are patients diagnosed with breast cancer before age 50 years ever cured? *J Clin Oncol*. 2004;22:432-438
16. Taylor R, Davis P, Boyages J. Long-term survival of women with breast cancer in new south wales. *Eur J Cancer*. 2003;39:215-222
17. Menard S, Balsari A, Casalini P, Tagliabue E, Campiglio M, Bufalino R, Cascinelli N. Her-2-positive breast carcinomas as a particular subset with peculiar clinical behaviors. *Clin Cancer Res*. 2002;8:520-525
18. Yoshimoto M, Tada K, Hori H, Morota A, Tanabe M, Nishimura S, Takahashi K, Makita M, Iwase T, Kasumi F, Takahashi S, Ito Y, Oguchi M, Yamashita T, Akiyama F, Sakamoto G. Improvement in the prognosis of japanese breast cancer patients from 1946 to 2001--an institutional review. *Jpn J Clin Oncol*. 2004;34:457-462
19. Nystrom L, Andersson I, Bjurstam N, Frisell J, Nordenskjold B, Rutqvist LE. Long-term effects of mammography screening: Updated overview of the swedish randomised trials. *Lancet*. 2002;359:909-919
20. Otto SJ, Fracheboud J, Looman CW, Broeders MJ, Boer R, Hendriks JH, Verbeek AL, de Koning HJ. Initiation of population-based mammography screening in dutch municipalities and effect on breast-cancer mortality: A systematic review. *Lancet*. 2003;361:1411-1417
21. Hatteville L, Mahe C, Hill C. Prediction of the long-term survival in breast cancer patients according to the present oncological status. *Stat Med*. 2002;21:2345-2354
22. Brenner H, Gefeller O, Hakulinen T. Period analysis for 'up-to-date' cancer survival data: Theory, empirical evaluation, computational realisation and applications. *Eur J Cancer*. 2004;40:326-335

23. Hooning MJ, Aleman BM, van Rosmalen AJ, Kuenen MA, Klijn JG, van Leeuwen FE. Cause-specific mortality in long-term survivors of breast cancer: A 25-year follow-up study. *Int J Radiat Oncol Biol Phys*. 2006;64:1081-1091
24. Menvielle G, Leclerc A, Chastang JF, Luce D. Social inequalities in breast cancer mortality among french women: Disappearing educational disparities from 1968 to 1996. *Br J Cancer*. 2006;94:152-155
25. Bouchardy C, Verkooijen HM, Fioretta G. Social class is an important and independent prognostic factor of breast cancer mortality. *Int J Cancer*. 2006
26. Thomson CS, Hole DJ, Twelves CJ, Brewster DH, Black RJ. Prognostic factors in women with breast cancer: Distribution by socioeconomic status and effect on differences in survival. *J Epidemiol Community Health*. 2001;55:308-315
27. Robsahm TE, Tretli S. Weak associations between sociodemographic factors and breast cancer: Possible effects of early detection. *Eur J Cancer Prev*. 2005;14:7-12
28. Wojcik BE, Spinks MK, Optenberg SA. Breast carcinoma survival analysis for african american and white women in an equal-access health care system. *Cancer*. 1998;82:1310-1318
29. Newman LA, Griffith KA, Jatoi I, Simon MS, Crowe JP, Colditz GA. Meta-analysis of survival in african american and white american patients with breast cancer: Ethnicity compared with socioeconomic status. *J Clin Oncol*. 2006;24:1342-1349
30. Vorgias G, Koukouras D, Paleogianni V, Tzoracoeleftherakis E. Prognostic significance of factors affecting disease free interval and overall survival for stage ii breast cancer in greece. A multivariate cohort study. *Eur J Obstet Gynecol Reprod Biol*. 2001;95:100-104
31. Warwick J, Tabar L, Vitak B, Duffy SW. Time-dependent effects on survival in breast carcinoma: Results of 20 years of follow-up from the swedish two-county study. *Cancer*. 2004;100:1331-1336
32. Weiss RB, Woolf SH, Demakos E, Holland JF, Berry DA, Falkson G, Cirrincione CT, Robbins A, Bothun S, Henderson IC, Norton L. Natural history of more than 20 years of node-positive primary breast carcinoma treated with cyclophosphamide, methotrexate, and fluorouracil-based adjuvant chemotherapy: A study by the cancer and leukemia group b. *J Clin Oncol*. 2003;21:1825-1835
33. Chia SK, Speers CH, Bryce CJ, Hayes MM, Olivotto IA. Ten-year outcomes in a population-based cohort of node-negative, lymphatic, and vascular invasion-negative early breast cancers without adjuvant systemic therapies. *J Clin Oncol*. 2004;22:1630-1637
34. Galea MH, Blamey RW, Elston CE, Ellis IO. The nottingham prognostic index in primary breast cancer. *Breast Cancer Res Treat*. 1992;22:207-219
35. Kitchen PR, Smith TH, Henderson MA, Goldhirsch A, Castiglione-Gertsch M, Coates AS, Gusterson B, Brown RW, Gelber RD, Collins JP. Tubular carcinoma of the breast: Prognosis and response to adjuvant systemic therapy. *ANZ J Surg*. 2001;71:27-31
36. Northridge ME, Rhoads GG, Wartenberg D, Koffman D. The importance of histologic type on breast cancer survival. *J Clin Epidemiol*. 1997;50:283-290
37. Reed W, Hannisdal E, Boehler PJ, Gundersen S, Host H, Marthin J. The prognostic value of p53 and c-erb b-2 immunostaining is overrated for patients with lymph node negative breast carcinoma: A multivariate analysis of prognostic factors in 613 patients with a follow-up of 14-30 years. *Cancer*. 2000;88:804-813
38. Vu-Nishino H, Tavassoli FA, Ahrens WA, Haffty BG. Clinicopathologic features and long-term outcome of patients with medullary breast carcinoma managed with breast-conserving therapy (bct). *Int J Radiat Oncol Biol Phys*. 2005;62:1040-1047
39. Gamel JW, Meyer JS, Feuer E, Miller BA. The impact of stage and histology on the long-term clinical course of 163,808 patients with breast carcinoma. *Cancer*. 1996;77:1459-1464
40. Tai P, Yu E, Shiels R, Pacella J, Jones K, Sadikov E, Mahmood S. Short- and long-term cause-specific survival of patients with inflammatory breast cancer. *BMC Cancer*. 2005;5:137
41. Harris JR, Lippman ME, Morrow M, Osborne CK. *Diseases of the breast*. Philadelphia: Lippincott Williams & Wilkins; 2004.
42. Gilchrist KW, Kalish L, Gould VE, Hirschl S, Imbriglia JE, Levy WM, Patchefsky AS, Penner DW, Pickren J, Roth JA, et al. Interobserver reproducibility of histopathological features in stage ii breast cancer. An ecog study. *Breast Cancer Res Treat*. 1985;5:3-10
43. Vincent-Salomon A, Carton M, Zafrani B, Freneaux P, Nicolas A, Massemin B, Fourquet A, Clough K, Pouillart P, Sastre-Garau X. Long term outcome of small size invasive breast carcinomas independent from angiogenesis in a series of 685 cases. *Cancer*. 2001;92:249-256
44. Kato T, Kameoka S, Kimura T, Soga N, Abe Y, Nishikawa T, Kobayashi M. Angiogenesis as a predictor of long-term survival for 377 japanese patients with breast cancer. *Breast Cancer Res Treat*. 2001;70:65-74

45. Tabar L, Duffy SW, Vitak B, Chen HH, Prevost TC. The natural history of breast carcinoma: What have we learned from screening? *Cancer*. 1999;86:449-462
46. Kollias J, Murphy CA, Elston CW, Ellis IO, Robertson JF, Blamey RW. The prognosis of small primary breast cancers. *Eur J Cancer*. 1999;35:908-912
47. Pinder SE, Murray S, Ellis IO, Trihia H, Elston CW, Gelber RD, Goldhirsch A, Lindtner J, Cortes-Funes H, Simoncini E, Byrne MJ, Golouh R, Rudenstam CM, Castiglione-Gertsch M, Gusterson BA. The importance of the histologic grade of invasive breast carcinoma and response to chemotherapy. *Cancer*. 1998;83:1529-1539
48. Frkovic-Grazio S, Bracko M. Long term prognostic value of nottingham histological grade and its components in early (pt1n0m0) breast carcinoma. *J Clin Pathol*. 2002;55:88-92
49. D'Eredita G, Giardina C, Martellotta M, Natale T, Ferrarese F. Prognostic factors in breast cancer: The predictive value of the nottingham prognostic index in patients with a long-term follow-up that were treated in a single institution. *Eur J Cancer*. 2001;37:591-596
50. Kato T, Kameoka S, Kimura T, Tanaka S, Nishikawa T, Kobayashi M. P53, mitosis, apoptosis and necrosis as prognostic indicators of long-term survival in breast cancer. *Anticancer Res*. 2002;22:1105-1112
51. Goldhirsch A, Glick JH, Gelber RD, Coates AS, Thurlimann B, Senn HJ. Meeting highlights: International expert consensus on the primary therapy of early breast cancer 2005. *Ann Oncol*. 2005;16:1569-1583
52. Lee AH, Pinder SE, Macmillan RD, Mitchell M, Ellis IO, Elston CW, Blamey RW. Prognostic value of lymphovascular invasion in women with lymph node negative invasive breast carcinoma. *Eur J Cancer*. 2006;42:357-362
53. Schoppmann SF, Bayer G, Aumayr K, Taucher S, Geleff S, Rudas M, Kubista E, Hausmaninger H, Samonigg H, Gnant M, Jakesz R, Horvat R. Prognostic value of lymphangiogenesis and lymphovascular invasion in invasive breast cancer. *Ann Surg*. 2004;240:306-312
54. Kato T, Kameoka S, Kimura T, Nishikawa T, Kobayashi M. Blood vessel invasion as a predictor of long-term survival for japanese patients with breast cancer. *Breast Cancer Res Treat*. 2002;73:1-12
55. Meunier-Carpentier S, Dales JP, Djemli A, Garcia S, Bonnier P, Andrac-Meyer L, Lavaut MN, Allasia C, Charpin C. Comparison of the prognosis indication of vegfr-1 and vegfr-2 and tie2 receptor expression in breast carcinoma. *Int J Oncol*. 2005;26:977-984
56. Dales JP, Garcia S, Carpentier S, Andrac L, Ramuz O, Lavaut MN, Allasia C, Bonnier P, Charpin C. Long-term prognostic significance of neoangiogenesis in breast carcinomas: Comparison of tie-2/tek, cd105, and cd31 immunocytochemical expression. *Hum Pathol*. 2004;35:176-183
57. Olivotto IA, Chua B, Allan SJ, Speers CH, Chia S, Ragaz J. Long-term survival of patients with supraclavicular metastases at diagnosis of breast cancer. *J Clin Oncol*. 2003;21:851-854
58. Nomura Y, Tsutsui S, Murakami S, Takenaka Y. Prognostic impact of second cancer on the survival of early breast cancer patients. *Int J Oncol*. 1999;14:1103-1109
59. Raymond JS, Hogue CJ. Multiple primary tumours in women following breast cancer, 1973-2000. *Br J Cancer*. 2006;94:1745-1750
60. Kollias J, Ellis IO, Elston CW, Blamey RW. Prognostic significance of synchronous and metachronous bilateral breast cancer. *World J Surg*. 2001;25:1117-1124
61. Wapnir IL, Anderson SJ, Mamounas EP, Geyer CE, Jr., Jeong JH, Tan-Chiu E, Fisher B, Wolmark N. Prognosis after ipsilateral breast tumor recurrence and locoregional recurrences in five national surgical adjuvant breast and bowel project node-positive adjuvant breast cancer trials. *J Clin Oncol*. 2006;24:2028-2037
62. Voogd AC, van Oost FJ, Rutgers EJ, Elkhuizen PH, van Geel AN, Scheijmans LJ, van der Sangen MJ, Botke G, Hoekstra CJ, Jobsen JJ, van de Velde CJ, von Meyenfeldt MF, Tabak JM, Peterse JL, van de Vijver MJ, Coebergh JW, van Tienhoven G. Long-term prognosis of patients with local recurrence after conservative surgery and radiotherapy for early breast cancer. *Eur J Cancer*. 2005;41:2637-2644
63. Galper S, Blood E, Gelman R, Abner A, Recht A, Kohli A, Wong JS, Smith D, Bellon J, Connolly J, Schnitt S, Winer E, Silver B, Harris JR. Prognosis after local recurrence after conservative surgery and radiation for early-stage breast cancer. *Int J Radiat Oncol Biol Phys*. 2005;61:348-357
64. Habel LA, Shak S, Jacobs MK, Capra A, Alexander C, Pho M, Baker J, Walker M, Watson D, Hackett J, Blick NT, Greenberg D, Fehrenbacher L, Langholz B, Quesenberry CP. A population-based study of tumor gene expression and risk of breast cancer death among lymph node-negative patients. *Breast Cancer Res*. 2006;8:R25
65. Obedian E, Fischer DB, Haffty BG. Second malignancies after treatment of early-stage breast cancer: Lumpectomy and radiation therapy versus mastectomy. *J Clin Oncol*. 2000;18:2406-2412

66. St. Clair P, Bugliari D, Chien S, Haider S, Hayden O, Hurd MD, Ilchuk S, Lopez G, Loughran D, Panis C, Pantoja P, Rastegar A, Reti M, Rowhwedder S, Roth E, Zissimopoulos J. Rand hrs data documentation version e. 2005
67. Costa SD, Lange S, Klinga K, Merkle E, Kaufmann M. Factors influencing the prognostic role of oestrogen and progesterone receptor levels in breast cancer--results of the analysis of 670 patients with 11 years of follow-up. *Eur J Cancer*. 2002;38:1329-1334
68. Pritchard KI, Shepherd LE, O'Malley FP, Andrulis IL, Tu D, Bramwell VH, Levine MN. Her2 and responsiveness of breast cancer to adjuvant chemotherapy. *N Engl J Med*. 2006;354:2103-2111
69. Ferrero-Pous M, Hacene K, Bouchet C, Le Doussal V, Tubiana-Hulin M, Spyratos F. Relationship between c-erbb-2 and other tumor characteristics in breast cancer prognosis. *Clin Cancer Res*. 2000;6:4745-4754
70. Haerslev T, Jacobsen GK, Zedeler K. Proliferating cell nuclear antigen (pcna) and c-erbb-2 oncoprotein in breast carcinoma with correlations to histopathological parameters and prognosis. *Oncology Reports*. 1995;2:99-105
71. Louwman WJ, van Beek MW, Schapers RF, Nolthenius-Puylaert MB, van Diest PJ, Roumen RM, Coebergh JW. Long-term survival of t1 and t2 lymph node-negative breast cancer patients according to mitotic activity index: A population-based study. *Int J Cancer*. 2005
72. van 't Veer LJ, Dai H, van de Vijver MJ, He YD, Hart AA, Mao M, Peterse HL, van der Kooy K, Marton MJ, Witteveen AT, Schreiber GJ, Kerkhoven RM, Roberts C, Linsley PS, Bernards R, Friend SH. Gene expression profiling predicts clinical outcome of breast cancer. *Nature*. 2002;415:530-536
73. Sotiriou C, Neo SY, McShane LM, Korn EL, Long PM, Jazaeri A, Martiat P, Fox SB, Harris AL, Liu ET. Breast cancer classification and prognosis based on gene expression profiles from a population-based study. *Proc Natl Acad Sci U S A*. 2003;100:10393-10398
74. van de Vijver MJ, He YD, van't Veer LJ, Dai H, Hart AA, Voskuil DW, Schreiber GJ, Peterse JL, Roberts C, Marton MJ, Parrish M, Atsma D, Witteveen A, Glas A, Delahaye L, van der Velde T, Bartelink H, Rodenhuis S, Rutgers ET, Friend SH, Bernards R. A gene-expression signature as a predictor of survival in breast cancer. *N Engl J Med*. 2002;347:1999-2009
75. Miki Y, Swensen J, Shattuck-Eidens D, Futreal PA, Harshman K, Tavtigian S, Liu Q, Cochran C, Bennett LM, Ding W, et al. A strong candidate for the breast and ovarian cancer susceptibility gene brca1. *Science*. 1994;266:66-71
76. Robson ME, Chappuis PO, Satagopan J, Wong N, Boyd J, Goffin JR, Hudis C, Roberge D, Norton L, Begin LR, Offit K, Foulkes WD. A combined analysis of outcome following breast cancer: Differences in survival based on brca1/brca2 mutation status and administration of adjuvant treatment. *Breast Cancer Res*. 2004;6:R8-R17
77. Eerola H, Vahteristo P, Sarantaus L, Kyyronen P, Pyrhonen S, Blomqvist C, Pukkala E, Nevanlinna H, Sankila R. Survival of breast cancer patients in brca1, brca2, and non-brca1/2 breast cancer families: A relative survival analysis from finland. *Int J Cancer*. 2001;93:368-372
78. Ferrero JM, Ramaioli A, Formento JL, Francoual M, Etienne MC, Peyrottes I, Ettore F, Leblanc-Talent P, Namer M, Milano G. P53 determination alongside classical prognostic factors in node-negative breast cancer: An evaluation at more than 10-year follow-up. *Ann Oncol*. 2000;11:393-397
79. Haerslev T, Jacobsen GK. An immunohistochemical study of p53 with correlations to histopathological parameters, c-erbb-2, proliferating cell nuclear antigen, and prognosis. *Hum Pathol*. 1995;26:295-301
80. Mirza AN, Mirza NQ, Vlastos G, Singletary SE. Prognostic factors in node-negative breast cancer: A review of studies with sample size more than 200 and follow-up more than 5 years. *Ann Surg*. 2002;235:10-26
81. Fitzgibbons PL, Page DL, Weaver D, Thor AD, Allred DC, Clark GM, Ruby SG, O'Malley F, Simpson JF, Connolly JL, Hayes DF, Edge SB, Lichter A, Schnitt SJ. Prognostic factors in breast cancer. College of american pathologists consensus statement 1999. *Arch Pathol Lab Med*. 2000;124:966-978
82. Berclaz G, Li S, Price KN, Coates AS, Castiglione-Gertsch M, Rudenstam CM, Holmberg SB, Lindtner J, Erien D, Collins J, Snyder R, Thurlimann B, Fey MF, Mendiola C, Werner ID, Simoncini E, Crivellari D, Gelber RD, Goldhirsch A. Body mass index as a prognostic feature in operable breast cancer: The international breast cancer study group experience. *Ann Oncol*. 2004;15:875-884
83. Dignam JJ, Wieand K, Johnson KA, Fisher B, Xu L, Mamounas EP. Obesity, tamoxifen use, and outcomes in women with estrogen receptor-positive early-stage breast cancer. *J Natl Cancer Inst*. 2003;95:1467-1476
84. Dignam JJ, Wieand K, Johnson KA, Raich P, Anderson SJ, Somkin C, Wickerham DL. Effects of obesity and race on prognosis in lymph node-negative, estrogen receptor-negative breast cancer. *Breast Cancer Res Treat*. 2005:1-10

85. Holmes MD, Stampfer MJ, Colditz GA, Rosner B, Hunter DJ, Willett WC. Dietary factors and the survival of women with breast carcinoma. *Cancer*. 1999;86:826-835
86. Byers T, Sedjo RL. A weight loss trial for breast cancer recurrence: Pre-menopausal, post-menopausal, both, or neither? *Cancer Causes Control*. 2006;17:1-3
87. Holmes MD, Chen WY, Feskanich D, Kroenke CH, Colditz GA. Physical activity and survival after breast cancer diagnosis. *Jama*. 2005;293:2479-2486
88. Brown JK, Byers T, Doyle C, Coumeya KS, Demark-Wahnefried W, Kushi LH, McTieman A, Rock CL, Aziz N, Bloch AS, Eldridge B, Hamilton K, Katzin C, Koonce A, Main J, Mobley C, Morra ME, Pierce MS, Sawyer KA. Nutrition and physical activity during and after cancer treatment: An american cancer society guide for informed choices. *CA Cancer J Clin*. 2003;53:268-291
89. Kroenke CH, Fung TT, Hu FB, Holmes MD. Dietary patterns and survival after breast cancer diagnosis. *J Clin Oncol*. 2005;23:9295-9303
90. Colditz GA. Estrogen, estrogen plus progestin therapy, and risk of breast cancer. *Clin Cancer Res*. 2005;11:909s-917s
91. Garcia-Closas M, Brinton LA, Lissowska J, Chatterjee N, Peplonska B, Anderson WF, Szeszenia-Dabrowska N, Bardin-Mikolajczak A, Zatonski W, Blair A, Kalaylioglu Z, Rymkiewicz G, Mazepa-Sikora D, Kordek R, Lukaszek S, Sherman ME. Established breast cancer risk factors by clinically important tumour characteristics. *Br J Cancer*. 2006;95:123-129
92. Suzuki R, Rylander-Rudqvist T, Ye W, Saji S, Wolk A. Body weight and postmenopausal breast cancer risk defined by estrogen and progesterone receptor status among swedish women: A prospective cohort study. *Int J Cancer*. 2006;119:1683-1689
93. Suzuki R, Ye W, Rylander-Rudqvist T, Saji S, Colditz GA, Wolk A. Alcohol and postmenopausal breast cancer risk defined by estrogen and progesterone receptor status: A prospective cohort study. *J Natl Cancer Inst*. 2005;97:1601-1608
94. Takeuchi H, Baba H, Kano T, Maehara Y. The time-related changes of the importance of prognostic factors in breast cancer. A sequential multivariate analysis of 1423 japanese patients. *Breast Cancer Res Treat*. 2005;94:273-278
95. Zahl PH, Tretli S. Long-term survival of breast cancer in norway by age and clinical stage. *Stat Med*. 1997;16:1435-1449
96. Liu S, Edgerton SM, Moore DH, 2nd, Thor AD. Measures of cell turnover (proliferation and apoptosis) and their association with survival in breast cancer. *Clin Cancer Res*. 2001;7:1716-1723
97. Alexander FE, Anderson TJ, Brown HK, Forrest AP, Hepburn W, Kirkpatrick AE, Muir BB, Prescott RJ, Smith A. 14 years of follow-up from the edinburgh randomised trial of breast-cancer screening. *Lancet*. 1999;353:1903-1908
98. Tabar L, Yen MF, Vitak B, Chen HH, Smith RA, Duffy SW. Mammography service screening and mortality in breast cancer patients: 20-year follow-up before and after introduction of screening. *Lancet*. 2003;361:1405-1410
99. Shen Y, Yang Y, Inoue LY, Munsell MF, Miller AB, Berry DA. Role of detection method in predicting breast cancer survival: Analysis of randomized screening trials. *J Natl Cancer Inst*. 2005;97:1195-1203
100. Joensuu H, Lehtimaki T, Holli K, Elomaa L, Turpeenniemi-Hujanen T, Kataja V, Anttila A, Lundin M, Isola J, Lundin J. Risk for distant recurrence of breast cancer detected by mammography screening or other methods. *Jama*. 2004;292:1064-1073
101. Peto R, Boreham J, Clarke M, Davies C, Beral V. Uk and USA breast cancer deaths down 25% in year 2000 at ages 20-69 years. *Lancet*. 2000;355:1822
102. Johnstone PA, Norton MS, Riffenburgh RH. Survival of patients with untreated breast cancer. *J Surg Oncol*. 2000;73:273-277
103. Fisher B, Jeong JH, Bryant J, Anderson S, Dignam J, Fisher ER, Wolmark N. Treatment of lymph-node-negative, oestrogen-receptor-positive breast cancer: Long-term findings from national surgical adjuvant breast and bowel project randomised clinical trials. *Lancet*. 2004;364:858-868
104. Clarke M, Collins R, Darby S, Davies C, Elphinstone P, Evans E, Godwin J, Gray R, Hicks C, James S, MacKinnon E, McGale P, McHugh T, Peto R, Taylor C, Wang Y. Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: An overview of the randomised trials. *Lancet*. 2005;366:2087-2106
105. Fisher B, Jeong JH, Anderson S, Wolmark N. Treatment of axillary lymph node-negative, estrogen receptor-negative breast cancer: Updated findings from national surgical adjuvant breast and bowel project clinical trials. *J Natl Cancer Inst*. 2004;96:1823-1831

106. Hurley J, Doliny P, Reis I, Silva O, Gomez-Fernandez C, Velez P, Pauletti G, Pegram MD, Slamon DJ. Docetaxel, cisplatin, and trastuzumab as primary systemic therapy for human epidermal growth factor receptor 2-positive locally advanced breast cancer. *J Clin Oncol*. 2006;24:1831-1838
107. Romond EH, Perez EA, Bryant J, Suman VJ, Geyer CE, Jr., Davidson NE, Tan-Chiu E, Martino S, Paik S, Kaufman PA, Swain SM, Pisansky TM, Fehrenbacher L, Kutteh LA, Vogel VG, Visscher DW, Yothers G, Jenkins RB, Brown AM, Dakhil SR, Mamounas EP, Lingle WL, Klein PM, Ingle JN, Wolmark N. Trastuzumab plus adjuvant chemotherapy for operable her2-positive breast cancer. *N Engl J Med*. 2005;353:1673-1684
108. Ernst MF, Voogd AC, Coebergh JW, Poortmans PM, Roukema JA. Using loco-regional recurrence as an indicator of the quality of breast cancer treatment. *Eur J Cancer*. 2004;40:487-493
109. Stefoski Mikeljevic J, Haward RA, Johnston C, Sainsbury R, Forman D. Surgeon workload and survival from breast cancer. *Br J Cancer*. 2003;89:487-491
110. Simunovic M, Rempel E, Theriault ME, Coates A, Whelan T, Holowaty E, Langer B, Levine M. Influence of hospital characteristics on operative death and survival of patients after major cancer surgery in ontario. *Can J Surg*. 2006;49:251-258
111. Houterman S, Janssen-Heijnen ML, van de Poll-Franse LV, Brenner H, Coebergh JW. Higher long-term cancer survival rates in southeastern netherlands using up-to-date period analysis. *Ann Oncol*. 2006
112. Haerslev T, Jacobsen GK, Zedeler K. Correlation of growth fraction by ki-67 and proliferating cell nuclear antigen (pcna) immunohistochemistry with histopathological parameters and prognosis in primary breast carcinomas. *Breast Cancer Res Treat*. 1996;37:101-113
113. Gaffney DK, Brohet RM, Lewis CM, Holden JA, Buys SS, Neuhausen SL, Steele L, Avizonis V, Stewart JR, Cannon-Albright LA. Response to radiation therapy and prognosis in breast cancer patients with brca1 and brca2 mutations. *Radiother Oncol*. 1998;47:129-136
114. Mansi JL, Gogas H, Bliss JM, Gazet JC, Berger U, Coombes RC. Outcome of primary-breast-cancer patients with micrometastases: A long-term follow-up study. *Lancet*. 1999;354:197-202
115. Page DL, Gray R, Allred DC, Dressler LG, Hatfield AK, Martino S, Robert NJ, Wood WC. Prediction of node-negative breast cancer outcome by histologic grading and s-phase analysis by flow cytometry: An eastern cooperative oncology group study (2192). *Am J Clin Oncol*. 2001;24:10-18
116. Houterman S, Janssen-Heijnen ML, Verheij CD, Louwman WJ, Vreugdenhil G, van der Sangen MJ, Coebergh JW. Comorbidity has negligible impact on treatment and complications but influences survival in breast cancer patients. *Br J Cancer*. 2004;90:2332-2337
117. Siegelmann-Danieli N, Khandelwal V, Wood GC, Mainali R, Prichard J, Murphy TJ, Evans JF, Yumen O, Bernath AM. Breast cancer in elderly women: Outcome as affected by age, tumor features, comorbidities, and treatment approach. *Clin Breast Cancer*. 2006;7:59-66

PART III

Risk of second primary cancer in breast cancer patients

Chapter 6

Rising incidence of breast cancer among female cancer survivors: Implications for surveillance

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Abstract

Background and objectives: The number of female cancer survivors has been rising rapidly, resulting in an increasing number of women at risk of second breast cancer. Thus, we assessed the increase in breast cancer incidence among cancer survivors to determine the need for surveillance.

Methods: We computed incidence of primary breast cancer in two cohorts of female cancer survivors with a first diagnosis of cancer at ages 30+ in the periods 1975-1979 and 1990-1994. Cohorts were followed for 10 years through a population-based cancer registry.

Results: Over a period of 20 years, the incidence rate of breast cancer among female cancer survivors doubled (rate ratio:1.9, 95%CI: 1.5-2.4). Age-adjustment reduced this increase by 43% (age-standardized rate ratio (RR-adj):1.5, 95%CI: 1.1-2.1). Increases over time were most marked for women who were first diagnosed with a non-breast cancer (RR-adj:2.1, 95%CI: 1.1-3.9), for women with second breast cancer stage II (RR-adj:3.1, 95%CI: 1.2-7.0) and for those diagnosed with a second breast cancer aged 75 years or more (RR-adj:3.6, 95%CI: 2.0-6.3). The proportion of second breast cancer stage II and III among the non-breast cancer survivors was 62% contrasting to only 32% among the breast cancer survivors (p-value=0.005).

Conclusions: A marked rise in breast cancer incidence among female cancer survivors was observed, particularly among survivors previously diagnosed with a non-breast cancer and those older than 75 years. Research to optimize follow-up strategies for these women to detect breast cancer at an early stage is warranted.

6.1. Introduction

Breast cancer is the most common cancer among women in general, but also among women who previously diagnosed with any type of cancer[1]. During the past three decades, a four-fold increase in the incidence of contralateral breast cancer has been reported, which is much higher than that of first primaries[2]. However in the same period a 9% decrease in the incidence of second breast cancer among former breast cancer patients was reported in the USA[3]. The increasing prevalence of patients ever diagnosed with cancer should theoretically result in an increase in the incidence of new primary cancer[4], i.e. breast cancer among cancer survivors. Changes in female reproductive behaviour and lifestyle, that underlie the increasing trend of first breast cancer, may also affect the increased risk of a second breast cancer[5, 6]. Furthermore, cancer survivors are exposed to additional carcinogenic factors such as high-dose radiation for the first cancer[7]. Using the data from a long-standing cancer registry in southern Netherlands, we investigated the incidence of breast cancer among cancer survivors since 1975. We assessed the change in incidence of a second breast cancer over time according to age, stage and type of treatment of the first cancer.

6.2. Methods

Data on cancer patients were obtained from the Eindhoven Cancer Registry (ECR), a population-based registry with follow-up data since 1970, including clinical aspects such as stage and initial treatment. The coverage area of the registry in the southern Netherlands has gradually increased, covering about 0.9 million people between 1975 and 1985 and over 2 million people since 1988.

The change in breast cancer incidence among cancer survivors over time was calculated using the fixed inception cohort method[3]. We defined 2 patient cohorts: women diagnosed with a primary cancer between 1975 and 1979 and those diagnosed between 1990 and 1994. We included all cancer types diagnosed in women aged 30 years or older within the given periods, excluding premalignant or in-situ cancer and basal cell carcinoma of the skin. The rules for multiple primary cancers from the International Agency for Cancer Research were used[8]. Only patients who survived six months or longer were included in the cohort. The follow-up time extended from the date of the initial cancer diagnosis to the date of a second cancer, death, loss to follow-up, or end of the study, whichever occurred first. We applied a 10-year follow-up for each patient cohort. Thus, the 1975-1979 cohort was followed until 1989 and the 1990-1994 cohort until 2004. We computed incidence rates per 100,000 person-years for each cohort of female cancer survivors, categorizing each subsequent breast cancer according to age (30-49 years, 50-74 years and 75+ years) and TNM-stage[9]. Furthermore, we stratified according to type of first primary cancer (breast and non-breast cancer) and treatment of the first primary (surgery, radiotherapy with or without surgery, systemic therapy with or without surgery, radiotherapy and systemic therapy with or without surgery, and no therapy). Rates were adjusted for age using the European standard population[10]. Risk ratio, rate (adjusted by age) ratio and their 95% confidence intervals (95%CI) were computed to assess the difference between the patient groups in the two periods[10].

6.3. Results

Within 10 years of the first cancer diagnosis, 100 of 3368 (3%) and 182 of 5507 (3%) female cancer survivors diagnosed in the 1970s and in the 1990s, respectively, were subsequently diagnosed with a second breast cancer. Cancer survivors diagnosed with a first cancer in the 1990s were 2.1 years older at first cancer diagnosis, and they received systemic treatment more often than patients diagnosed in the 1970s (risk ratio: 1.5; 95%CI: 1.3-1.6 and risk ratio: 2.1; 95%CI: 1.8-2.4, for systemic therapy and for systemic therapy in combination with radiotherapy, respectively) (Table 6.1).

Table 6.1. Characteristics of female cancer survivors diagnosed in 1975-1979 and in 1990-1994 with a 10-year follow-up.

Period of first primary cancer diagnosis	1975-1979		1990-1994			
Number of cancer survivors	3368		5507			
Women-years of follow-up	29,132		28,024			
Mean age at first cancer, years	60.6		62.7			
Mean follow-up time, years	5.7		4.9			
	N	%	N	%	Risk ratio*	95%CI
Age at diagnosis of first cancer						
30-49 years	791	23	1200	22	0.9	0.86-1.00
50-74 years	2070	61	3086	56	0.9	0.88-0.94
75+	507	15	1221	22	1.5	1.3-1.6
Treatment of first cancer						
Surgery	1417	42	2248	41	0.97	0.92-1.02
Radiotherapy ± surgery	1245	37	1450	26	0.7	0.7-0.8
Systemic therapy ± surgery	322	10	767	14	1.5	1.3-1.6
Radio- + systemic-therapy ± surgery	220	6	760	14	2.1	1.8-2.4
No therapy	164	5	282	5	1.0	0.9-1.3
Type of first cancer						
Breast cancer	1436	43	2199	40	0.94	0.89-0.99
Non-breast cancer**	1932	57	3308	60	1.05	1.01-1.09

N indicates number of cases and % indicates column's percentage

*Risk ratio compares proportion in 1990s with that in 1970s

** Non-breast cancer in 1970s consisted of 3% respiratory cancers, 40% digestive cancers, 34% urogenital cancers, 9% haematopoetic cancers and 15% other cancers, and in 1990s 7% respiratory cancers, 33% digestive cancers, 30% urogenital cancers, 10% haematopoetic cancers and 19.3% other cancers.

Compared with the first period, a 90% increase in breast cancer incidence for female cancer survivors was observed (rate ratio: 1.9; 95%CI: 1.5-2.4, Figure 6.1). After age-adjustment according to the European standard population, this ratio was attenuated to 1.5.

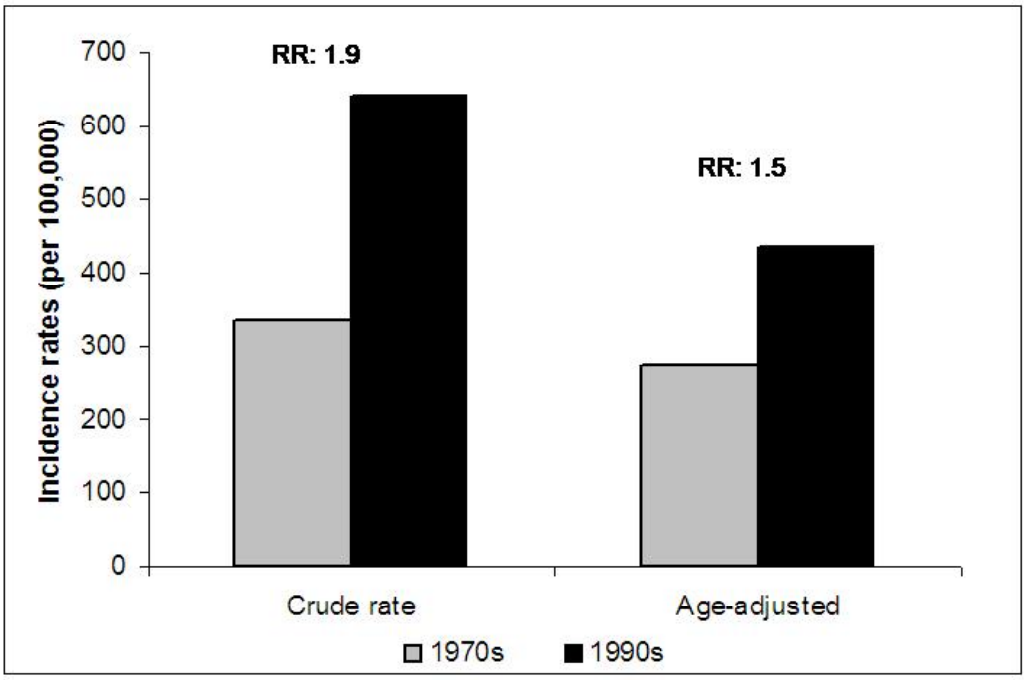

Figure 6.1. Rates of incidence of primary breast cancer in female cancer survivors
RR (rate ratio) compares incidence rate in 1990s with incidence rate in 1970s: for crude rate 1990s vs. 1970s 95%CI= 1.5-2.4, and for adjusted rate 1990s vs. 1970s 95%CI= 1.1-2.1.

There appeared to be a similar increase in breast cancer incidence across most treatment groups, albeit with wide confidence intervals. The incidence rate for stage I breast cancer increased by 60% (age-adjusted rate ratio (RR-adj): 1.6; 95%CI: 1.01-2.6) between the 1970s and the 1990s, whereas it tripled for stage II breast cancer (RR-adj: 3.1; 95%CI: 1.2-7.0). The largest increase in incidence of breast cancer was found for older cancer survivors (RR-adj: 3.6; 95%CI: 2.0-6.3) and those previously diagnosed with non-breast cancer (RR-adj: 2.1; 95%CI: 1.1-3.9).

Figure 6.2 illustrates the stage distribution of breast cancer for female survivors diagnosed with a first cancer in 1990-1994 categorized according to age at second breast cancer diagnosis and type of first cancer. A significant difference in stage distribution (p-value of chi-square test: 0.043) was found for the non-breast cancer survivors younger than 75 years at second breast cancer diagnosis compared to those with a previous breast cancer.

Table 6.2. Number (N) and European standardised incidence rates of second breast cancer per 100,000 women-years for female cancer survivors (breast and non-breast cancer)

Period of first primary cancer diagnosis	**1970s**		**1990s**		**Rate ratio***	**(95%CI)**
Mean age at breast cancer, years	**60.8**		**63.2**			
	N	Incidence (100,000)	N	Incidence (100,000)		
Age at breast cancer (second primary - age-specific rates)						
30-49 years	23	659	43	880	1.3	0.8-2.2
50-74 years	61	371	94	590	1.6	1.2-2.2
75+	16	174	45	624	3.6	2.0-6.3
Stage of breast cancer (second primary)						
I	41	175	82	285	1.6	1.01-2.6
II	13	69	57	212	3.1	1.2-7.0
III	11	30	18	71	2.3	0.96-5.6
IV	9	71	14	49	0.7	0.3-2.0
Unknown	26	90	11	38	0.4	0.2-1.1
Type of first primary cancer						
Breast cancer	77	664	127	1009	1.5	1.0-2.2
Non-breast cancer	23	142	55	292	2.1	1.1-3.9
Treatment of first primary cancer						
Surgery	39	290	74	519	1.8	1.0-3.2
Radiotherapy ± surgery	48	576	64	844	1.5	0.9-2.4
Systemic therapy ± surgery	5	249	15	468	1.9	0.5-6.5
Radiotherapy + systemic therapy ± surgery	7	801	25	796	0.99	0.4-2.7
No therapy	1	13	4	244	18.5	1.8-192.0

N indicates number of cases. *ESR: European Standardised Rates**Rate ratio compares incidence rate in 1990s with incidence rate in 1970s, if adjusted rates are presented than rate ratio is based on the standardised rates.

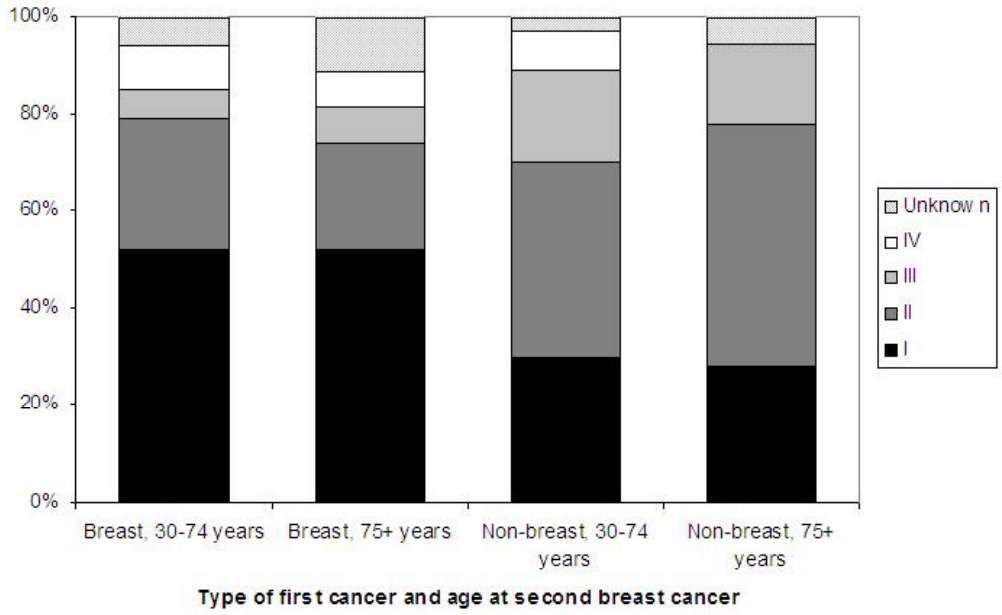

Figure 6.2. Stage distribution of breast cancer in female cancer survivors diagnosed with a first cancer in 1990-1994 according to type of first cancer and age at (second) breast cancer diagnosis

6.4. Discussion

The incidence of breast cancer among female cancer survivors has doubled within a period of 20 years, especially among the elderly and for second breast cancer stage II. Part of this increase can be attributed to the fact that patients have become older. Ageing of the patient population accounted for approximately 43% of the observed increased trend in breast cancer incidence among female cancer survivors, because adjusting for age reduced the increase from 89% to 51% in the 20-year period. The increase in breast cancer incidence among cancer survivors may also be due to other changes such as: (1) application of more combined therapies with higher carcinogenic potential; (2) mass screening, started in the early 90's in our population and (3) lifestyle, reproductive and hormonal factors, such as a longer interval between menarche and date of first birth and alcohol use.

Changes in therapy for first primary cancer may have modified the incidence of second breast cancer over time. Radiotherapy has been associated with an approximately 40% higher risk of developing subsequent breast cancer compared to systemic hormonal or cytotoxic treatment[11, 12]. A similar increase in the incidence of breast cancer was observed over time for those who were irradiated and those who only underwent surgery. The increasing incidence of breast cancer among those who were irradiated could therefore not be attributed to radiotherapy. However, because we followed patients for only 10 years, we may have missed late adverse effects of radiation[13]. Although the use of systemic cancer treatment had doubled during the last 20 years, the increase in the incidence of breast cancer was similar for those who received systemic treatment and surgically treated patients, whereas a decrease in incidence was expected[14, 15]. Thus, application of new carcinogenic therapy may have taken place in the meantime.

In the early 1990's, biennial mass screening for breast cancer was implemented for all women aged 50-69 years and in 1998 this program was expanded to include women up to the age of 75[16]. Due to the intensified use of mammography for mass screening the incidence of breast cancer increased by about 30%[17] and may thus also be responsible for the increased incidence of breast cancer among cancer survivors. We observed a significant increase in the proportion of female survivors diagnosed with early breast cancer (stage I and II being 54% in 1970s versus 76% in 1990s, risk ratio: 1.4; 95%CI: 1.2-1.7) and a 60% (95%CI: 1.2-2.2) increase in rate for the screening age group, i.e. those aged 50-74 years. However, a much larger increase in the incidence of breast cancer over time was observed among those older than 74 years (rate ratio: 3.6 95%CI: 2.0-6.3), suggesting a role of risk factors other than screening, e.g. older age at first childbirth, fewer children, alcohol and other determinants of post-menopausal obesity[18].

In the Netherlands, patients with breast cancer are generally subject to enhanced surveillance: annual mammography until the age of 60, followed by a biennial mammography up to the age of 74[19]. This intense surveillance pattern is likely to contribute to an increase in detection rates for slow-growing tumours that would have remained in the pre-clinical phase longer without screening mammography[20]. Thus, breast cancer survivors are probably diagnosed more often and earlier with a low-grade breast cancer, that may require less aggressive treatment than survivors of other cancers[21].

In view our results, the following groups may need a more intensive follow-up for breast cancer. Firstly, the non-breast cancer survivors. These patients had a larger proportion of stage II cancers than with patients with a first diagnosis of breast cancer. Among non-breast cancer patients diagnosed in 1990-1994 and followed-up for 10 years, 29% of second breast cancers was stage 1, 44% stage 2, 18% stage III, and 5% stage IV. For breast cancer patients, the corresponding percentages were 52% for stage I, 26% for stage II, 6% for stage III, and 9% for stage IV (p-value of Chi-square: 0.005). Thus, although the absolute risks (2% during 10-years follow-up) remain small, female survivors of non-breast cancer would probably benefit from a more intensive follow-up than just the mass screening program, such as an additional biennial clinical breast examination.[22] A second group is female survivors older than 75 years.[23] Survivors of this age group exhibited the largest increase in breast cancer incidence over time. Furthermore, compared to the general population, they had a 3-fold higher risk of breast cancer than the general population.[24] Given a worse stage distribution especially among those diagnosed with a non-breast cancer, it seems logical to extend the screening program to include these women. However, mortality due to other causes is high[25] and the existence of comorbidities would probably limit treatment choices.[26] Thus, a detailed cost-effectivity study, preferably adjusting for Quality of Life, is warranted. A last group is cancer survivors younger than 50 years. Although the incidence of breast cancer has not increased much over time, incidence was highest for survivors aged 30-49 years. This group may merit the same screening regimen as women with a genetic predisposition towards breast cancer, i.e. with an MRI.

In summary, we found a considerable increase in the incidence of breast cancer among female cancer survivors, especially for survivors aged 75 and above. The increase in second breast cancers was most striking for stage II cancers. These observations mean there is ample room for improvement of follow-up strategies in order to detect breast cancer at an early stage in the elderly.

References

1. Mariotto AB, Rowland JH, Ries LA, Scoppa S, Feuer EJ. Multiple cancer prevalence: A growing challenge in long-term survivorship. *Cancer Epidemiol Biomarkers Prev*. 2007;16:566-571
2. Louwman WJ, Voogd AC, van Dijck JAAM, Nieuwenhuijzen GAP, Ribot JG, Pruijt JFM, Coebergh JWW. On the rising trends of incidence and prognosis for breast cancer patients diagnosed 1975-2004: A long-term population-based study in southeastern netherlands. *Cancer Causes and Control*. 2007
3. Yu GP, Schantz SP, Neugut AI, Zhang ZF. Incidences and trends of second cancers in female breast cancer patients: A fixed inception cohort-based analysis (united states). *Cancer Causes Control*. 2006;17:411-420
4. Fraumeni JFJ, Curtis R, Edwards BK, Tucker MA. *Introduction*. Bethesda, MD: National Cancer Institute; 2006.
5. Largent JA, Capanu M, Bernstein L, Langholz B, Mellemkjaer L, Malone KE, Begg CB, Haile RW, Lynch CF, Anton-Culver H, Wolitzer A, Bernstein JL. Reproductive history and risk of second primary breast cancer: The wecare study. *Cancer Epidemiol Biomarkers Prev*. 2007;16:906-911
6. Dignam JJ, Wieand K, Johnson KA, Fisher B, Xu L, Mamounas EP. Obesity, tamoxifen use, and outcomes in women with estrogen receptor-positive early-stage breast cancer. *J Natl Cancer Inst*. 2003;95:1467-1476
7. van Leeuwen FE, Travis LB. *Second cancers*. Philadelphia: Lippincott Williams and Wilkins; 2005.
8. International rules for multiple primary cancers (icd-0 third edition). *Eur J Cancer Prev*. 2005;14:307-308
9. Sobin LH, Fleming ID. Tnm classification of malignant tumors, fifth edition (1997). Union internationale contre le cancer and the american joint committee on cancer. *Cancer*. 1997;80:1803-1804
10. Breslow NE, Day NE. Statistical methods in cancer research. Volume ii--the design and analysis of cohort studies. *IARC Sci Publ*. 1987:1-406
11. Schaapveld M, Visser O, Louwman WJ, Willemse PH, de Vries EG, van der Graaf WT, Otter R, Coebergh JW, van Leeuwen FE. The impact of adjuvant therapy on contralateral breast cancer risk and the prognostic significance of contralateral breast cancer: A population based study in the netherlands. *Breast Cancer Res Treat*. 2007
12. Soerjomataram I, Louwman WJ, Lemmens VE, de Vries E, Klokman WJ, Coebergh JW. Risks of second primary breast and urogenital cancer following female breast cancer in the south of the netherlands, 1972-2001. *Eur J Cancer*. 2005;41:2331-2337
13. Travis LB. The epidemiology of second primary cancers. *Cancer Epidemiol Biomarkers Prev*. 2006;15:2020-2026
14. Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: An overview of the randomised trials. *Lancet*. 2005;365:1687-1717
15. van Leeuwen FE, Klokman WJ, Stovall M, Dahler EC, van't Veer MB, Noordijk EM, Crommelin MA, Aleman BM, Broeks A, Gospodarowicz M, Travis LB, Russell NS. Roles of radiation dose, chemotherapy, and hormonal factors in breast cancer following hodgkin's disease. *J Natl Cancer Inst*. 2003;95:971-980
16. Verbeek AL, Broeders MJ. Evaluation of the netherlands breast cancer screening programme. *Ann Oncol*. 2003;14:1203-1205
17. Fracheboud J, Otto SJ, van Dijck JA, Broeders MJ, Verbeek AL, de Koning HJ. Decreased rates of advanced breast cancer due to mammography screening in the netherlands. *Br J Cancer*. 2004;91:861-867
18. Althuis MD, Dozier JM, Anderson WF, Devesa SS, Brinton LA. Global trends in breast cancer incidence and mortality 1973-1997. *Int J Epidemiol*. 2005;34:405-412
19. NABON_Nationaal_Borstkanker_Overleg_Nederland. Breast cancer treatment: National guidelines. 2005;2007
20. Shen Y, Yang Y, Inoue LY, Munsell MF, Miller AB, Berry DA. Role of detection method in predicting breast cancer survival: Analysis of randomized screening trials. *J Natl Cancer Inst*. 2005;97:1195-1203
21. Moody-Ayers SY, Wells CK, Feinstein AR. "Benign" Tumors and "Early detection" In mammography-screened patients of a natural cohort with breast cancer. *Arch Intern Med*. 2000;160:1109-1115
22. Rijnsburger AJ, van Oortmarssen GJ, Boer R, Draisma G, To T, Miller AB, de Koning HJ. Mammography benefit in the canadian national breast screening study-2: A model evaluation. *Int J Cancer*. 2004;110:756-762
23. Boer R, de Koning HJ, van Oortmarssen GJ, van der Maas PJ. In search of the best upper age limit for breast cancer screening. *Eur J Cancer*. 1995;31A:2040-2043

24. Comprehensive_Cancer_Centre. http://www.ikcnet.nl. Accessed July 2007.
25. Hooning MJ, Aleman BM, van Rosmalen AJ, Kuenen MA, Klijn JG, van Leeuwen FE. Cause-specific mortality in long-term survivors of breast cancer: A 25-year follow-up study. *Int J Radiat Oncol Biol Phys*. 2006;64:1081-1091
26. Louwman WJ, Janssen-Heijnen ML, Houterman S, Voogd AC, van der Sangen MJ, Nieuwenhuijzen GA, Coebergh JW. Less extensive treatment and inferior prognosis for breast cancer patient with comorbidity: A population-based study. *Eur J Cancer*. 2005;41:779-785

Chapter 7

Primary malignancy after primary female breast cancer in the south of the Netherlands, 1972-2001: a population-based longitudinal study

Soerjomataram I, Louwman WJ, de Vries E, Lemmens VE, Klokman WJ, Coebergh JW. Primary malignancy after primary female breast cancer in the south of the netherlands, 1972-2001. Breast Cancer Res Treat. 2005;93:91-95.

Abstract

Background and objectives: To assess the risk of second primary cancers among women with previous breast cancer and calculate the excess burden of second cancer in the population.

Material: A population-based longitudinal study was conducted using the Eindhoven cancer registry data on 9919 breast cancer patients diagnosed in the period 1972-2000 and followed until 2001. Standardized Incidence Ratios (SIR) and Absolute Excess Risks (AER) were calculated.

Results: In total, 1298 (13%) women developed a second primary cancer. The risk of overall second cancer was higher among breast cancer patients compared to the general population (SIR: 2.4; 95%CI: 2.3-2.5), with an absolute excess risk (AER) of 115 second cancers for every 10,000 breast cancer patients per year. High SIR and AER were observed for breast cancer (SIR: 3.5; 95%CI: 3.2-3.8; AER: 64/10,000 patients/year), colon cancer (SIR: 1.5; 95%CI: 1.1-1.5; AER: 4.5/10,000 patients/year) and ovarian cancer (SIR: 1.7; 95%CI: 1.3-2.4; AER: 2.8/10,000 patients/year).

Conclusions: Our recent data show that women with previous breast cancer have an elevated risk of developing a second cancer compared to the general population. Excess burden for the population is especially high for second cancers of the breast, ovary and colon. Closer monitoring of breast cancer patients may be justified for second breast cancer and for ovary cancer in women diagnosed with breast cancer before menopause and for colon cancer in breast cancer patients diagnosed after 50 years old.

7.1. Introduction

Breast cancer is one of the most prevalent diseases among women in the developed world. Improvements in breast cancer treatment have prolonged life among cancer patients [1]. In Eindhoven, the 5-year relative survival of breast cancer patients increased from 60% in 1970-1978 to 80% in 1988-1997 [2]. This longer survival after the occurrence of a first cancer resulted in an increased risk to develop a second cancer [3].

The study of second cancer risk has important implications for public health. Firstly, the study of second cancer risk is necessary for assessment of the short- and long-term effects of breast cancer treatment. Secondly, an association between the first and second cancer may exist. Thus, the study of this relationship may provide information about the possible determinants or risk factors for second cancers [3].

Some studies suggest that women with a history of breast cancer have an elevated risk of developing a second cancer, particularly ovarian and endometrium cancer [4-8]. Increased risks of tumours of the salivary gland [9;10], connective tissue [8;11;12], lung [5;9;13], oesophagus [14;15], stomach [7;16], colon [17;18] and thyroid [5;14;19] have been reported less consistently. There are indications that the risk of liver [16] and gall bladder cancer [6;20] may be lower among patients with a history of breast cancer compared to the general female population.

Our cohort comprises the most recent data on second breast cancer, with a long follow-up and a sufficient number of cases. The aim of this population-based cohort study was to assess the incidence of second primary cancers among breast cancer patients and compare it to the incidence expected in the general population. Furthermore, we examined the excess burden of second primary cancer among these patients in relation to the age at diagnosis of the primary breast cancer. For this purpose, relative and absolute risks of developing second cancer following breast cancers were calculated.

7.2. Materials and methods

The cohort

Breast cancer patients were obtained from the Comprehensive Cancer Center South in Eindhoven, situated in the south of the Netherlands. This is a population-based cancer registry covering 2.4 million inhabitants in 2004. The cancer registries in the Netherlands receive lists of newly diagnosed cases on a regular basis from the Pathology and Haematology Departments in the region. All pathology laboratories have a combined automated archive (PALGA). In addition, lists of all hospitalised cancer patients were obtained. These lists are based on data from the national Registry of Hospital Discharge Diagnoses, which collects data from hospital medical records. Active follow-up of vital status through municipal population registries and the Central Bureau for Genealogy was conducted. All malignant and in situ malignancies diagnosed since 1972 in individuals residing in Eindhoven were registered (including superficial bladder cancer), with the exception of carcinomas in situ of the cervix [2].

Eligible participants for this study were Dutch women older than 25 years at the time of breast cancer diagnosis in the period 1972-2000 (n=11835). Patients with other malignancies diagnosed before breast cancer and patients with a secondary cancer that were metastasis were excluded beforehand. Among the eligible women we excluded breast cancer patients with less than 1 year of follow-up time (n=1458), as well as patients with in situ primary breast cancer (n=458). For the calculation of secondary ovarian cancer, patients who were oophorectomised as treatment for breast cancer were not included in the analyses (n=9). Thus, 9919 patients which 1298 of them diagnosed with a second primary cancer after breast cancer remained for analysis.

Methods

We used the person-years analysis to study the incidence of second neoplasms after diagnosis of breast cancer. We compared the incidence of second tumours among patients with a diagnosis of breast cancer (the observed incidence) with the incidence of the same tumours in the reference population (the expected incidence). We took into account the amount of time that had passed between the diagnosis of the first and second tumour, adjusting for age (in 5-year categories) and calendar year of breast cancer diagnosis [21;22]. Through the adjusted person-years obtained, we calculated the expected subsequent primary cancer relative risk for the general population. The observed and expected numbers were compared in order to determine the standardised incidence ratio (SIR). The statistical significance and 95% confidence intervals were calculated using exact Poisson probability [23]. Additionally, we calculated the absolute excess risk (AER) in order to assess the excess incidence of overall second cancers. This measure estimates the excess number of second malignancies per 10,000 patients per year [3]. Risk estimates were calculated for the total study population and for pre- and postmenopausal patients separately. All statistical analyses were performed using SPSS 11.5 for Windows (Statistical Products and Service Solution, Inc, Chicago, USA).

7.3. Results

Between 1972 and 2000, 9919 women were diagnosed with primary breast cancer, yielding 65,938 person years. Average age at diagnosis of primary breast cancer was 58.8 years, whereas average follow-up time was 6.6 years.

Overall, 1298 breast cancer patients developed a second cancer, in contrast to 468 expected cases in the population (SIR: 2.4; 95%CI: 2.3-2.5). This resulted in an annual excess of 115 tumours per 10,000 persons. Breast cancer patients had a significantly increased risk of developing a second breast cancer (SIR: 3.5; 95%CI: 3.2-3.8), salivary gland cancer (SIR: 4.6; 95%CI: 1.2-12.5), and connective tissue cancer (SIR: 3.2; 95%CI: 1.2-7.3). Almost two-fold elevated risks were evident for cancer of colon, ovary, skin (melanoma) and bladder.

The SIR and AER were considerably higher among women diagnosed with breast cancer before the age of 50 compared to women diagnosed after age 50 (SIR: 4.5 and 2.0; AER: 143.0 and 100.5, respectively). Three to seven-fold increased risks of developing salivary, stomach, bone, skin, breast and ovarian cancer were found for the younger age group. In contrast, among women diagnosed after the age of 50 only slightly increased risks of breast, colon and bladder cancer were observed. Of all second cancers, breast cancer represented the highest AER in both age groups (AER: 95.2 and 47.6) (Table 7.1).

Table 7.1. Relative (SIR)* and absolute risks (AER)** among breast cancer patients in the south of Netherlands.

	All Patients				Pre-menopause¶			Post-menopause†		
Num. of patients	9919				2950			6969		
Num. of person years	65,938				22,546			43,392		
Site of second cancer	Obs[a]	SIR	95% CI[b]	AER	Obs	SIR	AER	Obs	SIR	AER
All second cancers	1298	2.4‡	2.3-2.5	115.0	415	4.5‡	143.0	883	2.0‡	100.5
Mouth and pharynx	12	1.7	0.9-3.1	0.8	4	2.9	1.2	8	1.4	0.6
Salivary glands	4	4.6‡	1.2-12.5	0.5	3	18.9‡	1.3	1	1.4	0.1
Pharynx	3	2.0	0.4-6.4	0.2	0	E 0.4§	-0.2	3	2.7	0.4
Digestive tract	196	1.3‡	1.1-1.5	7.2	27	1.9‡	5.8	169	1.3‡	8.0
Oesophagus	7	1.5	0.6-3.3	0.4	1	2.1	0.2	6	1.5	0.4
Stomach	33	1.3	0.9-1.8	1.1	8	4.4‡	2.7	25	1.1	0.3
Colon	90	1.5‡	1.1-1.8	4.5	10	1.8	2.0	80	1.5‡	5.9
Rectum	36	1.3	1.0-2.0	1.1	7	2.0	1.5	29	1.2	0.9
Gall bladder	12	1.1	0.6-2.0	0.2	0	E 0.6§	-0.3	12	1.2	-0.4
Pancreas	16	1.1	0.6-1.8	0.2	1	0.7	-0.2	15	1.1	0.5
Respiratory tract	36	1.2	0.9-1.7	1.0	12	2.0	2.6	24	1.0	0.1
Lung	34	1.3	0.9-1.8	1.1	11	2.0	2.5	23	1.1	0.4
Pleura	2	3.5	0.4-14.4	0.2	1	10.9	0.4	1	2.1	0.1
Bone	2	3.2	0.4-13.5	0.2	2	21.6‡	0.8	0	E 0.5§	-0.1
Connective Tissue	6	3.2‡	1.2 - 7.3	0.6	2	4.3	0.7	4	2.8	0.6
Melanoma	21	1.8‡	1.1 - 2.7	1.4	12	3.2‡	3.7	9	1.1	0.2
Breast	588	3.5‡	3.2-3.8	63.9	255	6.3‡	95.2	333	2.6‡	47.6
Urogenital tract	137	1.5‡	1.2-1.7	6.6	40	2.5‡	10.6	97	1.3	4.5
Cervix uteri	9	0.9	0.4-1.7	-0.2	5	1.8	1.0	4	0.5	-0.8
Corpus uteri	40	1.4	1.0- 1.9	1.8	8	1.6	1.4	32	1.4	2.0
Ovarium	43	1.7‡	1.3-2.4	2.8	21	3.9‡	6.9	22	1.1	0.6
Vagina Vulva	6	1.3	0.4-2.6	0.1	1	2.6	0.3	5	1.0	0
Kidney	17	1.2	0.7-2.0	0.5	2	1.1	0.1	15	1.2	0.7
Bladder	22	1.9‡	1.2-2.9	1.6	3	3.5	0.9	19	1.8‡	1.9
Brain	6	1.2	0.5-3.2	0.2	3	2.6	0.8	3	0.8	-0.2
Thyroid	2	0.8	0.1-3.3	-0.1	2	2.9	0.6	0	E 2.3§	-0.5
Non-Hodgkin's lymphoma	12	0.8	0.4-1.4	-0.5	3	1.3	0.3	9	0.7	-1.0
Myeloma	4	0.5	0.1-1.4	-0.6	1	1.4	0.1	3	0.4	-1.0
Leukaemia	15	1.3	0.9-2.6	0.8	1	0.8	-0.1	14	1.7	1.3

* SIR: standardised incident ratio

** AER: Absolute excess risk per 10,000 person per year

[a] Obs: Observed numbers of second primary cancers diagnosed in 1972-2001

[b] 95% CI: 95 % confidence interval

¶ I Age at primary breast cancer diagnosis less than 50 years old

† Age at primary breast cancer diagnosis more than or equal to 50 years old

‡ 95 % Confidence interval excludes 1

§ E: Expected numbers of second primary cancers in the south of Netherlands

7.4. Discussion

Our results confirm that women with a history of breast cancer have an elevated risk of secondary cancer. Every year, 115 excess cancers were diagnosed among 10,000 breast cancer patients. Higher risks of cancer of the salivary gland, bone, colon, breast, ovary, connective tissue and skin (melanoma) were observed for women with a previous diagnosis of breast cancer, particularly those diagnosed before the age of 50. Increased risks of second breast, colon and bladder cancer were evident for women diagnosed with breast cancer after the age of 50.

We observed an elevated risk of second breast, ovarian, connective tissue and stomach cancer among breast cancer patients. Genetic factors may play a role in the explanation of these findings. The growth of breast [1] and ovarian cancer [24] has been found to be related to mutation of BRCA1 or BRCA2. However, genetic factors account for only 5-10% of cancer cases in the population, especially in young and middle-aged patients [25;26]. Similarly, Li and Fraumeni identified a familial tendency for connective tissue cancer and breast cancer [27] and Dhillon observed the same familial pattern for gastric and breast cancer [28].

The increased risk of salivary gland, bone, stomach, breast and connective tissue cancer could be related to the radiotherapy undergone by breast cancer patients as initial therapy [8;11;12;15;29]. Radiotherapy has been shown to cause second cancer especially in younger patients as might be demonstrated in our study [1]. Unlike other studies, no elevation in the risk of endometrial cancer was found. [8;30-33]. Use of tamoxifen, which is related to an increased risk of endometrial cancer, by breast cancer patients over 50 years was not initiated until the late 1980s [34]. Our study began earlier, which might underestimate the risk of second endometrial cancer.

The results of our study are consistent with findings from previous studies suggesting a higher risk of ovarian and colon cancer among breast cancer patients. The association between breast cancer and these cancers may be explained by the risk factors shared by these conditions, such as reproductive and dietary factors [35-38].

An increased risk of melanoma was observed among breast cancer patients, particularly those diagnosed with breast cancer before menopause. Mutation of BRCA2 has been suggested as a possible determinant of the higher incidence of melanoma among breast cancer patients [39;40]. In addition, elevated levels of oestrogen in women, which induced breast cancer in the first place, might stimulate melanogenesis resulting in an increased risk of melanoma [41;42]. Finally, higher levels of radiation exposure during breast cancer treatment may partly contribute to the elevated risk of melanoma among these patients [43].

The elevated SIR for bladder cancer observed in our study remains unexplained. Scattered radiation during breast cancer radiotherapy [13] and cyclophosphamide could possibly cause an increased risk of bladder cancer [3]. However this treatment combination is more common among breast cancer patients below 50 years, whereas we observed a higher risk of bladder cancer among older women.

We found an excess of 115 second cancers for every 10,000 breast cancer patients per year, a slightly lower excess than that observed in a previous study in the United States [44]. Our study comprises more recent data, which may indicate a reduction in second cancer risk. This may be due to an improvement in breast cancer treatment during recent decades or an increased awareness of second cancer in the population. Furthermore, our results indicate that a high risk for a certain cancer does not necessarily mean a substantial excess burden in the population. For instance, we found a marked increase in the risk of second salivary and bone cancers among women diagnosed before the age of 50. However, the absolute excess risks are rather low. On the other hand, AER for second breast and ovarian cancer in the same group are much higher, although their SIR's are not as high as those for salivary or bone cancer. This shows that monitoring for second breast and ovarian cancer may benefit the population more.

Some limitations of our study should be considered. Firstly, we were able to collect data on the occurrence of second cancers, but we did not have individual exposure data on the most important risk factors associated with cancer. Thus, we were not able to assess the role of the prominent risk factors in the explanation of the increased risk of second cancer among breast cancer patients. Secondly, during the long follow-up period in our study, the approach to breast cancer treatment may have changed. For instance, intensive radiotherapy may have become less common during the last years of our study. Therefore, due to the fact that patients may have received different types of treatment during the study period, we may have underestimated the effect of some specific treatments on the second cancer risk.

7.5. Conclusion

Our study suggests that breast cancer patients have an elevated risk of second cancer of the breast, ovary, salivary gland, colon, connective tissue and skin, particularly at younger ages. On the other hand, an increased risk of certain cancers does not always correlate with a high absolute excess risk and burden for the population. Surveillance should be directed towards early detection of second breast and ovarian cancers among women diagnosed before the age of 50. Among older breast cancer patients, awareness of second breast and colon cancer should be increased. Further epidemiological research on possible explanations of multiple cancers is necessary. Such studies may serve as guidelines for rational follow-up programs for breast cancer patients.

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References

1. Harris J, Morrow M, Norton L. Malignant tumors of the breast. In DeVita VT, Hellman S, Rosenberg AS, eds. *Cancer: principles & practice of oncology*, pp 1557-616. Philadelphia: Lippicott-Raven Publishers, 1997.
2. Coebergh, J. W. W., Janssen-Heijnen, M. L. G., Louwman, W. J., and Voogds, A. C. Cancer incidence, care and survival in the South of Netherlands, 1955-1999: a report of the Eindhoven Cancer Registry with cross-border implications. 1-47. 2001. Eindhoven, the Netherlands , Comprehensive Cancer Centre South (IKZ).
3. van Leeuwen FE. Second Cancers. In DeVita VT Jr, Hellman S, Rosenberg AS, eds. *Cancer: principles & practice of oncology*, pp 2773-93. Philadelphia: Lippcott-Raven Publishers, 1997.
4. Levi F, Randimbison TV, La Vecchia C. Second primary cancers in breast cancer patients in Vaud, Switzerland. *Cancer Causes Control* 1997;8:764-70.
5. Volk N,.Pompe-Kirn V. Second primary cancers in breast cancer patients in Slovenia. *Cancer Causes Control* 1997;8:764-70.
6. Brenner H, Siegle S, Stegmaier C, Ziegler H. Second primary neoplasms following breast cancer in Saarland, Germany, 1968-1987. *Eur.J.Cancer* 1993;29A:1410-4.
7. Murakami R, Hiyama T, Hanai A, Fujimoto I. Second primary cancers following female breast cancer in Osaka, Japan--a population-based cohort study. *Jpn.J.Clin.Oncol.* 1987;17:293-302.
8. Rubino C, de Vathaire F, Diallo I, Shamsaldin A, Le MG. Increased risk of second cancers following breast cancer: role of the initial treatment. *Breast Cancer Res.Treat.* 2000;61:183-95.
9. Ewertz M,.Mouridsen HT. Second cancer following cancer of the female breast in Denmark, 1943-80. *Natl.Cancer Inst.Monogr* 1985;68:325-9.
10. Horn-Ross PL, Ljung BM, Morrow M. Environmental factors and the risk of salivary gland cancer. *Epidemiology* 1997;8:414-9.
11. Levi F, Te V-C, Randimbison L, La Vecchia C. Cancer risk in women with previous breast cancer. *Ann.Oncol.* 2003;14:71-3.
12. Rubino C, de Vathaire F, Shamsaldin A, Labbe M, Le MG. Radiation dose, chemotherapy, hormonal treatment and risk of second cancer after breast cancer treatment. *Br.J.Cancer* 2003;89:840-6.
13. Mattsson A, Hall P, Ruden BI, Rutqvist LE. Incidence of primary malignancies other than breast cancer among women treated with radiation therapy for benign breast disease. *Radiat.Res.* 1997;148:152-60.
14. Harvey EB,.Brinton LA. Second cancer following cancer of the breast in Connecticut, 1935-82. *Natl.Cancer Inst.Monogr* 1985;68:99-112.
15. Shapiro CL,.Recht A. Side effects of adjuvant treatment of breast cancer. *N.Engl.J.Med.* 2001;344:1997-2008.
16. Adami HO, Bergkvist L, Krusemo U, Persson I. Breast cancer as a risk factor for other primary malignant diseases. A nationwide cohort study. *J.Natl.Cancer Inst.* 1984;73:1049-55.
17. Newcomb PA, Solomon C, White E. Tamoxifen and risk of large bowel cancer in women with breast cancer. *Breast Cancer Res.Treat.* 1999;53:271-7.
18. Newschaffer CJ, Topham A, Herzberg T, Weiner S, Weinberg DS. Risk of colorectal cancer after breast cancer. *Lancet* 2001;357:837-40.
19. Li CI, Rossing MA, Voigt LF, Daling JR. Multiple primary breast and thyroid cancers: role of age at diagnosis and cancer treatments. *Cancer Causes Control* 2000;11:805-11.
20. Teppo L, Pukkala E, Saxen E. Multiple cancer--an epidemiologic exercise in Finland. *J.Natl.Cancer Inst.* 1985;75:207-17.
21. van Leeuwen FE, Klokman WJ, Hagenbeek A, Nozon R, van de Belt-Dusenbout AW, van Kerkhoff EH *et al*. Second cancer risk following Hodgkin's disease: a 20-year follow up study. *J.Clin.Oncol.* 1994;12:312-25.
22. Soerjomataram, I, Louwman, WJ, Lemmens, VEPP, de Vries, E, Klokman, WJ, and Coebergh, JWW. Risks of second primary breast and urogenital cancer following female breast cancer in the south of the Netherlands, 1972-2001. Eur.J.Cancer . 2005.
23. Breslow NE,.Day NE. Statistical methods in cancer research. Volume II--The design and analysis of cohort studies. *IARC Sci.Publ.* 1987;1-406.

24. Ozols RF, Schwartz PE, Eifel PJ. Ovarian cancer, fallopian tube carcinoma, and peritoneal carcinoma. In De Vita VT, Hellman S, Rosenberg AS, eds. *Cancer: principles & practice of oncology*, pp 1502-39. Philadephia: Lippincott-Raven Publishers, 1997.
25. Arver B, Du Q, Chen J, Luo L, Lindblom A. Hereditary breast cancer: a review. *Semin.Cancer Biol.* 2000;10:271-88.
26. Hemminki K, Vaittinen P, Easton D. Familial cancer risks to offspring from mothers with 2 primary breast cancers: leads to cancer syndromes. *Int.J.Cancer* 2000;88:87-91.
27. Li FP,.Fraumeni JF, Jr. Soft Tissue Sarcomas, Breast Cancer, and other neoplasms. A familial syndrom? *Ann.Intern.Med.* 1969;71:747-52.
28. Dhillon PK, Farrow DC, Vaughan TL, Chow WH, Risch HA, Gammon MD *et al*. Family history of cancer and risk of esophageal and gastric cancers in the United States. *Int.J.Cancer* 2001;93:148-52.
29. Ron E. Cancer risks from medical radiation. *Health Phys.* 2003;85:47-59.
30. Curtis RE, Boice JD, Jr., Shriner DA, Hankey BF, Fraumeni JF, Jr. Second cancers after adjuvant tamoxifen therapy for breast cancer. *J.Natl.Cancer Inst.* 1996;88:832-4.
31. Fisher B, Costantino JP, Wickerham DL, Redmond CK, Kavanah M, Cronin WM *et al*. Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. *J.Natl.Cancer Inst.* 1998;90:1371-88.
32. Rutqvist LE, Johansson H, Signomklao T, Johansson U, Fornander T, Wilking N. Adjuvant tamoxifen therapy for early stage breast cancer and second primary malignancies. Stockholm Breast Cancer Study Group. *J.Natl.Cancer Inst.* 1995;87:645-51.
33. van Leeuwen FE, Benraadt J, Coebergh JW, Kiemeney LA, Gimbrere CH, Otter R *et al*. Risk of endometrial cancer after tamoxifen treatment of breast cancer. *Lancet* 1994;343:448-52.
34. Fornander T, Rutqvist LE, Cedermark B, Glas U, Mattsson A, Silfversward C *et al*. Adjuvant tamoxifen in early breast cancer: occurrence of new primary cancers. *Lancet* 1989;1:117-20.
35. Barrett JC, Davis BJ, Bennett LM. Pregnancy and protection from hormonally associated tumor development. *Epidemiology* 2003;14:139-40.
36. Lumachi F, Ermani M, Brandes AA, Basso U, Paris M, Basso SM *et al*. Breast cancer risk in healthy and symptomatic women: results of a multivariate analysis. A case-control study. *Biomed.Pharmacother.* 2002;56:416-20.
37. Thomson CA, Flatt SW, Rock CL, Ritenbaugh C, Newman V, Pierce JP. Increased fruit, vegetable and fiber intake and lower fat intake reported among women previously treated for invasive breast cancer. *J.Am.Diet.Assoc.* 2002;102:801-8.
38. Levi F, Pasche C, Lucchini F, La Vecchia C. Dietary fibre and the risk of colorectal cancer. *Eur.J.Cancer* 2001;37:2091-6.
39. Goggins W, Gao W, Tsao H. Association between female breast cancer and cutaneous melanoma. *Int.J.Cancer* 2004;111:792-4.
40. Hehir DJ, Dawson KJ, Parbhoo SP. Primary breast carcinoma in patients with malignant melanoma. *Eur.J.Surg.Oncol.* 1992;18:77-9.
41. de Braud F, Khayat D, Kroon BBR, Valdagni R, Bruzzi P, Cascinelli N. Malignant melanoma. *Crit Rev Oncol Hematol* 2003;47:35-63.
42. Holly EA, Cress RD, Ahn DK. Cutaneous melanoma in women: ovulatory life, menopause and use of exogenous estrogens. *Cancer Epidemiol.Biomarkers Prev.* 1994;3:661-8.
43. Sigurdson AJ, Doody MM, Rao RS, Freedman DM, Alexander BH, Hauptmann M *et al*. Cancer incidence in the US radiologic technologists health study, 1983-1998. *Cancer* 2003;97:3080-9.
44. Boice JD, Jr., Harvey EB, Blettner M, Stovall M, Flannery JT. Cancer in the contralateral breast after radiotherapy for breast cancer. *N.Engl.J.Med.* 1992;326:781-5.

Chapter 8

Increased risk of second malignancies after in situ breast carcinoma in a population-based registry

Soerjomataram I, Louwman WJ, van der Sangen MJ, Roumen RM, Coebergh JW. Increased risk of second malignancies after in situ breast carcinoma in a population-based registry. Br J Cancer. 2006;95:393-397

Abstract

Background and objectives: Incidence of breast carcinoma in situ (BCIS) has increased dramatically. However, studies on risk of cancer after BCIS diagnosis are scarce. We examined the risk patterns and determinants of second malignancies after BCIS and compared them with those after breast carcinoma.

Methods: We calculated SIR (standardized incidence ratio), AER (absolute excess risk) and cumulative risk of second cancer after BCIS in 1972–2003 in Southern Netherlands.

Results: Among 1276 primary BCIS patients diagnosed in 1972-2002, 11% developed a second cancer. BCIS patients exhibited a two-fold risk of second cancer (SIR: 2.1, 95% confidence interval [95% CI]: 1.7-2.5). The highest risk was found for a second breast cancer (SIR: 3.4; 95% CI: 2.6-4.3, AER: 66 patients/10,000/year) followed by skin cancer (SIR: 1.7; 95% CI: 1.1-2.6, AER: 17 patients/10,000/year). The increased risk of second breast cancer was similar for the ipsilateral (SIR: 1.9; 95% CI: 1.3-2.7) and contralateral (SIR: 2.0; 95% CI: 1.4-2.8) breast.

Conclusions: Risk of second cancer was independent of age at diagnosis, type of initial therapy, histologic type of BCIS and period of diagnosis. SIR of second cancer after BCIS (SIR: 2.3 95% CI: 1.8-2.8) resembled that of after invasive breast cancer (SIR: 2.2 95% CI: 2.1-2.4). Surveillance should be directed towards second (ipsi- and contralateral) breast cancer.

Keywords: breast carcinoma in situ, population-based, risk, second cancer.

8.1. Introduction

Diagnosis of in situ and early stage breast carcinoma has increased over the past decades in the Netherlands, partly as a consequence of screening [1]. The incidence rate of DCIS (ductal carcinoma in situ) has increased from 0.3 per 100,000 in 1975 to 13.4 per 100,000 in 1997 [2]. Women with previous breast cancer are known to carry a 2-fold risk of second cancer in comparison to the general population [3, 4]. Studies assessing the risk of second cancer following the diagnosis of BCIS (breast carcinoma in situ) are however scarce or only focused on the risk of second breast cancer [5-9].

Research has shown an increased risk of 2.0-7.2 for breast cancer following the diagnosis of BCIS [6, 10]. The probability that a breast cancer will develop in BCIS patients is 26% after 20 years of follow-up [9]. This is as high as the risk of second breast cancer found for patients with malignant breast carcinoma [11]. Excess risk of second breast cancer is not explained by treatment choice (i.e. radiotherapy) for BCIS [8], suggesting the role of a shared aetiology (hereditary or lifestyle) for both first and second cancer. In addition to second breast cancer, other cancers were diagnosed in 17% of DCIS and 3.2% of lobular carcinoma in situ (LCIS) patients [12]. However, no previous studies assessed the risks of different types of second cancer in BCIS patients.

The aim of the study is to assess the risk pattern for second cancer after diagnosis of BCIS and to compare it with that found for malignant breast carcinoma, thereby examining the impact of age, breast cancer screening policy at the time of primary BCIS diagnosis and treatment for various subtypes of BCIS.

8.2. Materials and methods

Data collection

Data were obtained from the population-based ECR (Eindhoven Cancer Registry) that is located in southern Netherlands and covered 2.4 million inhabitants in 2004. The cancer registry receives lists of newly diagnosed cases on a regular basis from the Pathology Departments in the region. In addition, lists of all hospitalised cancer patients were obtained. Active follow-up of vital status was conducted through the Central Bureau for Genealogy that receives data from municipal population registries. In the ECR, any new tumour, not classified as a recurrence or direct extension of a previously known tumour, is recorded as a new primary tumour. This registry is unique because it contains incidence data on first BCC (basal cell carcinoma) of the skin. A detailed description of the data collection has been presented elsewhere [3].

Study population

We identified 1402 women older than 25 years diagnosed with in situ breast cancer (ICD-O behaviour code /2) from 1 January 1972, through 31 December 2002. Among patients eligible for the study, those with less than 1 year follow-up time (n = 174) and those with unknown morphological code (n = 5) were excluded. End of follow-up was 31 December 2003, date of death, date of last follow-up or date of second cancer diagnosis, whichever

occurred first. Thus, 1223 women remained for analysis, 143 of whom (11.2%) developed a second cancer, 170 (13.3%) died and 2 (0.2%) were lost to follow-up. The maximum follow-up time was of 32 years.

Statistical methods

We calculated SIR (standardised incidence ratio) to measure the relative risk of developing second tumours by comparing the incidence of second cancer among patients with a diagnosis of BCIS to the incidence of similar cancer in the general population. We adjusted for age (in 5-year categories) and calendar year of BCIS diagnosis. The 95% confidence intervals (95% CI) were calculated using exact Poisson probability [13]. We also calculated the absolute excess risk (AER) examining the excess incidence of second cancers per 10,000 patients in each year [14]. Furthermore, the cumulative risk of developing second cancer, which is the proportion of patients alive at time t who can be expected to develop a second cancer, was calculated using the life table method [15].

The following categorization of BCIS histological type was made; LCIS (ICD-O 8520/2) and DCIS including Paget's disease (ICD-O 8500/2, 8010/2, 8050/2, 8140/2, 8201/2, 8230/1, 8501/2, 8503/2, 8504/2, 8507/2, 8521/1, 8523/2, 8540/2) [16]. Year 1993 was considered the starting point of breast cancer screening, that was fully implemented in 1996 [1, 17]. Calculation of risk for the ipsilateral and contralateral second breast cancer was performed using only patients with information on laterality of first BCIS and second breast cancer (excluded for this analysis $n = 52$).

SIRs for selected cancers after malignant breast cancer were obtained from a previous study done in ECR [3] and compared with that of BCIS in the current study. In the earlier study, we estimated the risk of subsequent cancers in 9919 women diagnosed with malignant breast cancers in 1972-2000 followed until 2001. To allow comparison, we added second non-melanotic skin cancer cases (BCC: 192 & Squamous Cell Carcinoma: 42) for the analysis of second skin cancer. We used similar method to calculate SIR and 95% confidence interval as explained before. A detailed description of this study has been described elsewhere [3].

All statistical analyses were performed using SPSS 11.5 for Windows (Statistical Products and Service Solution, Inc, Chicago, IL, USA).

8.3. Results

The mean follow-up time for the cohort was 6.3 years. A large proportion of BCIS patients was older than 50 years and was diagnosed with DCIS (95%) in 1993-2002 (table 8.1).

Table 8.1. Characteristics at diagnosis of BCIS (breast carcinoma in situ)

	BCIS		
Mean age at BCIS diagnosis	57.1 years		
Mean follow-up time	6.3 years		
	Subsequent cancer		Total (%)
	No (%)	Yes (%)	
Age at BCIS diagnosis			
≤49 years	288 (26)	30 (27)	318 (26)
≥50 years	822 (74)	83 (73)	905 (74)
Initial treatment			
No Radiotherapy	765 (69)	68 (60)	833 (68)
With Radiotherapy	345 (31)	45 (40)	390 (32)
Follow-up			
1-4 years	549 (49)	64 (57)	613 (50)
5-9 years	396 (36)	34 (30)	430 (35)
≥10 years	165 (15)	15 (13)	180 (15)
Subtype of initial cancer			
DCIS[a]	1052 (95)	105 (93)	1157 (95)
LCIS[b]	58 (5)	8 (7)	66 (5)
Time of diagnosis[c]			
1972-1992	165 (15)	41 (36)	206 (17)
1993-2002	945 (85)	72 (64)	1017 (83)
Total	1110	113	1223 (100)

[a] DCIS: ductal carcinoma in situ; [b] LCIS: lobular carcinoma in situ; [c] breast cancer screening in southern Netherlands began to have impact in 1993 [1].

Table 8.2 shows the SIRs and AERs for second breast and other cancers. We found an increased risk of second breast cancer (SIR: 2.1 95% CI: 1.7-2.5) and other non-breast cancers (SIR: 1.4 95% CI: 1.1-1.9). An excess of 66 patients with second breast cancer for every 10,000 BCIS patients per year was observed. An increased risk of second breast cancer was found for both the ipsilateral (SIR: 1.9 95% CI: 1.3-2.7) and contralateral breast (SIR: 2.0 95% CI: 1.4-2.8). Almost a two-fold elevated risk of skin cancer (SIR: 1.7 95% CI: 1.1-2.5) was found.

Table 8.2. SIR (standardized incidence ratio) and AER (absolute excess risk) for all second cancers diagnosed in 1972-2003 following BCIS (breast carcinoma in situ) in southern Netherlands

Site of second cancer	Relative and absolute risks[a]				
	Observed	Expected	SIR	95% CI	AER
All sites	113	54.4	2.1[b]	1.7-2.5	90
All sites excluding breast[c]	52	36.2	1.4[b]	1.1-1.9	24
Digestive Tract[d]	11	10.4	1.1	0.5-1.9	1
Stomach	3	1.6	1.8	0.4-5.3	2
Colon	6	5.2	1.2	0.4-2.5	1
Lung	5	3.5	1.4	0.5-3.3	2
Skin[e]	27	15.8	1.7[b]	1.1-2.5	17
Melanoma	4	1.4	3.0	0.8-7.6	4
Basal Cell Carcinoma	22	12.8	1.7[b]	1.1-2.6	14
Breast	61	18.1	3.4[b]	2.6-4.3	66
Ipsilateral[f]	29	15.5	1.9[b]	1.3-2.7	24
Contralateral[f]	31	15.5	2.0[b]	1.4-2.8	28
Urogenital Tract[g]	4	7.2	0.6	0.2-1.4	-5
Ovary	2	2.5	0.8	0.1-2.8	-1
Lymphoma and Multiple Myeloma	2	2.5	0.8	0.1-2.9	-1

[a] excluding patients with less than 1-year follow-up; [b] 95 % confidence interval excludes 1; [c] 3 observed are primary cancers of unknown origin; [d] also includes: pancreas [1] and rectum [1]; [e] also includes: squamous cell carcinoma of the skin [1]; [f] only includes patients with known laterality of BCIS and second breast cancer; [g] also includes: corpus uteri [1] and bladder [1].

A three- to four fold increased risk of second breast cancer was found during the first ten years of follow-up (table 8.3), which was relatively higher than the SIR for the last follow-up period (≥ 10 years). As for the risk of second non-breast cancer, we observed similar SIRs across all follow-up periods.

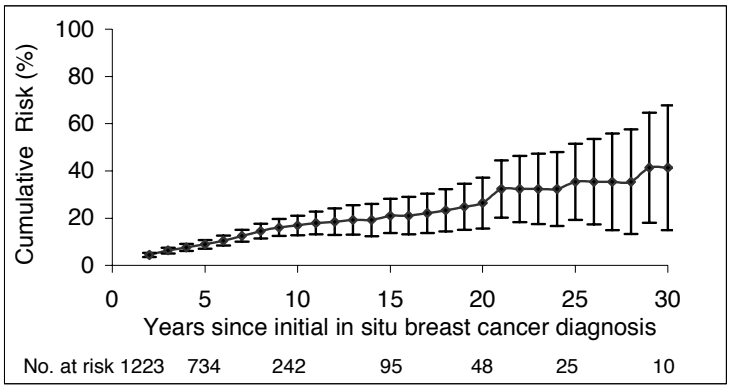
Table 8.3. SIR (standardized incidence ratio) and AER (absolute excess risk) for second breast cancer and second other cancers after BCIS (breast carcinoma in situ), according to follow-up time.

Period of follow-up	PYR[a]	Second breast cancer				Other second cancers			
		Obs[b]	Exp[c]	SIR	AER	Obs[b]	Exp[c]	SIR	AER
1-4 years	3596	33	9.7	3.4[d]	65	31	18.9	1.6[d]	34
5-9 years	1815	22	5.0	4.4[d]	94	12	10.1	1.2	11
≥ 10 years	1127	6	3.3	1.8	24	9	7.4	1.2	14

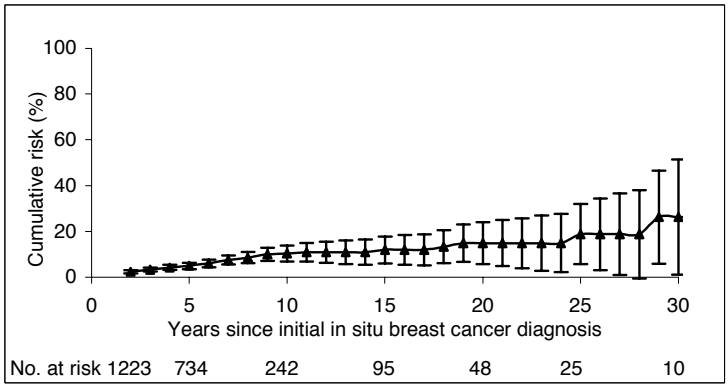
[a] PYR: person-years; [b] Obs: observed numbers of second primary cancers; [c] Exp: expected numbers of second primary cancers; [d] 95% confidence interval excludes 1

Increased risks of second breast or other cancers were not influenced by age at BCIS diagnosis, type of initial therapy, histological type of BCIS and time of BCIS diagnosis (table 8.4). Ipsi- and contralateral breast cancer risks were slightly higher for BCIS patients who received radiotherapy (SIR: 2.1 95% CI: 1.0-4.0 & SIR: 2.4 95% CI: 1.2-4.3, respectively), compared to patients who did not receive radiotherapy (SIR: 1.7 95% CI: 1.1-2.8 & SIR: 1.8 95% CI: 1.1-2.8). The cumulative 10-year risk of developing any second cancer was 17% (±5%), whereas the 15-year corresponding risk was 21% (±8%) (figure 8.1).

a)



b)



c)

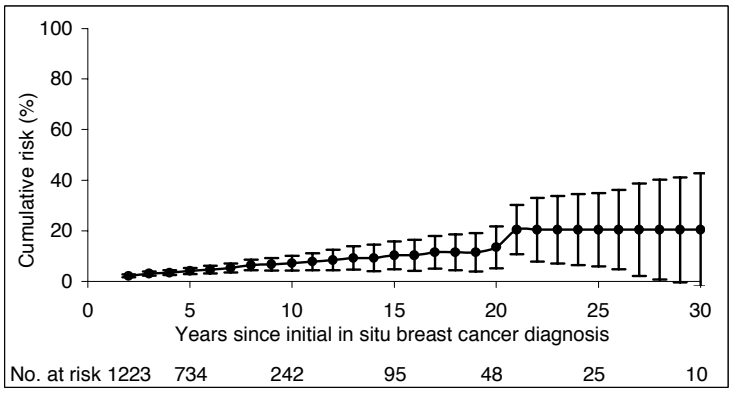


Figure 8.1. Cumulative risk of second cancer after the diagnosis of carcinoma in situ of the breast. a) All sites. b) Breast cancer. c) Other sites excluding breast. No. at risk represented patients still at risk at the beginning of each period

Table 8.4. SIR (standardized incidence ratio) and AER (absolute excess risk) for all second cancers diagnosed 1972-2003 following BCIS (breast carcinoma in situ) in southern Netherlands, according to women's characteristics at the time of BCIS diagnosis

Characteristic	PYR[a]	Second breast cancer				Second other cancers			
		Obs[b]	Exp[c]	SIR	AER	Obs[b]	Exp[c]	SIR	AER
Age at diagnosis									
≤ 49 years	2334	20	4.9	4.0[d]	65	10	6.6	1.5	15
≥ 50 years	4204	41	13.1	3.1[d]	66	42	29.8	1.4[d]	29
Treatment									
No Radiotherapy	4474	39	12.4	3.1[d]	59	29	25.2	1.1	8
With Radiotherapy	2064	22	5.6	3.9[d]	79	23	11.1	2.1[e]	57
Subtype of initial cancer									
DCIS									
LCIS	6106	58	16.8	3.4[d]	67	47	34.3	1.4[d]	21
	432	3	1.2	2.5	42	5	2.1	2.4	67
Time of diagnosis [e]									
1972-1992	2708	24	7.0	3.4[d]	63	17	14.4	1.2	9
1993-2002	3830	37	11.0	3.4[d]	68	35	21.9	1.6[d]	34

[a] PYR: person-years; [b] Obs: observed numbers of second primary cancers; [c] Exp: expected numbers of second primary cancers; [d] 95% confidence interval excludes 1; [e] breast cancer screening in southern Netherlands began to have impact in 1993 [1].

Figure 8.2 compares the SIRs for second cancer after BCIS with those after invasive breast cancer for selected malignancies. The SIRs for second cancer of the lung, colon, skin and breast after BCIS were similar to those after invasive breast cancer. The risk pattern of second cancer at all sites after BCIS (SIR: 2.3 95% CI: 1.8-2.8) were similar to that of second cancer after invasive breast cancer (SIR: 2.2 95% CI: 2.1-2.4).

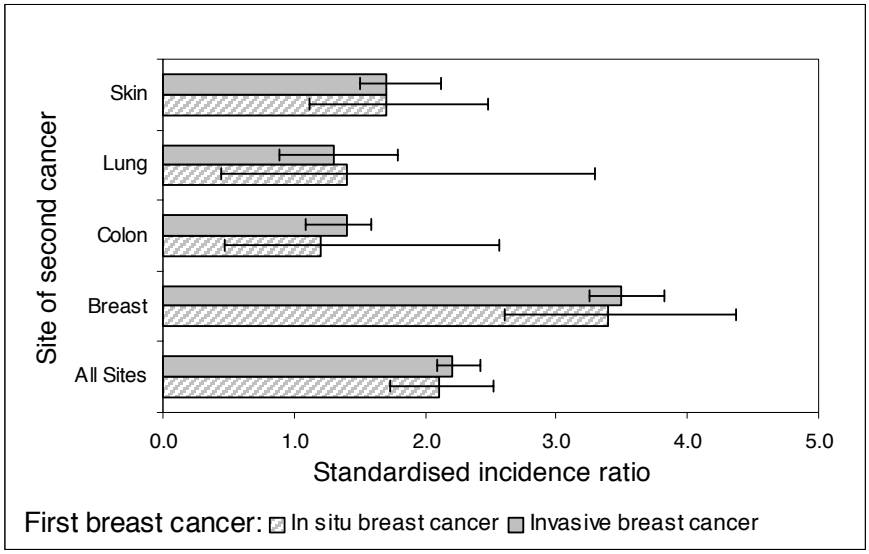


Figure 8.2. SIR (standardized incidence ratio) for second cancer among women diagnosed with breast carcinoma in situ and with invasive breast carcinoma [3]

8.4. Discussion

Women previously diagnosed with in situ breast carcinoma had an increased risk of second cancer, in particular second breast and skin cancer. An excess of 90 second cancers per 10,000 BCIS patients was found. Similar to previous studies,[10] we observed a 21% increased risk for a second cancer after 15 years of survival.

Some limitations of our study should be considered. Firstly, as most women were diagnosed after 1993, the majority had less than 10 years of follow-up. Furthermore the absolute numbers of our study is relatively small. Thus, we may not have estimated correctly the long-term risk of less common cancers such as ovarian cancer which exhibits an increased risk among long-term survivors of invasive breast cancer [18]. Secondly, increased medical surveillance of women with a diagnosis of BCIS may have increased detection of second cancers [14]. In our cohort 60% (30 patients) were diagnosed with second cancer within the first year after BCIS diagnosis. Therefore, we excluded patients with less than 1-year of follow-up and those with a second carcinoma in situ. Thirdly, AER in this article should be interpreted with caution because BCIS accounts for only approximately 13% of all breast cancer diagnoses [1]. Thus, given the same AER, the absolute number of second cancers after BCIS will be considerably smaller than that after invasive breast cancer at the population level. Lastly, no individual data were available on risk factors for cancer [18]. Hence, the contribution of these factors to the risk of second cancer could not be assessed.

Risk pattern

After the diagnosis of BCIS, there was an increased risk of second breast and skin cancer. The question is whether second malignancies share a common aetiology with the first cancer or whether they are associated with treatment for the first cancer [14]. It is likely that factors including reproductive characteristics, lifestyle and genetic predisposition such as BRCA2 play a more important role in the excess risk of both second breast and skin cancer after BCIS [19, 20]. We did not find an increased risk of second ovarian cancer among BCIS patients as in patients with malignant breast cancer. However, most patients in this study had less than 10 years of follow-up and the risk of ovarian cancer after breast cancer was highest after more than 15 years of follow-up [18].

Determinants

Age

Age at the time of BCIS diagnosis did not seem to influence the risk for second cancer, although we observed a slightly higher risk of second breast cancer among women diagnosed with BCIS before age 50. A higher risk of second breast cancer has been found among in situ and malignant breast cancer patients diagnosed before the age of 50 [6, 18]. This is partly due to genetic predisposition, which usually becomes manifest at a relatively young age.

Treatment

The risk for second (ipsi- and contralateral) breast and other cancers was slightly higher among BCIS patients who received radiotherapy. Radiation after breast-conserving

treatment reduces recurrences in the ipsilateral breast, [21, 22] but its effect on the risk of new (ipsi- or contralateral) breast cancer is less conclusive [8, 23]. We found only a slightly increased risk of second breast cancer after radiation that was not significantly different from that of patients without radiotherapy. Thus, the benefit of radiation after surgery for the overall survival of DCIS patients seems to outweigh the increased risk of second breast cancer [21].

Screening

The risk of second cancer after BCIS remained elevated and of a similar magnitude after implementation of the national screening policy in the Netherlands. In Sweden, the risk of second breast cancer increased at the beginning of the screening period and only decreased after long implementation of national screening [6]. Thus, in the coming decades, we might observe a decrease in the risk of second cancer after BCIS.

Comparison with invasive breast cancer cohort

The pattern of second cancer after BCIS seems to be similar to that after malignant breast cancer. Cancers of the colorectum, ovarium, lung and skin were some of the most common cancers in women previously diagnosed with an invasive breast cancer [3]. In the USA, colorectal, cervical and endometrial cancer were reported as the most prevalent cancers among BCIS patients [12]. Thus, we could probably expect an increased incidence of second cancers resembling that of malignant breast cancer within a larger study population and a longer follow-up of BCIS cases.

In conclusion, we found increased relative and absolute risks of second cancer after BCIS diagnosis, similar to that after invasive breast cancer. Monitoring for second breast cancer should be conducted in both the ipsilateral and the contralateral breast. Furthermore, prevention, such as lifestyle changes, maybe relevant for these patients and might lower the risk of second other cancers such as skin, lung and colorectal cancer. Nonetheless, our findings highlight the need to conduct further research on the determinants of second malignancies after BCIS in order to contribute to the development of strategies for the prevention of subsequent cancer**.**

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References

1. Fracheboud J, Otto SJ, van Dijck JA, Broeders MJ, Verbeek AL, de Koning HJ. Decreased rates of advanced breast cancer due to mammography screening in the netherlands. *Br J Cancer*. 2004;91:861-867
2. Voogd AC, Crommelin MA, Repelaer van Driel OJ, Nolthenius-Puylaert MC, van der Heijden LH, Coebergh JW. [trends in incidence and treatment of ductal carcinoma in situ of the breast in southeast netherlands] trends in incidentie en behandelbeleid van ductaal carcinoma in situ van de mamma in zuidoost-nederland. *Ned Tijdschr Geneeskd*. 2000;144:659-663
3. Soerjomataram I, Louwman WJ, de Vries E, Lemmens VE, Klokman WJ, Coebergh JW. Primary malignancy after primary female breast cancer in the south of the netherlands, 1972-2001. *Breast Cancer Res Treat*. 2005;93:91-95
4. Rubino C, de Vathaire F, Shamsaldin A, Labbe M, Le MG. Radiation dose, chemotherapy, hormonal treatment and risk of second cancer after breast cancer treatment. *Br J Cancer*. 2003;89:840-846
5. Warnberg F, Yuen J, Holmberg L. Risk of subsequent invasive breast cancer after breast carcinoma in situ. *Lancet*. 2000;355:724-725
6. Rawal R, Lorenzo Bermejo J, Hemminki K. Risk of subsequent invasive breast carcinoma after in situ breast carcinoma in a population covered by national mammographic screening. *Br J Cancer*. 2005;92:162-166
7. Habel LA, Moe RE, Daling JR, Holte S, Rossing MA, Weiss NS. Risk of contralateral breast cancer among women with carcinoma in situ of the breast. *Ann Surg*. 1997;225:69-75
8. Claus EB, Stowe M, Carter D, Holford T. The risk of a contralateral breast cancer among women diagnosed with ductal and lobular breast carcinoma in situ: Data from the connecticut tumor registry. *Breast*. 2003;12:451-456
9. Levi F, Randimbison L, Te VC, La Vecchia C. Invasive breast cancer following ductal and lobular carcinoma in situ of the breast. *Int J Cancer*. 2005;116:820-823
10. Franceschi S, Levi F, La Vecchia C, Randimbison L, Te VC. Second cancers following in situ carcinoma of the breast. *Int J Cancer*. 1998;77:392-395
11. Chen Y, Semenciw R, Kliewer E, Shi Y, Mao Y. Incidence of second primary breast cancer among women with a first primary in manitoba, canada. *Breast Cancer Res Treat*. 2001;67:35-40
12. Ward BA, McKhann CF, Ravikumar TS. Ten-year follow-up of breast carcinoma in situ in connecticut. *Arch Surg*. 1992;127:1392-1395
13. Breslow NE, Day NE. Statistical methods in cancer research. Volume ii--the design and analysis of cohort studies. *IARC Sci Publ*. 1987:1-406
14. van Leeuwen FE, Travis, L.B. Second cancers. In: DeVita VTJ, Hellman, S., Rosenberg, A.S., ed. *Cancer: Principles & practices of oncology*. Philadelphia: Lippcott-Ravens Publishers; 2005:2575-2602.
15. Cutler SJ, Ederer F. Maximum utilization of the life table method in analyzing survival. *J Chronic Dis*. 1958;8:699-712
16. Vereniging van Integrale Kankercentra. Mammacarcinoom landelijke richtlijn versie 3.0. 2005
17. Fracheboud J, de Koning HJ, Beemsterboer PM, Boer R, Hendriks JH, Verbeek AL, van Ineveld BM, de Bruyn AE, van der Maas PJ. Nation-wide breast cancer screening in the netherlands: Results of initial and subsequent screening 1990-1995. National evaluation team for breast cancer screening. *Int J Cancer*. 1998;75:694-698
18. Soerjomataram I, Louwman WJ, Lemmens VE, de Vries E, Klokman WJ, Coebergh JW. Risks of second primary breast and urogenital cancer following female breast cancer in the south of the netherlands, 1972-2001. *Eur J Cancer*. 2005
19. Arver B, Du Q, Chen J, Luo L, Lindblom A. Hereditary breast cancer: A review. *Semin Cancer Biol*. 2000;10:271-288
20. Goggins W, Gao W, Tsao H. Association between female breast cancer and cutaneous melanoma. *Int J Cancer*. 2004;111:792-794
21. Fisher B, Costantino J, Redmond C, Fisher E, Margolese R, Dimitrov N, Wolmark N, Wickerham DL, Deutsch M, Ore L, et al. Lumpectomy compared with lumpectomy and radiation therapy for the treatment of intraductal breast cancer. *N Engl J Med*. 1993;328:1581-1586
22. Julien JP, Bijker N, Fentiman IS, Peterse JL, Delledonne V, Rouanet P, Avril A, Sylvester R, Mignolet F, Bartelink H, Van Dongen JA. Radiotherapy in breast-conserving treatment for ductal carcinoma in situ: First

results of the eortc randomised phase iii trial 10853. Eortc breast cancer cooperative group and eortc radiotherapy group. *Lancet*. 2000;355:528-533

23. Warnberg F, Bergh J, Zack M, Holmberg L. Risk factors for subsequent invasive breast cancer and breast cancer death after ductal carcinoma in situ: A population-based case-control study in sweden. *Cancer Epidemiol Biomarkers Prev*. 2001;10:495-499.

Chapter 9

Risks of second primary breast and urogenital cancer following female breast cancer in the south of The Netherlands, 1972-2001

Soerjomataram I, Louwman WJ, Lemmens VE, de Vries E, Klokman WJ, Coebergh JW. Risks of second primary breast and urogenital cancer following female breast cancer in the south of the netherlands, 1972-2001. Eur J Cancer. 2005;41:2331-2337

Abstract

Background and objectives: A cohort of 9919 breast cancer patients registered in the population-based Eindhoven registry was followed for vital status and development of second cancer.

Methods: Person-year analysis was applied to determine the risk of second primary breast or urogenital cancer among breast cancer patients and to assess its relationship to age, treatment and time since the first breast cancer diagnosis.

Results: Women with previous breast cancer have an elevated risk of overall second breast or urogenital cancer. The largest relative risk was observed for second breast cancer (SIR [Standardised Incidence Ratio]: 3.5; 95%CI: 3.2-3.8) and second ovarian cancer (SIR: 1.7; 95%CI: 1.2-2.3). The absolute excess rate was highest for second breast cancer (64/10,000 patients per year). On the other hand, breast cancer has an inverse relationship to risk of cervical cancer.

Conclusion: Changes in behavioural risk factors are important for lowering the risk of second cancer after breast cancer.

Keywords: breast cancer, long term, second primary breast or urogenital cancer, treatment.

9.1. Introduction

A history of breast cancer is a risk indicator for second primary cancer among women, especially for second primary breast and genital cancer. Higher risks of second breast cancer[1;2], subsequent ovarian cancer[2] and uterine cancer[3;4] after primary breast cancer[5] have been found. However, the association with cervical cancer and cancer of the vagina-vulva has not been well studied in detailed[2]. Only a few studies have shown an increased risk of second primary kidney and bladder cancer among breast cancer patients[6;7].

Examination of the association between breast cancer and second primary cancer may contribute to the development of preventive interventions. Understanding these issues may also help identify the treatment that carries the lowest risk of second cancer for breast cancer patients. In addition, it may also contribute to early detection of second cancer. Common risk factors, such as dietary habits, reproductive characteristics, exogenous oestrogen exposure and genetic factors play an important role in the aetiology of second female cancers, particularly breast, uterine and ovarian cancer[8]. Breast cancer treatments, such as radiotherapy, systemic chemotherapy[6;9] and hormonal therapy, may be associated with a higher risk of certain second primary cancers among breast cancer patients. In addition, hormonal therapy with tamoxifen has been found to increase the risk of cancer of the uterine, in particular mixed mullerian tumours[10-12].

The effect of factors such as latency time, cancer treatment and the age at diagnosis, on the risk of second female cancer remains unknown. Our cohort comprises the most recent data, with a long follow-up time and a large number of cases. This enables us to assess the role of important risk factors in the development of second primary cancer. The aim of this population-based cohort study was to determine the incidence of second primary breast and urogenital cancers among breast cancer patients in the south of the Netherlands, compared to the incidence expected in the general population, and to relate this incidence to the initial breast cancer treatment, follow-up time, and age at breast cancer diagnosis.

9.2. Patients and methods

Patients

Breast cancer patients were obtained from the Eindhoven Cancer Registry in the south of the Netherlands. This is a population-based cancer registry, which covered almost 2.3 million individuals in 2004. A detailed description of the data collection has been reported elsewhere [13].

We excluded patients with less than 1 year of follow-up time (n=1458), patients with in situ primary breast cancer (n=458), patients with other malignancies diagnosed before breast cancer as well as patients with a second cancer that appeared to be a metastasis (n=44). For the calculation of risks of second ovarian cancer, patients who were oophorectomised as treatment for breast cancer were not included in the analyses (n=9). As a result, in the period 1972-2000, 9919 breast cancer patients older than 25 years were available for analysis.

Analyses were stratified according to age at diagnosis of the initial tumour (categories: premenopause [age < 50 years] and postmenopause [age ≥ 50] years); initial treatment combination of breast cancer (categories: Surgery [S], radiotherapy ± S, chemotherapy ± S, hormonal therapy ± S, radiotherapy and chemotherapy ± S, radiotherapy and hormonal therapy ± S; and other treatments [chemotherapy and hormonal therapy ± S, radio- and chemo- and hormonal therapy ± S, no treatment and unknown treatment); and follow-up time after diagnosis (categories: 1-4 years, 5-9 years, 10-14 years and longer than 15 years).

Methods

The risk of developing a second cancer was investigated by means of person-years analysis, corrected for age and calendar-year period to the date of death, date of last follow-up, date of diagnosis of the second cancer or end of the study (December 31, 2001) which ever came first [14]. We compared the incidence of second primary tumours among patients with a diagnosis of breast cancer (the observed incidence) with the incidence for the same tumours in the general population (the expected incidence), which is expressed as the Standardised Incidence Ratio (SIR). Calculation of the expected subsequent primary cancer was derived from the same population, using EUROCIM 4.2. The statistical significance and 95% confidence intervals were determined by means of exact Poisson probability[15]. The Absolute Excess Risk (AER) was calculated by subtracting the expected number from the observed number and then dividing the difference by person-years at risk (per 10,000 breast cancer patients/year)[8]. All statistical analyses were performed using SPSS 11.5 for Windows (Statistical Products and Service Solution, Inc, Chicago, USA).

9.3. Results

Our cohort yielded 65,938 person-years. General characteristics at the time of primary breast cancer diagnosis are shown in table 9.1. The average age at breast cancer diagnosis was 58.8 years, the average follow-up time was 6.6 years, and the median follow-up time was 4.9 years. Overall, 725 breast cancer patients developed second breast and urogenital cancer, compared to the expected 266 patients in the population (SIR: 2.7; 95%CI: 2.5-2.9)

(table 9.2). The relative risk of developing second urogenital cancer after excluding all second breast cancers was higher among breast cancer patients than in the general population (SIR: 1.9; 95%CI: 1.6-2.3). Markedly increased risks of second breast cancer (SIR: 3.5; 95%CI: 3.2-3.8) and ovarian cancer (SIR: 1.7; 95%CI: 1.2-2.3) were also observed among these patients. The absolute excess risk (AER) was highest for second breast cancer (64/10000 person years).

Table 9.1. Characteristics at diagnosis of first primary female breast cancer patients, diagnosed in the south of the Netherlands, 1972-2000.

Characteristics	**Number (%)**	**Second cancer (% of first primaries)**
Period of diagnosis of first primary		
1972-1981	2676 (27.0)	267 (10.0)
1982-1991	3590 (36.2)	273 (7.6)
1992-2000	3653 (36.8)	185 (5.1)
Age at diagnosis		
< 50 years	2950 (29.7)	295 (10.0)
≥ 50 years	6969 (70.3)	430 (6.2)
Treatment combination		
Surgery (S)	2163 (21.8)	181 (8.4)
Radiotherapy ± S	4534 (45.7)	398 (8.8)
Chemotherapy ± S	301 (3.0)	12 (4.0)
Hormonal therapy ± S	609 (6.1)	21 (3.5)
Radio- and chemotherapy ± S	865 (8.7)	52 (3.4)
Radio- and hormonal therapy ± S	1214 (12.2)	48 (4.0)
Others	233 (2.3)	13 (5.6)
Follow-up period		
1-4 years	5004 (50.4)	367 (7.3)
5-9 years	2758 (27.8)	205 (7.4)
10-14 years	1215 (12.2)	79 (6.5)
≥ 15 years	942 (9.5)	74 (6.4)
Total	9919	725 (7.9)

Table 9.2. Observed (Obs) and expected (Exp) numbers of second primary female urogenital and breast cancers diagnosed in 1972-2001 and standardised incident ratio (SIR) with 95 % confidence interval (CI) for breast cancer patients in the south of the Netherlands, diagnosed 1972-2000.

Site of second cancer	**Obs**	**Exp**	**SIR**	**CI**	**AER***
All second cancer	725	265.9	2.7‡	2.5 – 2.9	69.6
Female Urogenital	137	70.4	1.9‡	1.6 – 2.3	10.1
Breast	588	167.6	3.5‡	3.2 - 3.8	63.8
Female Genital tract					
Cervix uteri	9	9.8	0.9	0.4 - 1.8	-0.1
Corpus uteri	40	31.1	1.3	0.9 – 1.8	1.4
Ovarium	43	25.2	1.7‡	1.2 - 2.3	2.7
Vagina Vulva	6	4.2	1.4	0.5 - 3.2	0.3
Female Urinary tract					
Kidney	17	13.8	1.2	0.7-2.0	0.5
Bladder	22	16.7	1.3	0.8-2.0	0.8

* AER: Absolute Excess Risk per 10,000 patients/year
‡ 95 % Confidence interval excludes 1

Age

In general, the increased risk of overall second urogenital cancer (SIR: 2.1; 95%CI: 1.9-2.3), second breast cancer (SIR: 2.6; 95%CI: 2.4-2.9) and second ovarian cancer (SIR: 1.1; 95%CI: 0.7-1.7) was more marked among patients who were diagnosed with breast cancer before menopause (table 9.3). In contrast, no differences in the SIR were observed between patients diagnosed before and after menopause for second uterine, cervix, vagina-vulva, kidney and bladder cancer. A higher incidence rate and absolute excess of second breast and ovarian cancer were observed among women diagnosed before menopause.

Table 9.3. Observed (Obs) and expected (Exp) numbers of second primary urogenital and breast cancers diagnosed in 1972-2001, standardised incident ratio (SIR) and absolute excess risk (AER) among breast cancer patients according to age at breast cancer diagnosis in the south of the Netherlands, diagnosed 1972-2000.

Site of second cancer	Pre-menopausal primary				Post-menopausal primary			
	Person years: 22,546				Person year: 43,392			
	Obs	Exp	SIR	AER†	Obs	Exp	SIR	AER†
All second cancer	295	58.2	5.1‡	105.0	430	207.7	2.1‡	51.2
Female Urogenital	40	14.5	2.7‡	11.3	97	55.8	1.7‡	9.5
Breast	255	40.8	6.3‡	95.0	333	126.8	2.6‡	47.5
Female Genital tract								
Cervix uteri	5	2.9	1.7	0.9	4	6.9	0.6	-0.7
Corpus uteri	8	5.7	1.4	1.0	32	25.3	1.3	1.5
Ovarium	21	5.5	3.8‡	1.0	22	19.8	1.1	0.5
Vagina and vulva	1	0.5	2.2	0.2	5	3.8	1.3	0.3
Female Urinary tract								
Kidney	2	1.8	1.1	0.09	15	12.0	1.2	0.7
Bladder	3	1.8	1.7	0.5	19	14.9	1.3	0.9

* AER: Absolute Excess Risk per 10,000 patients/ year

‡ 95 % Confidence interval excludes 1

Treatment

The risk of second breast cancer was elevated for breast cancer patients receiving any treatment, compared to those undergoing surgical treatment (SIR: 3.4; 95%CI: 2.9-4.0). Treatment was not associated with the elevated risks of cervix, endometrial, vagina-vulva, kidney or bladder cancer compared to patients treated surgically (table 9.4).

Furthermore, we assessed whether the excess risk of second breast and endometrial cancer among women aged 50 years and older receiving hormonal treatment ± radiotherapy was higher than the excess risk among women undergoing surgical treatment (data are not shown). We observed a significantly lower SIR for second breast cancer among women who received hormonal treatment ± radiotherapy (SIR: 1.6 95%CI: 1.2-2.2) than those who were treated surgically (SIR: 2.8; 95%CI: 2.3-3.4). In contrast, we observed a higher SIR for second endometrial cancer (SIR: 1.7; 95%CI: 0.7-3.4) among patients receiving hormonal treatment ± radiotherapy than among those undergoing surgical therapy (SIR: 0.7 95%CI: 0.2-1.8).

Table 9.4. Observed (Obs) and expected (Exp) numbers of second primary urogenital cancers diagnosed in 1972-2001 and standardised incident ratio (SIR) according to breast cancer treatment for patients diagnosed with breast cancer in the south of the Netherlands in 1972-200

Site of second cancer	Surgical			Radiotherapy [a]			Chemotherapy [b]			Hormonal therapy [c]			Radio- & Chemotherapy [d]			Radio- & Hormonal therapy [e]			Others [f]		
	Person years: 17,323			Person years: 33,444			Person years: 1676			Person years: 2489			Person years: 4590			Person years: 5611			Person years : 817		
	Obs	Exp	SIR	Obs	Exp	SIR	Obs	Exp	SIR	Obs	Exp	SIR	Obs	Exp	SIR	Obs	Exp	SIR	Obs	Exp	SIR
All cancer	181	72.5	2.5‡	398	132.6	3.0‡	12	5.1	3.5‡	21	11.5	1.8‡	52	12.7	4.1‡	48	27.3	1.8‡	13	2.8	4.6‡
Female urogenital	29	19.1	1.5	71	35.5	2.0‡	4	1.3	3.1	3	3.2	0.9	8	3.2	2.5‡	21	7.3	2.9‡	1	0.7	1.4
Breast	152	45.1	3.4‡	327	83.5	3.9‡	8	3.5	2.3	18	8.0	2.3‡	44	8.8	5.0‡	27	17.0	1.6‡	12	1.9	6.3‡
Female genital																					
Cervix uteri	2	2.7	0.8	6	5.0	1.2	0	0.2	0	0	0.4	0	1	0.6	1.6	0	0.8	0	0	0.1	0
Corpus uteri	7	8.4	0.8	20	15.7	1.3	1	0.6	1.8	1	1.4	0.7	3	1.3	2.3	8	3.5	2.3	0	0.3	0
Ovarium	13	6.8	1.9	22	12.9	1.7‡	2	0.5	4.2	0	1.1	0	2	1.2	1.7	3	2.6	1.1	1	0.3	4.0
Vagina Vulva	2	1.3	1.5	1	2.0	0.5	0	0.1	0	1	0.3	3.5	1	0.1	8.4	1	0.4	2.4	0	0.0	0
Female Urinary																					
Kidney	1	4.0	0.3	10	6.9	1.5	1	0.2	5.1	0	0.7	0	0	0.4	0	5	1.5	3.3‡	0	0.1	0
Bladder	4	4.9	0.8	12	8.1	1.5	0	0.2	0	1	1.1	0.9	1	0.5	2.2	4	1.9	2.2	0	0.2	0

‡ 95 % Confidence interval excludes 1; [a] Radiotherapy ± S; [b] Chemotherapy ± S; [c] Hormonal therapy ± S; [d] Radiotherapy and chemotherapy ± S

[e] Radiotherapy and hormonal therapy ± S; [f] Chemotherapy and hormonal therapy ± S, radio- and chemo- and hormonal therapy ± S, no treatment and unknown treatment

Follow-up time

The SIR for second breast cancer was 4.6 (95%CI: 4.0-5.1) during the first 4 years of follow-up then it decreased steadily to 14 years of follow-up and then increased again after 15 years (SIR: 4.7; 95%CI: 3.5-6.1) (figure 9.1). The SIR for ovarian cancer increased after 5-9 years of follow-up (SIR: 2.2 95%CI: 1.2-3.7) and again after 15 years of follow-up (SIR: 5.5 95%CI: 2.7-10.4). The SIR for cervical, endometrial, vagina-vulva, kidney, and bladder cancer did not vary according to follow-up time. However, after 5 years of observation, the SIR for cervical cancer remained below 1.

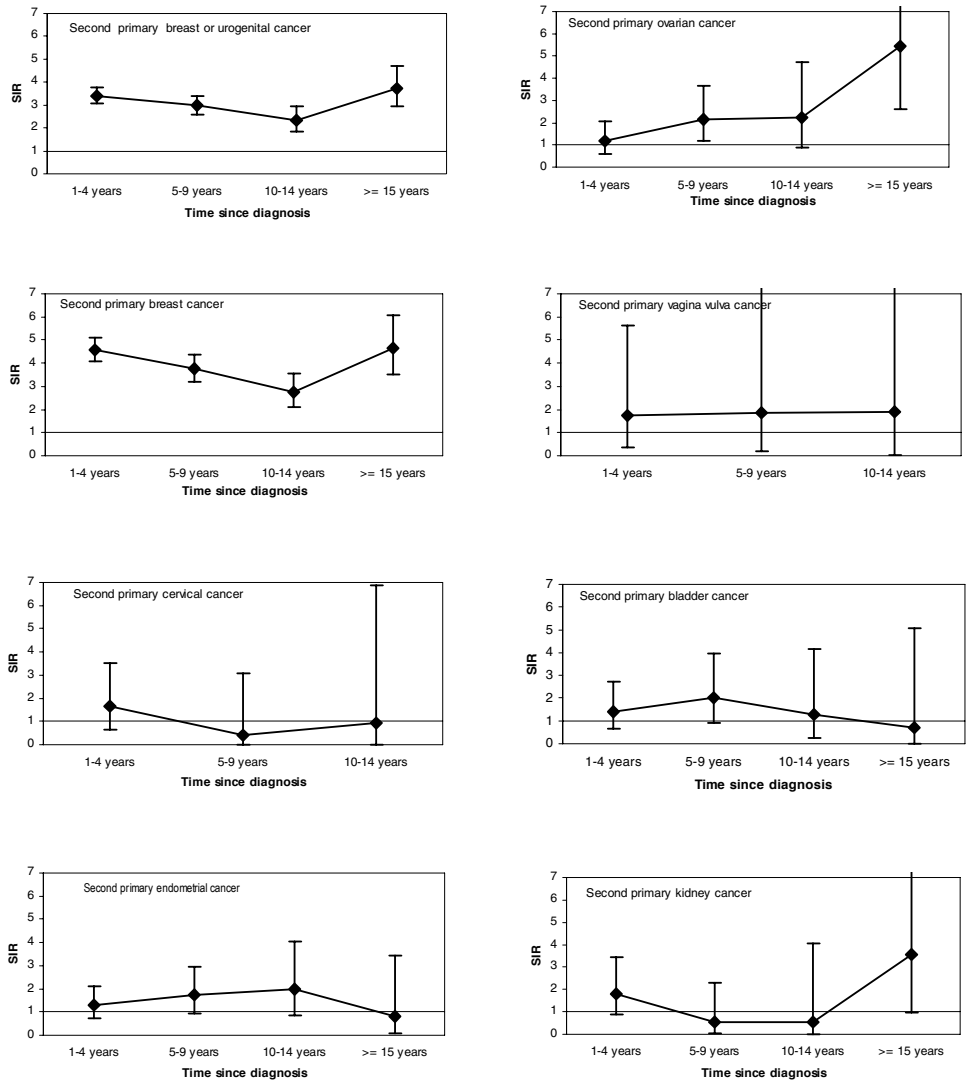

Figure 9.1. Standardised Incident Ratio (SIR) with 95 % Confidence Interval for second primary breast cancer and urogenital cancer diagnosed in 1972-2001 among breast cancer patients in the south of the Netherlands, diagnosed 1972-2000.

9.4. Discussion

Our results suggest that women diagnosed with a primary breast cancer are at increased risk of developing a second breast and ovarian cancer. This is in line with previous studies[1;4-6;16;17]. Elevated risks were particularly marked among pre-menopausal women. In the south of the Netherlands (area of Eindhoven Cancer Registry), every year, 11 of every 1000 breast cancer patients develop second a cancer (I. Soerjomataram, Netherlands Institute of Health Sciences), half of which are second primary breast cancers. Common risk profiles, side-effects of the initial breast cancer treatment and genetic factors have been proposed to cause the elevated risk of second female cancer in breast cancer patients.

Age at first breast cancer diagnosis is an important determinant of the incidence of second breast and ovarian cancers: the risk for women diagnosed before the age of 50 was significantly higher than that observed for those diagnosed at older ages, as reported in previous studies[6;18]. This highlights the importance of female hormones in the pathogenesis of second breast and ovarian cancer. Nonetheless, other common risk factors, which initially induced the breast cancer, may also be involved in the aetiology of the second breast cancer, including genetic factors. BRCA1 and BRCA2 mutation would explain 5-10 % of breast and ovarian cancer cases[19;20].

Age at breast cancer diagnosis was closely related to the treatment choice. A higher risk of second uterine cancer in post-menopausal breast cancer patients taking on hormonal therapy was found, as has been reported by other authors[11;17]. Tamoxifen, a hormonal therapy, which has been widely used since the late 80's for post-menopausal women, has been suggested to cause the increase in uterine cancer in breast cancer patients, although controversy exists[4;10]. In our study we found a decreased risk of second endometrial cancer after 15 years of follow-up, which might suggest a latency period of less than 15 years for tamoxifen to induce second endometrial cancer.

However, the risk of second breast cancer among post-menopausal breast cancer patients who received tamoxifen was lower in comparison to that for women who underwent surgical treatment (SIR: 1.6 vs. 2.8). In addition to the side-effects of tamoxifen in inducing cancer of the uterine, some potential beneficial effects in post-menopausal breast cancer patients are now being examined: for example, the anti-oestrogenic role of tamoxifen in mammary cells was found to protect against second breast cancer[9;21].

We found an elevated risk of second breast cancer during the total follow-up period. It has been reported that after radiation there is a latency period of at least 10 years[22]. During the last decades, both radiotherapy and chemotherapy for breast cancer treatment have improved. This includes lower radiation dose, better protection of the normal tissue and more effective polychemotherapy regimens. These changes have diminished some side-effects of radiotherapy in breast cancer patients[23]. Our result supported this fact by showing no difference in second breast cancer risk between women who underwent surgical or radiotherapy.

We observed declining risks of cervical cancer during the follow-up period, which reached 0 in the last follow-up period. This may be related to the human papilloma virus's (HPV)

latency period of ± 17 years (the time needed from infection to formation of invasive cancer)[24], suggesting sexual behaviour changes among breast cancer women. Some authors have also noticed the lowered risk of cervical cancer among breast cancer patients[2;5;18;25]. In contrast to cervical cancer, breast cancer is observed more often among women with a higher socio-economic position and among women who had their first child at an older age[26;27]. This may also relate to the lower risk of cervical cancer in breast cancer patients.

During 28 years of follow-up only 6 patients developed carcinoma of the vagina and vulva. These cancers are rare and represent only 7-8 % of gynaecological cancers[26]. Consequently, we could not draw any conclusion on the association between breast cancer and cancer of the vagina and vulva. However, vagina and vulva cancer have been related to HPV infection. The risk of second vagina and vulva cancer became 0 after a follow-up of more than 15 years, as found for second cervical cancer in our study. This suggests a possible inverse relationship between breast cancer and second vagina-vulva cancer. Breast cancer patients may change their lifestyle towards a healthier one that protects against vagina and vulva cancer.

We could not find an excess risk for second primary kidney or bladder cancer after breast cancer. A few studies found a slightly increased risk of second kidney and bladder cancer among breast cancer patients[6;7]. Elevated kidney and bladder cancer risk was found for women receiving high radiation exposure in the pelvic area such as radiotherapy for cervical cancer[28]. The bladder is one of the organs that receives a considerable amount of scattered radiation during radiotherapy for breast cancer treatment[29]. However, this seems to be insufficient to induce bladder or kidney cancer.

We could not collect information for some of the main risk factors such as reproductive characteristics or lifestyles of the patients and did not adjust for potential confounders or effect modifiers. Also, there may be some bias caused by metastases of the primary breast cancer. We expect this bias to be minimal because trained personnel from the cancer registry checked each patient's medical record.

In conclusion, our results show that breast cancer patients are at increased risk of developing second breast and ovarian cancer. Initial breast cancer treatment plays a limited role in causing second breast cancer, this suggesting a bigger role for common risk factors that induce both primary and second primary breast cancer. This stresses the importance of behaviour modification among breast cancer patients, in addition monitoring in order to prevent increased morbidity and mortality caused by second breast cancer. As for second ovarian cancer, women diagnosed with breast cancer before menopause may benefit from a longer follow-up directed to the early detection of second ovarian cancer. As our understanding of the relationship between risk factors and the occurrence of a second cancer develops, more questions will arise. Thus, extensive studies on multiple cancers will continue to play an important role in the medical sciences. Such studies may serve as a foundation for understanding the environmental and genetic determinants of cancer.

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References

1. Murakami R, Hiyama T, Hanai A, Fujimoto I. Second primary cancers following female breast cancer in Osaka, Japan--a population-based cohort study. *Jpn.J.Clin.Oncol.* 1987;17:293-302.
2. Brenner H, Siegle S, Stegmaier C, Ziegler H. Second primary neoplasms following breast cancer in Saarland, Germany, 1968-1987. *Eur.J.Cancer* 1993;29A:1410-4.
3. Levi F, Te V-C, Randimbison L, La Vecchia C. Cancer risk in women with previous breast cancer. *Ann.Oncol.* 2003;14:71-3.
4. Adami HO, Bergstrom R, Weiderpass E, Persson I, Barlow L, McLaughlin JK. Risk for endometrial cancer following breast cancer: a prospective study in Sweden. *Cancer Causes Control* 1997;8:821-7.
5. Levi F, Randimbison TV, La Vecchia C. Second primary cancers in breast cancer patients in Vaud, Switzerland. *Cancer Causes Control* 1997;8:764-70.
6. Rubino C, de Vathaire F, Diallo I, Shamsaldin A, Le MG. Increased risk of second cancers following breast cancer: role of the initial treatment. *Breast Cancer Res.Treat.* 2000;61:183-95.
7. Teppo L, Pukkala E, Saxen E. Multiple cancer--an epidemiologic exercise in Finland. *J.Natl.Cancer Inst.* 1985;75:207-17.
8. van Leeuwen FE. Second Cancers. In De Vita VT, Hellman S, Rosenberg AS, eds. *Cancer: principles & practice of oncology*, pp 2773-93. Philadelphia: Lippcott-Raven Publishers, 1997.
9. Shapiro CL,.Recht A. Side effects of adjuvant treatment of breast cancer. *N.Engl.J.Med.* 2001;344:1997-2008.
10. Bergman L, Beelen ML, Gallee MP, Hollema H, Benraadt J, van Leeuwen FE. Risk and prognosis of endometrial cancer after tamoxifen for breast cancer. Comprehensive Cancer Centres' ALERT Group. Assessment of Liver and Endometrial cancer Risk following Tamoxifen. *Lancet* 2000;356:881-7.
11. Cook LS, Weiss NS, Potts MS. Second cancers after adjuvant tamoxifen therapy for breast cancer. *J.Natl.Cancer Inst.* 1997;89:657-9.
12. Sasco AJ, Raffi F, Satge D, Goburdhun J, Fallouh B, Leduc B. Endometrial mullerian carcinosarcoma after cessation of tamoxifen therapy for breast cancer. *Int.J.Gynaecol.Obstet.* 1995;48:307-10.
13. Coebergh, JWW, Janssen-Heijnen, MLG, Louwman, WJ, and Voogds, AC. Cancer incidence, care and survival in the South of Netherlands, 1955-1999: a report of the Eindhoven Cancer Registry with cross-border implications. 1-47. 2001. Eindhoven, the Netherlands , Comprehensive Cancer Centre South (IKZ).
14. van Leeuwen FE, Klokman WJ, Hagenbeek A, Nozon R, van de Belt-Dusenbout AW, van Kerkhoff EH *et al*. Second cancer risk following Hodgkin's disease: a 20-year follow up study. *J.Clin.Oncol.* 1994;12:312-25.
15. Breslow NE,.Day NE. Statistical methods in cancer research. Volume II--The design and analysis of cohort studies. *IARC Sci.Publ.* 1987;1-406.
16. Ewertz M,.Storm HH. Multiple primary cancers of the breast, endometrium and ovary. *Eur.J.Cancer Clin.Oncol.* 1989;25:1927-32.
17. Volk N,.Pompe-Kirn V. Second primary cancers in breast cancer patients in Slovenia. *Cancer Causes Control* 1997;8:764-70.
18. Adami HO, Bergkvist L, Krusemo U, Persson I. Breast cancer as a risk factor for other primary malignant diseases. A nationwide cohort study. *J.Natl.Cancer Inst.* 1984;73:1049-55.
19. Arver B, Du Q, Chen J, Luo L, Lindblom A. Hereditary breast cancer: a review. *Semin.Cancer Biol.* 2000;10:271-88.
20. Hemminki K, Vaittinen P, Easton D. Familial cancer risks to offspring from mothers with 2 primary breast cancers: leads to cancer syndromes. *Int.J.Cancer* 2000;88:87-91.
21. Early Breast Cancer Trialists' Collaborative Group. Tamoxifen for early breast cancer: an overview of the randomised trials. *Lancet* 1998;351:1451-67.
22. Boice JD, Jr., Harvey EB, Blettner M, Stovall M, Flannery JT. Cancer in the contralateral breast after radiotherapy for breast cancer. *N.Engl.J.Med.* 1992;326:781-5.
23. Boice JD, Jr., Harvey EB, Blettner M, Stovall M, Flannery JT. Cancer in the contralateral breast after radiotherapy for breast cancer. *N.Engl.J.Med.* 1992;326:781-5.
24. Schiffman M,.Krüger Kjaer S. Chapter 2: Natural History of Anogenital Human Papillomavirus Infection and Neoplasia. *J.Natl.Cancer Inst.Monogr.* 2003;31:14-9.

25. Ewertz M,.Mouridsen HT. Second cancer following cancer of the female breast in Denmark, 1943-80. *Natl.Cancer Inst.Monogr* 1985;68:325-9.
26. Eifel PJ, Berek JS, Thigpen JT. Cancer of the cervix, vagina and vulva. In De Vita VT, Hellman S, Rosenberg AS, eds. *Cancer: principles & practice of oncology*, pp 1433-78. Philadephia: Lippincott-Raven Publishers, 1997.
27. Harris J, Morrow M, Norton L. Malignant tumors of the breast. In DeVita VT, Hellman S, Rosenberg AS, eds. *Cancer: principles & practice of oncology*, pp 1557-616. Philadelphia: Lippicott-Raven Publishers, 1997.
28. Hall EJ. Etiology of cancer: physical factors. In DeVita VT, Hellman S, Rosenberg AS, eds. *Cancer: principles & practice of oncology*., pp 203-18. Philadelphia: Lippincott-Raven Publishers, 1997.
29. Mattsson A, Hall P, Ruden BI, Rutqvist LE. Incidence of primary malignancies other than breast cancer among women treated with radiation therapy for benign breast disease. *Radiat.Res.* 1997;148:152-60.

PART IV

Risk of second primary cancer in skin cancer patients

Chapter 10

A cohort of skin cancer patients: a source for aetiological studies

Soerjomataram I, Coebergh JWW, de Vries E. A cohort of skin cancer patients: a source for aetiological studies

10.1. A cohort of skin cancer patients: a source for aetiological studies

Skin cancer has been and largely still is, a disease on the increase. In Caucasian populations, it is the most commonly occurring malignancy. In the Eindhoven cancer registry, new primary basal cell carcinoma of the skin accounted for 18.7%, squamous cell carcinoma for 3.5% and melanoma for 2.7% of the total number of incident cancers in 2000-02.[1] Many skin cancers are detected at an early stage where they can be easily and effectively treated and consequently the mortality and morbidity of these tumours is limited. The majority of these cancers, the non-melanoma skin cancers (basal cell and squamous cell carcinomas) have a low malignant potential, which also reduces their fatality. The relatively rare melanomas have a high malignant potential and a relative mortality between 15% and 20%. Melanoma accounts for the vast majority of the skin cancer fatalities, even though comprising at most 10% of all newly diagnosed skin cancer patients.[1]

Incidence of all types of skin cancer in the Netherlands is expected to continue to rise in the near future[2], placing an ever increasing burden on dermatologists and other health practitioners involved in the detection and treatment of skin cancer.

Aetiology: Sunlight and skin cancer

There is a linear relationship between the degree of sun exposure and squamous cell carcinoma of the skin.[3, 4] However, the relationship between melanoma, the most aggressive type of skin cancer, and sunlight, is more complicated.[4, 5] Intermittent sun exposure at young age causing severe sunburn seems most important in people with fair skin types, whereas a certain degree of chronic exposure may have a preventive effect.[6-8] Moreover, sun exposure might be associated with increased survival, independent of Breslow thickness, mitotic index and anatomic location from cutaneous melanoma.[9]

In addition to sun exposure, endogenous factors such as fair skin type, ability to tan and the number of both normal and atypical naevi, both congenital and acquired determine the development of a skin cancer.[10]

Possibilities for research: skin cancer cohort as a tool for aetiological studies

The combination of its high incidence rates and low case-fatality rates makes skin cancer, besides being the most commonly occurring cancer, also the most prevalent cancer (figure). According to estimations, the age-standardised 20-year prevalence of melanoma in the Netherlands will be about 206 for males and 544 for females in the year 2015 a doubling since 2005.[11] The prevalence of SCC and BCC is unknown, but should be much higher, because of the lower mortality and for BCC also much higher incidence.[2] Cohorts of skin cancer patients can contribute to further research in a large group of patients i.e. for studies on the occurrence of multiple cancers. The interest in multiple cancer studies is derived from its use to give indication of follow-up strategies of patients, such as monitoring for new cancer occurrence or on adverse effects of the potentially carcinogenic treatment of the first cancer. It may therefore be of great value to provide etiological insight for cancer in general. The advantage of using a skin cancer cohort is its low case-fatality and non-aggressive treatment, hence a perfect cohort to study the role of environmental or genetic factors

without confounding of mostly surgical treatment. Radiotherapy or chemotherapy is applied only in a small proportion of patients with nodal involvement or metastasis.[12-14]

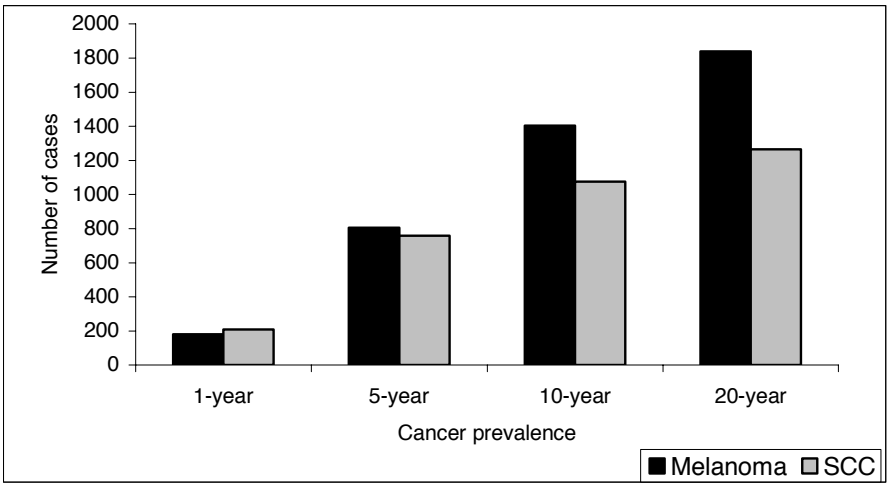

Figure. 1-, 5-, 10-, and 20-years melanoma and squamous cell carcinoma of the skin prevalence on January 1st 2003 in the Eindhoven Cancer Registry East.[1]

Protective role of UV exposure on cancer

There has been growing evidence on the beneficial effect of sun exposure on reducing the risk of some major cancers including prostate, colorectal and breast cancer. Knowing that skin cancer patients have received substantial amounts of UV-exposure during their lifetime, cohorts of skin cancer patients are a valuable starting point to test hypotheses regarding sunlight and cancer aetiology.

A recent review of studies concerning sun exposure and cancer, excluding skin cancer, reported that the available evidence on a risk reducing effect of sun exposure for colon carcinoma is quite convincing[15]. For prostate, breast, and ovarian cancer, in addition to ecologic studies, several case-control and prospective studies were available, all showing a significantly inverse correlation between sunlight and mortality and/or incidence. In contrast, for non-Hodgkin lymphoma (NHL) mortality and sunlight conflicting results were reported, though all case-control and prospective studies found a significant inverse association between the incidence of NHL and sunlight. The north-south gradients showed in the ecologic studies and the finding that increased chronic exposure gave increased protection suggests a dose-response curve between sunlight and the incidence and/or mortality from these cancers: the more sunlight received, the higher the preventive effect.[16]

As an explanation for the preventive effect of sunlight on cancer, usually the role of UVB in Vitamin D (Vit D) synthesis is given. Most humans obtain 80-90% of their requirement for Vit D through UV-exposure, mostly via sunlight; few types of food (mainly oily fish) naturally contain Vit D and only in fish-consuming populations a major part of Vit D is ingested with fish oil.

Vit D3 is synthesized from its precursor 7-dehydrocholesterol in the skin by the direct action of sunlight. The steroid hormone $1,25(OH)_2D3$ is much more active than its precursors and is produced by 25-hydroxylation of Vit D3 in the liver, followed by 1α-hydroxylation in the kidney.[17] Vit D is a well-known regulator of cell proliferation and differentiation, apoptosis, tumour invasion and angiogenesis and consequently it is a potential candidate to regulate cancer progression. The risk of colorectal, prostate and breast cancer have been examined directly in relation to Vit D status exhibiting an inhibiting effect on colorectal carcinogenesis.[15, 18, 19] In addition, both epidemiological and biological data support a role for Vit D in the prevention of breast[20, 21] and probably prostate cancer.[22]

Besides the above-described mechanism of a potential protective mechanism, there are other ways in which sun exposure may influence cancer risk. The Vit D production in the skin is controlled by a self-regulating mechanism, preventing hypervitaminosis D, which can cause liver- and kidney damage. As dose-response curves were found for sun exposure and cancer risk, it seems therefore likely that other mechanisms also play a role. Sunlight is known to influence the circadian rhythm of the body[23] and the functioning of the immune system.

Furthermore, multiple cancer studies within a skin cancer cohort may also provide clues on other aspects of the aetiology of skin cancer itself, by assessing the relationship with other cancers, with well-identified risk factors, such as smoking and viral infections.

Smoking

Smokers were reported to have a 2-fold increased risk of SCC as compared to non-smokers.[24] On the other hand, no clear association between smoking and basal cell carcinoma[25] or melanoma was found.[24] Consistently, a 20-50% higher risk of lung cancer has been observed among cohorts of SCC patients.[26-29] This supports the studies reporting the association between cigarettes smoking and risk of squamous cell carcinoma of the skin.[24] In contrast to melanoma, which is most prevalent among higher socio-economic classes, smoking prevalence and lung cancer incidence are more common among the lower socio-economic groups. Moreover, melanoma and lung cancer do not share known risk factors,[30] therefore, risk of second lung cancer in CM patients is expected to be close to unity.[31] A similar observation was reported in BCC patients.[29, 32]

Viral infections

Current evidence is clear on the role of human papillomavirus as the main cause of anogenital cancers such as cervical cancer and probably also head and neck cancers. Studies have demonstrated a clustering of cervical, head and neck cancer, rectal and squamous cell carcinoma of the skin, leading to the hypothesis that skin cancer (SCC) might be related to viral infection such HPV.[33] Consistently, SCC patients exhibited a 3-fold risk of anogenital and oral cancer. Though here smoking may have biased the results as it is correlated to oral, anogenital and SCC, this finding presents a starting point to investigate the role of HPV infection in the development of SCC.[34]

Hereditary factors in the occurrence of skin cancer

Many studies have shown the importance of a hereditary component in the development of melanoma. A family history of melanoma confers to 2-fold risk of melanoma.[35] In contrast to patients with only one primary melanoma, those who suffered from multiple melanomas had a higher familial occurrence of this cancer: only 3.8% of patients with one primary melanoma had a positive family history as compared to 15% among patients with multiple melanomas.[36] Patients with a family history of melanoma had a 5 times higher risk of multiple melanomas as compared to those lacking family history.[36] On the other hands risk of a second melanoma among those without a family history was also higher than expected. The majority of cases with multiple melanoma lacked a family history, suggesting the stronger role of common risk factor and/or a polygenic model to explain their occurrence.

Furthermore, an increased risk of melanoma among female breast cancer cohort,[37] and vice versa, has been, among others, attributed to mutations in BRCA2 and CDKN2A.[38, 39] Among young breast cancer patients the increased risk of melanoma is higher than that of the older patients with breast cancer, being consistent with a genetic-related cancer risk profile.[40] Such finding may enable us to identify a group of patients with a higher risk of a second cancer and may ultimately improve survival by early detection.

10.2. Conclusion

Most population-based cancer registries in the world collect information on cutaneous malignant melanoma and squamous cell skin cancer; fewer collect reliable information on the occurrence of basal cell non-melanoma skin cancers. Because of the presence of a dermatologist in the initiating phase the Eindhoven cancer registry who attempted to record all newly diagnosed first primary skin cancer cases since the 1950's, this registry constitutes an important source of data for studies in the field of skin cancer.

Due to the large number of patients inflicted with skin cancer, this group has become a valuable group to study the occurrence of multiple cancers. Beside of clinical importance serving as base for follow-up strategy, such study may provide etiological clue of skin cancer or other cancers in general.

References

1. Janssen-Heijnen ML, Louwman M, van de Poll-Franse LV, Coebergh JW, Houterman S, Lemmens VE, Mols F, van der Sanden GAC, Vulto JCM, Masseling HGMB, van der Heijden LH. Van meten naar weten: 50 jaar kankerregistratie. 2005
2. de Vries E, van de Poll-Franse LV, Louwman WJ, de Gruijl FR, Coebergh JW. Predictions of skin cancer incidence in the netherlands up to 2015. *Br J Dermatol*. 2005;152:481-488
3. Armstrong BK, Kricker A. The epidemiology of uv induced skin cancer. *J Photochem Photobiol B*. 2001;63:8-18
4. Zanetti R, Rosso S, Martinez C, Nieto A, Miranda A, Mercier M, Loria DI, Osterlind A, Greinert R, Navarro C, Fabbrocini G, Barbera C, Sancho-Garnier H, Gafa L, Chiarugi A, Mossotti R. Comparison of risk patterns in carcinoma and melanoma of the skin in men: A multi-centre case-case-control study. *Br J Cancer*. 2006;94:743-751
5. Solomon CC, White E, Kristal AR, Vaughan T. Melanoma and lifetime uv radiation. *Cancer Causes Control*. 2004;15:893-902
6. Kaskel P, Sander S, Kron M, Kind P, Peter RU, Krahn G. Outdoor activities in childhood: A protective factor for cutaneous melanoma? Results of a case-control study in 271 matched pairs. *Br J Dermatol*. 2001;145:602-609
7. Osterlind A, Tucker MA, Stone BJ, Jensen OM. The danish case-control study of cutaneous malignant melanoma. Ii. Importance of uv-light exposure. *Int J Cancer*. 1988;42:319-324.
8. Elwood JM, Jopson J. Melanoma and sun exposure: An overview of published studies. *Int J Cancer*. 1997;73:198-203.
9. Berwick M, Armstrong BK, Ben-Porat L, Fine J, Kricker A, Eberle C, Barnhill R. Sun exposure and mortality from melanoma. *J Natl Cancer Inst*. 2005;97:195-199
10. de Vries E, Coebergh JW. Cutaneous malignant melanoma in europe. *Eur J Cancer*. 2004;40:2355-2366
11. Kanker in nederland. Trends, prognoses, en implicatie voor zorgvraag. 2004
12. Thompson JF, Scolyer RA, Kefford RF. Cutaneous melanoma. *Lancet*. 2005;365:687-701
13. Alam M, Ratner D. Cutaneous squamous-cell carcinoma. *N Engl J Med*. 2001;344:975-983
14. Rubin AI, Chen EH, Ratner D. Basal-cell carcinoma. *N Engl J Med*. 2005;353:2262-2269
15. van der Rhee HJ, de Vries E, Coebergh JW. Does sunlight prevent cancer? A systematic review. *Eur J Cancer*. 2006;42:2222-2232
16. de Vries E, Soerjomataram I, Houterman S, Louwman MW, Coebergh JW. Decreased risk of prostate cancer after skin cancer diagnosis: A protective role of ultraviolet radiation? *Am J Epidemiol*. 2007;165:966-972
17. Holick MF. Vitamin d deficiency. *N Engl J Med*. 2007;357:266-281
18. Wu K, Feskanich D, Fuchs CS, Willett WC, Hollis BW, Giovannucci EL. A nested case control study of plasma 25-hydroxyvitamin d concentrations and risk of colorectal cancer. *J Natl Cancer Inst*. 2007;99:1120-1129
19. Oh K, Willett WC, Wu K, Fuchs CS, Giovannucci EL. Calcium and vitamin d intakes in relation to risk of distal colorectal adenoma in women. *Am J Epidemiol*. 2007;165:1178-1186
20. Knight JA, Lesosky M, Barnett H, Raboud JM, Vieth R. Vitamin d and reduced risk of breast cancer: A population-based case-control study. *Cancer Epidemiol Biomarkers Prev*. 2007;16:422-429
21. Robien K, Cutler GJ, Lazovich D. Vitamin d intake and breast cancer risk in postmenopausal women: The iowa women's health study. *Cancer Causes Control*. 2007;18:775-782
22. Gann PH, Ma J, Hennekens CH, Hollis BW, Haddad JG, Stampfer MJ. Circulating vitamin d metabolites in relation to subsequent development of prostate cancer. *Cancer Epidemiol Biomarkers Prev*. 1996;5:121-126
23. Jongbloet PH. Do sunlight and vitamin d reduce the likelihood of colon cancer? Time for a paradigm shift? *Int J Epidemiol*. 2006;35:1359-1360
24. De Hertog SA, Wensveen CA, Bastiaens MT, Kielich CJ, Berkhout MJ, Westendorp RG, Vermeer BJ, Bouwes Bavinck JN. Relation between smoking and skin cancer. *J Clin Oncol*. 2001;19:231-238
25. Corona R, Dogliotti E, D'Errico M, Sera F, Iavarone I, Baliva G, Chinni LM, Gobello T, Mazzanti C, Puddu P, Pasquini P. Risk factors for basal cell carcinoma in a mediterranean population: Role of recreational sun exposure early in life. *Arch Dermatol*. 2001;137:1162-1168
26. Efird JT, Friedman GD, Habel L, Tekawa IS, Nelson LM. Risk of subsequent cancer following invasive or in situ squamous cell skin cancer. *Ann Epidemiol*. 2002;12:469-475
27. Levi F, Randimbison L, La Vecchia C, Erler G, Te VC. Incidence of invasive cancers following squamous cell skin cancer. *Am J Epidemiol*. 1997;146:734-739
28. Maitra SK, Gallo H, Rowland-Payne C, Robinson D, Moller H. Second primary cancers in patients with squamous cell carcinoma of the skin. *Br J Cancer*. 2005;92:570-571
29. Nugent Z, Demers AA, Wiseman MC, Mihalcioiu C, Kliewer EV. Risk of second primary cancer and death following a diagnosis of nonmelanoma skin cancer. *Cancer Epidemiol Biomarkers Prev*. 2005;14:2584-2590
30. Bhatia S, Estrada-Batres L, Maryon T, Bogue M, Chu D. Second primary tumors in patients with cutaneous malignant melanoma. *Cancer*. 1999;86:2014-2020

31. Levi F, La Vecchia C, Randimbison L, Te VC, Erler G. Incidence of invasive cancers following cutaneous malignant melanoma. *Int J Cancer*. 1997;72:776-779
32. Levi F, La Vecchia C, Te VC, Randimbison L, Erler G. Incidence of invasive cancers following basal cell skin cancer. *Am J Epidemiol*. 1998;147:722-726
33. Hemminki K, Jiang Y, Dong C. Second primary cancers after anogenital, skin, oral, esophageal and rectal cancers: Etiological links? *Int J Cancer*. 2001;93:294-298
34. Struijk L, Bouwes Bavinck JN, Wanningen P, van der Meijden E, Westendorp RG, Ter Schegget J, Feltkamp MC. Presence of human papillomavirus DNA in plucked eyebrow hairs is associated with a history of cutaneous squamous cell carcinoma. *J Invest Dermatol*. 2003;121:1531-1535
35. Cho E, Rosner BA, Feskanich D, Colditz GA. Risk factors and individual probabilities of melanoma for whites. *J Clin Oncol*. 2005;23:2669-2675
36. Dong C, Hemminki K. Multiple primary cancers of the colon, breast and skin (melanoma) as models for polygenic cancers. *Int J Cancer*. 2001;92:883-887
37. Soerjomataram I, Louwman WJ, de Vries E, Lemmens VE, Klokman WJ, Coebergh JW. Primary malignancy after primary female breast cancer in the south of the netherlands, 1972-2001. *Breast Cancer Res Treat*. 2005;93:91-95
38. Borg A, Sandberg T, Nilsson K, Johannsson O, Klinker M, Masback A, Westerdahl J, Olsson H, Ingvar C. High frequency of multiple melanomas and breast and pancreas carcinomas in cdkn2a mutation-positive melanoma families. *J Natl Cancer Inst*. 2000;92:1260-1266
39. Cancer risks in brca2 mutation carriers.The breast cancer linkage consortium. *J Natl Cancer Inst*. 1999;91:1310-1316
40. Goggins W, Gao W, Tsao H. Association between female breast cancer and cutaneous melanoma. *Int J Cancer*. 2004;111:792-794

Chapter 11

Are patients with skin cancer at lower risk of developing colorectal or breast cancer?

Soerjomataram I, Louwman W, Lemmens VEPP, Coebergh JWW, de Vries E. Are patients with skin cancer at lower risk of developing colorectal or breast cancer? (submitted)

Abstract

Background and objectives: UV exposure may reduce the risk of colorectal and breast cancer due to rising vitamin D levels. Because skin cancer is positively related to sun exposure, we hypothesized a lower incidence of breast and colorectal cancer after skin cancer diagnosis.

Method: Using data collected by the population-based cancer registry in the southern Netherlands, we analysed the incidence of colorectal and breast cancer among 26,916 newly diagnosed skin cancer patients (4089 squamous cell carcinoma (SCC), 19,319 basal cell carcinoma (BCC), 3,508 cutaneous melanoma (CM)). Standardized incidence ratios (SIR) were calculated to compare cancer risk with that of the general population.

Results: A markedly decreased risk of colorectal cancer was found for subgroups supposedly associated with the highest accumulated sun exposure i.e. men (SIR:0.83, 95%CI:0.71-0.97), patients with SCC (SIR:0.62; 95%CI:0.43-0.93), older patients at SCC diagnosis (SIR:0.59, 95%CI:0.37-0.88), and patients with a SCC or BCC lesion on the head and neck area (SIR:0.59, 95%CI:0.36-0.92 for SCC and SIR:0.78, 95%CI:0.63-0.97 for BCC). This reduced risk was most pronounced during the first year after diagnosis, gradually normalizing. Furthermore, patients with CM exhibited an increased risk of developing a subsequent breast cancer, especially advanced breast cancer (SIR:2.20, 95%CI:1.10-3.94), mainly patients who developed CM after the age of 60 (SIR:1.87, 95%CI:1.14-2.89).

Conclusions: Decreased risk of colorectal cancer was most pronounced for males and SCC cases, suggesting a protective role of continuous sun exposure. The higher risk of breast cancer among CM patients may be related to socio-economic class, both being more common in the affluent group.

11.1. Introduction

Colorectal and breast cancer are two of the most common cancers worldwide.[1] Geographical variation in their occurrence has led to the theory of a beneficial effect of greater sun exposure on the incidence of and mortality from breast and colorectal cancer.[2, 3] Because the majority of skin cancers are caused by exposure to ultraviolet (UV) radiation, we expect a lower risk of colorectal and breast cancer for skin cancer patients compared to the general population.[4, 5]

The inverse association between UV exposure and some cancers - including breast and colorectal cancer - was derived mainly from ecological studies, reporting a north-south gradient with higher cancer occurrence or mortality in less sunny areas compared to sunnier areas.[2, 3, 6] These studies may have been confounded at the group level, being unable to adjust for regional differences between other risk factors. For example, fish intake may reduce the risk of colorectal cancer [7] and fish is probably more widely available in coastal areas where it is sunnier. Studies on the association between sunlight and cancer incidence or mortality with information on individual sun exposure generally found a preventive effect on breast and colorectal cancer.[6] However, out of 5 case-control and cohort studies only one demonstrated a significant reduction of death from breast or colorectal cancer. A meta-analysis of the risk of cancer after skin cancer showed a significant reduction of colon cancer among patients with previous squamous cell carcinoma of the skin, but not when stratified according to gender and not for breast cancer.[8]

In this study we investigated the association between sun exposure and risk of colorectal and breast cancer by assessing the risks of these cancers following skin cancer. Analyses were performed for all skin cancer patients combined as well as stratified according to skin cancer type (squamous cell carcinoma (SCC), basal cell carcinoma (BCC), and cutaneous malignant melanoma (CMM)). We expected to observe lower risks of colorectal and breast cancer among patients who are typically associated with more chronic sun exposure: patients with SCC, elderly skin cancer patients and patients with skin cancer on the head or the neck area.[9] Furthermore, we also examined the relative risk of breast and colorectal cancer according to time since skin cancer diagnosis and stage of breast and colorectal cancer at the time of their diagnosis: if sunlight not only protects against the occurrence of cancer but also slows down the progression, then one would expect to see a decreased incidence of specifically advanced disease. In addition we analysed separately the risk for colon and rectal cancer following diagnosis of the three skin cancer types.

11.2. Methods

Data

We retrieved data on patients with skin cancer who were diagnosed with a first primary in southern Netherlands between 1972 and 2002. Patient data were recorded within the framework of the population-based Eindhoven Cancer Registry that now covers almost 2.4 million inhabitants. The registry is regularly notified about new cancer cases by the pathology and haematology departments in the region. Detailed patient data were obtained from the hospitals and active follow-up of vital status for each patient was conducted through the Central Bureau for Genealogy. Within this study patients were followed until January 1, 2004, date of a second primary cancer diagnosis, date of death or lost to follow-up. Follow-up for vital status of patients with basal cell carcinoma (BCC) was started in 1990, thus for this cohort time at risk began in that year. Coding of multiple tumours was adopted from the rules proposed by the IARC (International Agency for Research on Cancer).[10]

Statistical analysis

In order to determine whether skin cancer patients were at a higher or lower risk of developing cancers than the general population, we compared the incidence of breast (females only) and colorectal cancer (both sexes) among these patients (observed incidence) to the incidence of the same tumours in the reference population. The expected incidence was calculated adjusting for gender, age (in 5-year age categories) and calendar time at skin cancer diagnosis. Standardized incidence ratios (SIR) were computed by dividing the observed incidence rates by the expected incidence rates. Confidence interval (95%) was calculated using exact Poisson probability.[11]

We computed SIR for: (1) skin cancer type (SCC, BCC and CM) (2) sex (male and female); (3) age at diagnosis of skin cancer (aged <60 vs. ≥60 years); (4) location of skin cancer (the head and neck area (not including lip cancer) vs. other body sites); (5) colon and rectum, separately (6) duration of follow-up until occurrence of breast or colorectal cancer (0-1 year, 1-2 years, 2-3 years, 3-4 years, 4-5 year, and 5+ years); and (7) stage of colorectal and breast cancer (colorectal: stage I and II vs. stage III and IV vs. unknown; similar for breast).

The tumour, node and metastasis (TNM) classification system was used. We excluded patients with missing information on body site (unknown-location squamous cell carcinoma: *n* = 20 (0.5%), basal cell carcinoma: *n* = 60 (0.3%), cutaneous malignant melanoma: *n* = 122 (3.4%); this exclusion did not significantly influence results). We finally had 26,916 patients with a previous skin cancer diagnosis in our analysis.

In addition, we calculated the risk of lung cancer for our skin cancer cohort to test the consistency of our hypothesis, since lung cancer has not been observed to be associated with sun exposure. On the contrary: we expected an increased risk of lung cancer in the cohort of SCC patients since cigarette smoking is a risk factor for both [12]. A decreased risk of lung cancer was expected among CM patients because the higher socio-economic group, which has the highest CM incidence, smoked less.[13]

11.3. Results

Women were diagnosed more frequently with CM but less often with SCC. Nonmelanoma skin cancer patients (NMSC: SCC and BCC) were generally older than CM patients and lesions were found more often on the head and neck area (table 11.1). Of the 4089 patients with SCC, 43 and 22 were diagnosed with colorectal and breast cancer, respectively, during 21,098 person-years of follow-up. Among 19,319 BCC cases with a follow-up of 111,098 person-years, a total of 224 colorectal and 174 breast cancers were diagnosed, and among 3508 CM patients 24 and 40 were subsequently diagnosed with colorectal and breast cancer, respectively.

Table 11.1. Characteristics of patients with skin cancer diagnosed in southern Netherlands in 1972-2002*

	Skin cancer types			
	SCC	BCC	CM	Total
No. of person-years	21,098	111,098	24,091	156,287
No. of patients (% of total)	4089 (15)	19,319 (72)	3508 (13)	26,916
Median age (years)				
At skin cancer diagnosis	74.1**	65.6	50.8	65.6
At colorectal cancer diagnosis	75.4	74.7	68.0	74.3
At breast cancer diagnosis	72.6	68.1	64.4	67.9
Median follow-up (years)	3.8	5.2	5.4	5.0
Gender				
Male (%)	2620 (64)	9501 (49)	1420 (40)	13,541 (50)
Female (%)	1469 (36)	9818 (51)	2088 (60)	13,375 (50)
Age at diagnosis				
<60 years (%)	610 (15)	7094 (37)	2422 (69)	10,126 (38)
≥60 years (%)	3479 (85)	12,225 (63)	1086 (31)	16,790 (62)
Location				
Head and neck (%)	2975 (73)	14,248 (74)	497 (15)	17,720 (67)
Others (%)	1094 (27)	5011 (26)	2889 (85)	8994 (33)
Second cancers				
Colorectal (%)	43 (66)	224 (56)	24 (37)	291 (55)
Female breast (%)	22 (34)	174 (44)	40 (63)	236 (45)
Total (% of total)	65 (12)	398 (75)	64 (12)	527 (100)

* BCC patients derived from patients diagnosed in 1990-2002

** Female patients with SSC who developed second breast cancer were diagnosed with SCC at (median) age of 69.7 years

Table 11.2 shows the numbers of colorectal cancer cases occurring in the skin cancer cohorts and the corresponding SIR for men and women together and separately according to various tumour characteristics. We observed a decreased risk of colorectal cancer especially among men with a previous SCC compared to the general population (SIR: 0.62 95%CI: 0.43-0.93). Men who were older than 60 years at SCC diagnosis (SIR: 0.59 95%CI: 0.37-0.88) and who were diagnosed with SCC on the head or neck area (SIR: 0.59 95%CI: 0.36-0.92) showed a significantly lower risk of colorectal cancer. In addition, males diagnosed with BCC on the head and neck exhibited a lower risk of colorectal cancer compared to the general population (SIR: 0.78; 95%CI: 0.63-0.97). SCC and BCC patients exhibited a significantly decreased risk of stage I and II colorectal cancers. The separate risk estimates for colon and rectal cancer after skin cancer are presented in table 11.3. A 35% reduction in the risk of colon cancer was observed (SIR: 0.64; 95%CI: 0.42-0.94).

Table 11.2. Primary colorectal cancer in skin cancer patients diagnosed between 1972 and 2002* and followed until 2004, according to gender

	Total			**Men**			**Women**		
	Cases	SIR	95%CI	Cases	SIR	95%CI	Cases	SIR	95%CI
All skin cancers	291	**0.89**	**0.79-0.99**	162	**0.83**	**0.71-0.97**	129	0.97	0.81-1.15
SCC	43	**0.69**	**0.50-0.94**	28	**0.64**	**0.43-0.93**	15	0.81	0.45-1.34
BCC	224	0.93	0.81-1.06	122	0.87	0.73-1.04	102	1.01	0.82-1.22
CM	24	0.95	0.61-1.42	12	1.05	0.54-1.83	12	0.87	0.45-1.52
SCC									
Age at diagnosis									
<60 years	8	1.38	0.60-2.72	5	1.15	0.37-2.69	3	2.05	0.42-6.00
≥60 years	35	**0.62**	**0.43-0.87**	23	**0.59**	**0.37-0.88**	12	0.71	0.36-1.23
Location									
Head and neck	32	**0.70**	**0.48-0.99**	20	**0.59**	**0.36-0.92**	12	0.98	0.51-1.71
Others	11	0.70	0.35-1.26	8	0.83	0.36-1.64	3	0.50	0.10-1.45
Colorectal cancer stage									
1 & 2	20	**0.63**	**0.38-0.98**	**12**	**0.53**	**0.27-0.94**	8	0.87	0.38-1.77
3 & 4	16	0.71	0.40-1.16	10	0.64	0.30-1.19	6	0.87	0.32-1.98
Unknown	7	0.93	0.37-1.99	6	1.19	0.44-2.71	1	0.41	0.01-2.98
BCC									
Age at diagnosis									
<60 years	39	1.08	0.77-1.48	23	1.12	0.71-1.68	16	1.03	0.59-1.68
≥60 years	185	0.90	0.78-1.04	99	0.83	0.68-1.01	86	1.00	0.80-1.24
Location									
Head and neck	167	0.88	0.75-1.02	87	**0.78**	**0.63-0.97**	80	1.01	0.80-1.25
Others	56	1.13	0.85-1.47	35	1.25	0.87-1.74	21	0.98	0.61-1.50
Colorectal cancer stage									
1 & 2	94	**0.75**	**0.61-0.92**	57	**0.77**	**0.58-0.99**	37	**0.72**	**0.51-1.00**
3 & 4	114	1.19	0.99-1.44	56	1.03	0.78-1.34	58	1.42	1.08-1.84
Unknown	16	0.79	0.45-1.30	9	0.83	0.38-1.62	7	0.75	0.30-1.60
Melanoma									
Age at diagnosis									
<60 years	11	1.06	0.53-1.89	6	1.37	0.50-2.99	5	0.83	0.27-1.94
≥60 years	13	0.88	0.47-1.50	6	0.85	0.31-1.85	7	0.90	0.36-1.85
Location									
Head and neck	5	0.95	0.31-2.22	3	1.05	0.22-3.07	2	0.83	0.10-3.01
Others	19	0.97	0.58-1.51	9	1.07	0.49-2.03	10	0.89	0.43-1.65
Colorectal cancer stage									
1 & 2	13	1.01	0.54-1.72	5	0.84	0.27-1.96	8	1.15	0.50-2.27
3 & 4	11	1.06	0.53-1.89	7	1.52	0.61-3.12	4	0.69	0.19-1.76
Unknown	-	-	-	-	-	-	-	-	-

* BCC patients derived from patients diagnosed in 1990-2002

The risk of breast cancer among women previously diagnosed with skin cancer is given in table 11.4. SCC patients showed a lower breast cancer risk compared with the other skin cancer types, with SIR: 0.87 vs. 0.99 vs. 1.19, among SCC, BCC and CM patients, respectively. Risks tended to be lower among those diagnosed with SCC after the age of 60 (SIR in patients ≥60: 0.66 vs. SIR in patients <60: 1.98) and when SCC was located on the head and neck area (SIR SCC on head and neck area: 0.79 vs. SIR SCC on other body parts: 0.92). More than two-thirds of the women were diagnosed with stage I and II breast cancer. Those diagnosed with BCC showed a decreased risk of breast cancer stage III and IV (SIR: 0.53; 95%CI: 0.30-0.88). In contrast, CM patients had an increased risk of stage III and IV breast cancer (SIR: 2.20; 95%CI: 1.10-3.94). Older CM patients exhibited a 90% higher risk of breast cancer compared to the general female population in southern Netherlands (SIR: 1.87; 95%CI: 1.14-2.89).

Table 11.3. Primary colon and rectal cancer in skin cancer patients diagnosed between 1972 and 2002* and followed until 2004, according to gender

Site of second cancer	SCC			BCC			CM			All skin cancers		
	Cases	SIR	95%CI	Cases	SIR	95%CI	Cases	SIR	95%CI	Cases	SIR	95%CI
Colon	26	**0.64**	**0.42-0.94**	147	0.93	0.79-1.09	18	1.11	0.66-1.76	191	0.89	0.77-1.03
Male	18	0.66	0.39-1.04	81	0.93	0.74-1.16	7	1.02	0.41-2.11	106	0.87	0.71-1.06
Female	8	0.61	0.27-1.21	66	0.93	0.72-1.19	11	1.18	0.59-2.10	85	0.91	0.73-1.13
Rectum	17	0.78	0.46-1.25	77	0.93	0.73-1.16	6	0.68	0.25-1.47	100	0.88	0.71-1.07
Male	10	0.61	0.29-1.13	41	0.78	0.56-1.06	5	1.13	0.37-2.64	56	0.77	0.58-1.00
Female	7	1.28	0.51-2.63	36	1.17	0.82-1.63	1	0.22	0.01-1.25	44	1.08	0.79-1.46

* BCC patients derived from patients diagnosed in 1990-2002

Table 11.4. Primary female breast cancer in skin cancer patients diagnosed between 1972 and 2002* and followed until 2004

	Cases	SIR	95%CI
All skin cancers	236	1.01	0.88-1.14
SCC	22	0.87	0.54-1.31
BCC	174	0.99	0.85-1.15
CM	40	1.19	0.85-1.63
SCC			
Age at diagnosis			
<60 years	8	1.98	0.85-3.89
≥60 years	14	0.66	0.36-1.10
Location			
Head and neck	13	0.79	0.42-1.35
Others	8	0.92	0.40-1.81
Breast cancer stage			
1 & 2	16	0.86	0.49-1.40
3 & 4	5	0.97	0.31-2.27
Unknown	1	0.60	0.02-3.32
BCC			
Age at diagnosis			
<60 years	60	1.01	0.77-1.30
≥60 years	114	0.98	0.81-1.18
Location			
Head and neck	124	0.95	0.79-1.13
Others	50	1.12	0.83-1.48
Breast cancer stage			
1 & 2	154	1.09	0.92-1.27
3 & 4	15	**0.53**	**0.30-0.88**
Unknown	5	0.83	0.27-1.94
Melanoma			
Age at diagnosis			
<60 years	20	0.88	0.53-1.35
≥60 years	20	**1.87**	**1.14-2.89**
Location			
Head and neck	6	1.38	0.50-2.99
Others	34	1.18	0.82-1.65
Breast cancer stage			
1 & 2	26	0.94	0.62-1.38
3 & 4	11	**2.20**	**1.10-3.94**
Unknown	-	-	-

* BCC patients derived from patients diagnosed in 1990-2002

When considering time since non-melanoma skin cancer (NMSC: SCC and BCC) diagnosis (table 11.5), the risk of developing a subsequent colorectal or breast cancer slowly increased with time and was lowest during the early years after skin cancer diagnosis. Within the first year of skin cancer diagnosis the risk of colorectal cancer was 30% lower than that of the general population (SIR: 0.71 95%CI: 0.49-0.99). After 4 years the risk became similar to that of the general population. For CM patients we found a 40% reduced risk of colorectal cancer during the first two years after diagnosis, followed by an increased risk in later years, but these results were not significant (data not shown). For breast cancer, we observed a significantly increased risk during the first year after diagnosis of CM (10 breast cancer cases, SIR: 2.62 95%: 1.25-4.81).

Table 11.5. Risk of second colorectal or female breast cancer following nonmelanoma skin cancer according to time since skin cancer diagnosis

Time since skin cancer diagnosis	**Site of second primary cancer**					
	Colorectum			Female breast		
	Cases	SIR	95%CI	Cases	SIR	95%CI
0-1 year	35	**0.71**	**0.49-0.99**	31	0.95	0.65-1.36
1-2 years	37	0.78	0.55-1.08	26	0.83	0.54-1.22
2-3 years	33	0.78	0.53-1.10	28	0.98	0.65-1.43
3-4 years	32	0.90	0.62-1.28	24	1.00	0.64-1.50
4-5 years	34	1.14	0.79-1.60	22	1.09	0.68-1.67
≥5 years	96	0.97	0.79-1.19	65	1.01	0.78-1.29

In our skin cancer cohorts 361 patients developed lung cancer, 86, 263, and 12 in SCC, BCC and CM patients, respectively (data not shown). We observed an increased risk of lung cancer after SCC (SIR: 1.21 95%CI: 0.97-1.49), a significantly decreased risk for CM patients (SIR: 0.47; 95%CI: 0.24-0.84) and a risk similar to that of the general population for BCC patients (SIR: 1.09; 95%CI: 0.96-1.23).

Table 11.6. Overview of population-based studies on breast or colorectal cancer after skin cancer [a]

Author, country (reference)	Skin cancer/ patient' characteristic	No. of skin cancer patients	No. of colorectal cancer patients	SIR	95%CI	No. of breast cancer patients	SIR	95%CI
Levi, Switzerland	BCC[39]	11,878	Colon : 103	1.0	0.8-1.2	126	1.2	1.0-1.4[f]
			Rectum: 47	0.8	0.6-1.0			
	SCC[24]	4,639	Colon: 29	0.7	0.5-1.0	32	1.0	0.7-1.4
			Rectum: 19	0.8	0.5-1.3			
	CM[40]	1,780	Colon: 12	1.6	0.8-2.7	16	1.3	0.7-2.0
			Rectum: 6	1.3	0.5-2.7			
Bhatia, USA[23]	CM, women	287	-	-	-	3	0.7	0.1-1.6
Hemminki, Sweden[21]	SCC							
	Men, <1 yr	11,409	Colon: 8	0.6	0.2-1.0	-	-	-
	Men, >1 yr		Colon: 123	1.2	1.0-1.5[5]			
	Women, <1yr	6,228	Colon: 3	0.4	0.1-1.1	-	-	-
	Women, >1yr		Colon: 50	1.0	0.7-1.3			
Milan, Finland[41]	BCC							
	Men	29,727	Colon: 258	1.26	1.2-1.3	-	-	-
	Women	42,197	Colon: 402	1.23	1.1-1.3	949	1.23	1.2-1.3
	Head & neck	52,536	Colon: 496	1.21	1.1-1.3	716	1.2	1.1-1.3
Friedman, USA[42b]	BCC							
	Men	1,648	30	0.9	0.6-1.4	-	-	-
	Women	1,516	30	1.1	0.7-1.7	87	2.1	1.3-3.6
Bower, UK[43]	BCC	13,961[d]	-	-	-	120	0.80	0.7-0.96
Efrid, US[44b]	SCC	822	15	1.7	0.9-3.2	8	0.8	0.3-1.8
Crocetti, Italy[45]	CM	1835	Colon: 4	0.5	0.2-1.4	14	1.5	0.8-2.5
			Rectum: 3	0.8	0.2-2.4			
Maitra, UK[46]	SCC							
	Men	16,962	Colon: 187	1.2	1.0-1.4[e]	-	-	-
	Women	8,769	Colon: 83	1.2	1.0-1.5[e]	140	1.0	0.8-1.1
Nugent, Canada[26]	BCC							
	Men	15,586	Colon: 253	1.00	0.9-1.1	-	-	-
			Rectum: 116	0.78	0.6-0.9			
	Women	13,370	Colon: 216	1.02	0.9-1.2	447	1.22	1.1-1.3
			Rectum: 63	0.85	0.6-1.1			
	SCC							
	Men	4,973	Colon: 86	1.07	0.9-1.3	-	-	-
			Rectum: 38	0.85	0.6-1.2			
	Women	2,860	Colon: 36	0.81	0.6-1.1	73	1.07	0.8-1.3
			Rectum: 11	0.75	0.4-1.3			
Freedman, SEER, US[20]	CM							
	Men	34,949	Colon: 313	1.00	p>0.05	-	-	-
			Rectum: 114	0.84				
	Women	31,110	Colon: 215	0.97	p>0.05	765	1.09	P<0.05
			Rectum: 66	0.92				
Tuohimaa, worldwide 13 registries[47c]	CM							
	Sunny-countries	98,051	494	1.13	1.0-1.2	318	1.03	0.9-1.2
	Less sunny	42,049	875	1.13	1.1-1.2	1035	1.26	1.2-1.3
	BCC	148,885						
	Sunny-countries	-	566	0.93	0.7-1.2	80	1.04	0.8-1.3
	Less sunny	-	2511	1.35	1.3-1.4	3062	1.41	1.4-1.5
	NMSC excl. BCC	127,149						
	Sunny-countries	-	29	0.73	0.5-1.1	10	0.9	0.4-1.7
	Less sunny	-	2612	1.27	1.2-1.3	1150	1.26	1.2-1.3

[a] studies were performed between 1997 and 2007. [b] nested case control study; analysis was corrected for smoking status, marital status, alcohol consumption, occupational exposure (chemicals etc.). [c] Ratio of colorectal after CM in sunny/less sunny countries: 0.99 (0.89-1.11), after BCC: 0.69 (0.53-0.85), after nonmelanoma skin cancer excl BCC: 0.58 (0.39-0.92); ratio of female breast cancer after CM in sunny/less sunny countries: 0.82 (0.73-0.93), after BCC: 0.74 (0.58-0.92), after nonmelanoma skin cancer excl BCC: 0.71 (0.34-1.32) [d] total number of cohorts, includes men and women. [e] 95% confidence interval did not include 1. [f] 95% confidence interval included 1.

11.4. Discussion

In this large, population-based study of nearly 27,000 skin cancer patients, we found for the first time a decreased risk of colorectal cancer, especially for men. The decreased risk was most apparent among those diagnosed with SSC, with a 29-36% lower risk of colorectal cancer for women and men compared to the general population. Older patients with SCC and patients with a lesion on the head and neck area also exhibited a reduced risk of colorectal cancer. Another novel result is the increasing risk over time after nonmelanoma skin cancer diagnosis, with the lowest risk in the early years. For women with a previous CM at ages older than 60, we observed almost a 2-fold increased risk of breast cancer. This increased risk was most marked for advanced stage breast cancer among female CM patients.

The beneficial influence of sun exposure on cancer is generally presumed to be through vitamin D.[14] Sunlight increases the synthesis of pre-vitamin D. Active vitamin D regulates cell growth and differentiation by binding to vitamin D receptors on various tissues.[15] The inverse association between dietary vitamin D intake and colorectal or breast cancer;[16-18] has not always been confirmed by others.[19] Out of 14 studies investigating the risk of colorectal or breast cancer after skin cancer diagnosis performed within the last 10 years, 4 and 5 studies demonstrated increased risks of colorectal and breast cancer after skin cancer, respectively (table 6). One observed a significantly reduced risk of rectal cancer and another for breast cancer. Several factors may explain the different findings across the studies. Firstly, many studies did not stratify according to gender; in our study men seemed to exhibit a larger risk reduction than women.[20, 21] Secondly confounding by age, those younger at their first cancer diagnosis showed higher risks of developing a second cancer.[22-24] Thirdly, skin cancer sub-site was not investigated separately, i.e. patients with a lesion on the head and neck area had the highest risk reduction. Finally, the studies listed had a long follow-up period[25], and the protective effect was most pronounced in the early period.[20, 21, 26] Thus, by including patients with longer follow-up, the risk may have been elevated back to that of the general population.

SCC has been related to cumulative sun exposure[9] and is more common in men probably due to their history of outdoor labour and the fact that women often have longer (and more) hair than men, protecting their scalp better against the sun. This high sun exposure would explain the highest protective effect of sunlight on colorectal cancer found for this group of patients. Physical activity may have been a confounding factor: more physical exercise lowers the risk of colorectal cancer,[27] and is related to more sun exposure and therefore a higher skin cancer risk.[28] However, physical activity increases intermittent sun exposure, which is related to the risk of CM[28] and not SCC, which exhibited the lowest colorectal cancer risk. As for BCC, compared to SCC, BCC patients have been reported to have the lower lifetime accumulated UV exposure, thus also the weaker risk reduction in our study.[29] Furthermore, the stronger beneficial effect of vitamin D was observed in the distal colon and the rectum[16, 30]. Like others[18], our finding did not indicate a different association for rectal cancer, though the low number of cases restricted our conclusion.

Although not significant, after a diagnosis of skin cancer we saw a similar pattern for breast cancer as that for colorectal cancer: SCC patients who were older than 60 years at diagnosis

with a lesion on the head and neck area had the lowest risk of breast cancer. Similar reasoning as that for colorectal cancer may apply here: greater sun exposure for these patients. Moreover, when the risk was compared for SCC vs. BCC vs. CM, an increasing trend was observed, which is in line with the amount of sun exposure among these cancer patients: highest for SCC and lowest for CM patients.[9] Previous studies reported an increased risk of breast cancer for CM patients.[20, 22] A reciprocal association was observed for women with breast cancer who have a higher risk of CM.[22, 31, 32] This may reflect a higher socio-economic status, thus having more intermittent sun exposure[33] but also fewer children, younger age at the first child's birth[34] and probably higher awareness of breast cancer leading to higher screening attendance rate. This clustering of risk factors among the more advantaged may explain the relationship between CM and breast cancer. In addition, genetic predisposition to both CM and breast cancer may have contributed to the elevated risk.[35, 36]

Vitamin D has been shown to delay cancer progression.[14, 37] We found a lower risk of less advanced stage colorectal cancer for patients with SCC and BCC but not for patients with CM. The risk of more advanced colorectal cancer was decreased among patients with SCC but not among patients with BCC and CM. Chronic sun exposure seems to protect against any stage of colorectal cancer, and as the lifetime UV exposure becomes lower, as in the case of BCC patients, the protective effect is only evident for early colorectal cancer. In addition, we demonstrated a significantly decreased risk of advanced stage breast cancer for BCC patients. Yet, patients with CM experienced a higher risk of advanced breast cancer. Genetic predisposition to both CM and breast cancer may partly explain this finding, e.g. BRCA2 mutation. Mutation carriers have been shown to have a higher grade of breast cancer compared to those without.[38] An elevated risk of breast cancer was also found for elderly CM patients, usually contrary to genetic-related cancer. However the breast cancer risk for BRCA2 carriers has been reported to persist even after menopause.[38]

The strength of this study is its population-based nature, enabling comparisons with the same population from which the cases were obtained from and avoiding selection bias of the control group. A population-based study also provides larger numbers for statistical analyses even after categorisation of the factors studied. In addition, the Eindhoven Cancer Registry is unique in that it systematically collected data on various skin cancer types, allowing us to compare the risk of second cancers among these groups with different sun exposure patterns.

Limitations of our study include the lack of individual breast or colorectal cancer risk factor data such as reproductive factors, external hormone or supplement intake, dietary information and physical activity level. Skin cancer was taken as a proxy for higher sun exposure and no information on actual sun exposure or other modifying factors such skin type was available. Methodological artefact seems to be an unlikely explanation because additional analyses showed an increased risk of lung cancer for SCC patients and a lower risk for CM patients than we had hypothesized. Furthermore, the decreased risk during the early period after skin cancer diagnosis does not seem to be biased. Cancer patients have higher alertness for cancer and may undergo a more intensive medical surveillance, which would have, theoretically, elevated their cancer risk compared to the general population. Finally, the registration of basal cell carcinoma may not be as complete as that of the other

skin malignancies. However, primary tumour tissues are sent for pathological review and the registry would be informed. In addition, it is highly unlikely that underreporting is related to the risk of breast or colorectal cancer.

For the first time we have reported a lower risk of colorectal cancer after skin cancer, especially among those who are most chronically exposed to the sun, probably due to sun-induced high levels of vitamin D. The beneficial influence of sun exposure in women was less evident, probably because it was diluted by other factors that might have increased the risk of skin as well as colorectal or breast cancer. Studies are needed to clarify the benefit of sun exposure and supplementation of vitamin D in preventing (as well as reducing) the progression of colorectal as well as breast cancer, so that public health measures and chemoprevention strategies can be adapted accordingly.

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References

1. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. *CA Cancer J Clin*. 2005;55:74-108
2. Garland CF, Garland FC. Do sunlight and vitamin d reduce the likelihood of colon cancer? *Int J Epidemiol*. 2006;35:217-220
3. Grant WB. An ecologic study of dietary and solar ultraviolet-b links to breast carcinoma mortality rates. *Cancer*. 2002;94:272-281
4. de Vries E, Bray FI, Coebergh JW, Parkin DM. Changing epidemiology of malignant cutaneous melanoma in europe 1953-1997: Rising trends in incidence and mortality but recent stabilizations in western europe and decreases in scandinavia. *Int J Cancer*. 2003;107:119-126
5. de Vries E, Louwman M, Bastiaens M, de Gruijl F, Coebergh JW. Rapid and continuous increases in incidence rates of basal cell carcinoma in the southeast netherlands since 1973. *J Invest Dermatol*. 2004;123:634-638
6. van der Rhee HJ, de Vries E, Coebergh JW. Does sunlight prevent cancer? A systematic review. *Eur J Cancer*. 2006;42:2222-2232
7. Norat T, Bingham S, Ferrari P, Slimani N, Jenab M, Mazuir M, Overvad K, Olsen A, Tjonneland A, Clavel F, Boutron-Ruault MC, Kesse E, Boeing H, Bergmann MM, Nieters A, Linseisen J, Trichopoulou A, Trichopoulos D, Tountas Y, Berrino F, Palli D, Panico S, Tumino R, Vineis P, Bueno-de-Mesquita HB, Peeters PH, Engeset D, Lund E, Skeie G, Ardanaz E, Gonzalez C, Navarro C, Quiros JR, Sanchez MJ, Berglund G, Mattisson I, Hallmans G, Palmqvist R, Day NE, Khaw KT, Key TJ, San Joaquin M, Hemon B, Saracci R, Kaaks R, Riboli E. Meat, fish, and colorectal cancer risk: The european prospective investigation into cancer and nutrition. *J Natl Cancer Inst*. 2005;97:906-916
8. Grant WB. A meta-analysis of second cancers after a diagnosis of nonmelanoma skin cancer: Additional evidence that solar ultraviolet-b irradiance reduces the risk of internal cancers. *J Steroid Biochem Mol Biol*. 2007;103:668-674
9. Armstrong BK, Kricker A. The epidemiology of uv induced skin cancer. *J Photochem Photobiol B*. 2001;63:8-18
10. International rules for multiple primary cancers (icd-0 third edition). *Eur J Cancer Prev*. 2005;14:307-308
11. Breslow NE, Day NE. Statistical methods in cancer research. Volume ii--the design and analysis of cohort studies. *IARC Sci Publ*. 1987:1-406
12. Grodstein F, Speizer FE, Hunter DJ. A prospective study of incident squamous cell carcinoma of the skin in the nurses' health study. *J Natl Cancer Inst*. 1995;87:1061-1066
13. Pukkala E. *Cancer risk by social class and occupation. A survey of 109,000 cancer cases among finns of working age.* Basel: Karger; 1995.
14. Giovannucci E. The epidemiology of vitamin d and cancer incidence and mortality: A review (united states). *Cancer Causes Control*. 2005;16:83-95
15. Lamprecht SA, Lipkin M. Chemoprevention of colon cancer by calcium, vitamin d and folate: Molecular mechanisms. *Nat Rev Cancer*. 2003;3:601-614
16. Oh K, Willett WC, Wu K, Fuchs CS, Giovannucci EL. Calcium and vitamin d intakes in relation to risk of distal colorectal adenoma in women. *Am J Epidemiol*. 2007;165:1178-1186
17. Robien K, Cutler GJ, Lazovich D. Vitamin d intake and breast cancer risk in postmenopausal women: The iowa women's health study. *Cancer Causes Control*. 2007;18:775-782
18. Wu K, Feskanich D, Fuchs CS, Willett WC, Hollis BW, Giovannucci EL. A nested case control study of plasma 25-hydroxyvitamin d concentrations and risk of colorectal cancer. *J Natl Cancer Inst*. 2007;99:1120-1129
19. Lin J, Zhang SM, Cook NR, Manson JE, Lee IM, Buring JE. Intakes of calcium and vitamin d and risk of colorectal cancer in women. *Am J Epidemiol*. 2005;161:755-764
20. Freedman DM, Miller BA, Tucker MA. *New malignancies following melanoma of the skin, eye melanoma, and non-melanoma eye cancer*. Bethesda, MD: National Cancer Institute; 2006.
21. Hemminki K, Dong C. Subsequent cancers after in situ and invasive squamous cell carcinoma of the skin. *Arch Dermatol*. 2000;136:647-651
22. Goggins W, Gao W, Tsao H. Association between female breast cancer and cutaneous melanoma. *Int J Cancer*. 2004;111:792-794
23. Bhatia S, Estrada-Batres L, Maryon T, Bogue M, Chu D. Second primary tumors in patients with cutaneous malignant melanoma. *Cancer*. 1999;86:2014-2020

24. Levi F, Randimbison L, La Vecchia C, Erler G, Te VC. Incidence of invasive cancers following squamous cell skin cancer. *Am J Epidemiol*. 1997;146:734-739
25. de Vries E, Soerjomataram I, Houterman S, Louwman MW, Coebergh JW. Decreased risk of prostate cancer after skin cancer diagnosis: A protective role of ultraviolet radiation? *Am J Epidemiol*. 2007;165:966-972
26. Nugent Z, Demers AA, Wiseman MC, Mihalcioiu C, Kliewer EV. Risk of second primary cancer and death following a diagnosis of nonmelanoma skin cancer. *Cancer Epidemiol Biomarkers Prev*. 2005;14:2584-2590
27. Samad AK, Taylor RS, Marshall T, Chapman MA. A meta-analysis of the association of physical activity with reduced risk of colorectal cancer. *Colorectal Dis*. 2005;7:204-213
28. Shors AR, Solomon C, McTiernan A, White E. Melanoma risk in relation to height, weight, and exercise (united states). *Cancer Causes Control*. 2001;12:599-606
29. Kricker A, Armstrong BK, English DR, Heenan PJ. A dose-response curve for sun exposure and basal cell carcinoma. *Int J Cancer*. 1995;60:482-488
30. Feskanich D, Ma J, Fuchs CS, Kirkner GJ, Hankinson SE, Hollis BW, Giovannucci EL. Plasma vitamin d metabolites and risk of colorectal cancer in women. *Cancer Epidemiol Biomarkers Prev*. 2004;13:1502-1508
31. Soerjomataram I, Louwman WJ, de Vries E, Lemmens VE, Klokman WJ, Coebergh JW. Primary malignancy after primary female breast cancer in the south of the netherlands, 1972-2001. *Breast Cancer Res Treat*. 2005;93:91-95
32. Mellemkjaer L, Friis S, Olsen JH, Scelo G, Hemminki K, Tracey E, Andersen A, Brewster DH, Pukkala E, McBride ML, Kliewer EV, Tonita JM, Kee-Seng C, Pompe-Kirn V, Martos C, Jonasson JG, Boffetta P, Brennan P. Risk of second cancer among women with breast cancer. *Int J Cancer*. 2006;118:2285-2292
33. MacKie RM, Hole DJ. Incidence and thickness of primary tumours and survival of patients with cutaneous malignant melanoma in relation to socioeconomic status. *Bmj*. 1996;312:1125-1128
34. Braaten T, Weiderpass E, Kumle M, Adami HO, Lund E. Education and risk of breast cancer in the norwegian-swedish women's lifestyle and health cohort study. *Int J Cancer*. 2004;110:579-583
35. Borg A, Sandberg T, Nilsson K, Johannsson O, Klinker M, Masback A, Westerdahl J, Olsson H, Ingvar C. High frequency of multiple melanomas and breast and pancreas carcinomas in cdkn2a mutation-positive melanoma families. *J Natl Cancer Inst*. 2000;92:1260-1266
36. Cancer risks in brca2 mutation carriers.The breast cancer linkage consortium. *J Natl Cancer Inst*. 1999;91:1310-1316
37. Robsahm TE, Tretli S, Dahlback A, Moan J. Vitamin d3 from sunlight may improve the prognosis of breast-, colon- and prostate cancer (norway). *Cancer Causes Control*. 2004;15:149-158
38. Verhoog LC, Berns EM, Brekelmans CT, Seynaeve C, Meijers-Heijboer EJ, Klijn JG. Prognostic significance of germline brca2 mutations in hereditary breast cancer patients. *J Clin Oncol*. 2000;18:119S-124S
39. Levi F, La Vecchia C, Te VC, Randimbison L, Erler G. Incidence of invasive cancers following basal cell skin cancer. *Am J Epidemiol*. 1998;147:722-726
40. Levi F, La Vecchia C, Randimbison L, Te VC, Erler G. Incidence of invasive cancers following cutaneous malignant melanoma. *Int J Cancer*. 1997;72:776-779
41. Milan T, Pukkala E, Verkasalo PK, Kaprio J, Jansen CT, Koskenvuo M, Teppo L. Subsequent primary cancers after basal-cell carcinoma: A nationwide study in finland from 1953 to 1995. *Int J Cancer*. 2000;87:283-288
42. Friedman GD, Tekawa IS. Association of basal cell skin cancers with other cancers (united states). *Cancer Causes Control*. 2000;11:891-897
43. Bower CP, Lear JT, Bygrave S, Etherington D, Harvey I, Archer CB. Basal cell carcinoma and risk of subsequent malignancies: A cancer registry-based study in southwest england. *J Am Acad Dermatol*. 2000;42:988-991
44. Efird JT, Friedman GD, Habel L, Tekawa IS, Nelson LM. Risk of subsequent cancer following invasive or in situ squamous cell skin cancer. *Ann Epidemiol*. 2002;12:469-475
45. Crocetti E, Carli P. Risk of second primary cancers, other than melanoma, in an italian population-based cohort of cutaneous malignant melanoma patients. *Eur J Cancer Prev*. 2004;13:33-37
46. Maitra SK, Gallo H, Rowland-Payne C, Robinson D, Moller H. Second primary cancers in patients with squamous cell carcinoma of the skin. *Br J Cancer*. 2005;92:570-571
47. Tuohimaa P, Pukkala E, Scelo G, Olsen JH, Brewster DH, Hemminki K, Tracey E, Weiderpass E, Kliewer EV, Pompe-Kirn V, McBride ML, Martos C, Chia KS, Tonita JM, Jonasson JG, Boffetta P, Brennan P. Does solar exposure, as indicated by the non-melanoma skin cancers, protect from solid cancers: Vitamin d as a possible explanation. *Eur J Cancer*. 2007

Chapter 12

Decreased risk of prostate cancer after skin cancer diagnosis: a protective role of ultraviolet radiation?

De Vries E, Soerjomataram I, Houterman S, Louwman MW, Coebergh JW. Decreased risk of prostate cancer after skin cancer diagnosis: A protective role of ultraviolet radiation? Am J Epidemiol. 2007;165:966-972

Abstract

Background and objectives: Ultraviolet radiation (UVR) causes skin cancer, but may protect against prostate cancer. We hypothesized that skin cancer patients had a lower prostate cancer incidence than the general population.

Methods: In the southeast of the Netherlands, a population-based cohort of male skin cancer patients diagnosed since 1970 (2620 squamous cell carcinomas, 9501 basal cell carcinomas and 1420 cutaneous malignant melanomas) was followed-up for incidence of invasive prostate cancer until January 1, 2005 within the framework of the Eindhoven cancer registry. Incidence rates of prostate cancer amongst skin cancer patients were compared to those in the reference population, resulting in Standardised Incidence Ratios (SIR).

Results: Skin cancer patients were at decreased risk of developing prostate cancer compared to the general population (SIR 0.89 (95% CI: 0.78, 0.99)), especially shortly after diagnosis. The risk of advanced prostate cancer was significantly decreased (SIR 0.73 (95% CI: 0.56, 0.94)), indicating a possible anti-progression effect of UVR. Patients with a skin cancer in the chronically UVR exposed head and neck area (SIR: 0.84 (95% CI 0.73, 0.97)) and those diagnosed after the age of 60 (SIR 0.86 (95% CI 0.75, 0.97)), had decreased prostate cancer incidence rates.

Conclusions: These results support the hypothesis that UVR protects against prostate cancer.

Keywords: skin neoplasms, cohort study, prostatic neoplasms, registries, second primary neoplasms

12.1. Introduction

Ultraviolet radiation (UVR) causes skin cancer, but has been hypothesized to protect against prostate cancer development and possibly progression. If this hypothesis were true, one would expect skin cancer patients to have a lower prostate cancer incidence than the general population and, more specifically, to have a lower incidence of advanced stage prostate cancer.

A striking epidemiological feature of prostate cancer is a gradient of increasing mortality rates among Caucasians with latitude (i.e. inverse correlation between geographic distributions of ultraviolet radiation (UVR) and prostate cancer mortality). Mortality from prostate cancer was found to increase with latitude in the USA [1-3] and Europe [4]. This is consistent with the hypothesis of an UVR-induced 'protective' effect on prostate cancer incidence and/or survival, because annual average UVR levels decrease with increasing latitude. A case-control study conducted in the United Kingdom found risk of prostate cancer to be two-thirds less in men with high than men with low lifetime sun exposure [5, 6], and risk of advanced prostate cancer was reduced by half in the group with the highest quintile of sun exposure index compared to the lowest quintile in a San Francisco Bay area population-based case-control study [7]. Risk of prostate cancer among white men was decreased by about one-third for men with a high solar radiation at their place of longest residence and was halved for men with a low solar radiation at the place of birth in a follow-up study conducted in the United States [8]

Most of these studies used measures of residential sun exposure [1, 2, 4, 8], sometimes combined with job histories [3, 7] as indicator of individual sun exposure, whereas individual behaviour can hugely influence the amount of sun exposure received. The case-control study [5, 6] collected individual sun exposure data using questionnaires, in which recall bias may influence exposure estimates.

In this study, we compared incidence of prostate cancer in the general male population to incidence of prostate cancer in cohorts of male skin cancer patients. It is generally accepted that the majority of skin cancers are caused by exposure to UVR [9, 10]. Therefore, although we do not have individual information on sun exposure, we may assume that these skin cancer cases had on average a higher UVR exposure than the general population in the same area. The association with UVR is most straightforward for squamous cell carcinomas of the skin (SCC) [9], which are related to cumulative UVR exposure. The association is less strong for basal cell carcinomas of the skin (BCC), which has been hypothesized to be etiologically more similar to melanoma [9]. Intermittent exposure to sunlight, especially during childhood, is thought to be the main risk factor for cutaneous malignant melanoma (CM)[11], particularly for people with a light skin phototype. Generally, skin cancers occurring in the head and neck region and those diagnosed at older age are associated with chronic exposure and skin cancers occurring at other body sites and at younger ages are associated with intermittent exposure and probably have a larger genetic component [12, 13]. To our knowledge, no previous study has investigated prostate cancer incidence after skin cancer taking into account body site of the skin cancer, age at and time since skin cancer diagnosis, and prostate cancer stage.

12.2. Materials and methods

Cohort

Data on skin cancer patients were obtained from the Eindhoven Cancer Registry, situated in the southeastern part of the Netherlands and serving a population of 2.4 million inhabitants. The Eindhoven Cancer Registry serves more than 12 general hospitals that are served by six pathologic laboratories, all participating in a nationwide pathology-network (PALGA), which also notifies the regional cancer registries. The registry receives lists of newly diagnosed cases on a regular basis from the pathology departments, including cases whose material was sent in by general practitioners. In addition, the medical records departments of the hospitals provide lists of outpatients and hospitalised cancer patients. Following this notification, the medical records of newly diagnosed patients (and tumors), often only available from the outpatient departments, are collected and trained registrars from the cancer registry abstract the necessary information. Data are checked for duplicate records. Records are assumed to be complete [14, 15]. Active follow-up of vital status until January 1, 2005 was conducted through municipal registries and the Central Bureau for Genealogy. The rules of the International Association of Cancer Registries (IACR) for coding multiple tumours were adopted [16]. A primary cancer is defined as a cancer that originates in a primary site or tissue and is thus neither an extension, nor a recurrence nor a metastasis. Only patients with a first primary skin cancer were included. Those diagnosed with a cancer before the skin cancer diagnosis were excluded.

Eligible participants for this study were Dutch males with an invasive SCC (n=2752) & CM (n=1449) diagnosed in the period 1972-2002, for patients with an invasive BCC the period of inclusion was 1990-2002 (n=9544) since active follow-up for BCC patients was initiated in 1990. Among the eligible men we excluded skin cancer patients with 0 follow-up time (SCC n=132, BCC n=43, CM=29), as they would have had no ‘time’ to develop a second tumour. Patients with 0 follow-up time were usually diagnosed with another (usually skin) cancer at the same day of the skin cancer diagnosis or were discovered during post-mortem examination. We excluded them because they would increase the nominator (number of patients with a second cancer) without contributing any follow-up time, and therefore would overestimate the relative risk. Included patients were followed for the development of invasive prostate cancer until January 1, 2005. In case of a diagnosis of another second tumour (not prostate cancer), follow-up ended at the date of diagnosis of this second tumour.

Clinical stage of prostate cancer was recorded according to the TNM classification [17]. Since pathological stage is only available after radical prostatectomy and treatment decisions are based on clinical stage, only the latter was used (except for lymph node involvement and distant metastasis which was based also on pathological stage, because this can still influence treatment decisions). The clinical tumour classification was simplified as T1, T2, T3, T4 or as ‘unknown’ if sufficient information was not available for accurate staging.

Thus, 2620 patients diagnosed with a SCC, 9501 patients with a BCC and 1420 diagnosed with CM were included for analysis.

Statistical methods

We used the person-years analysis to study the incidence of second neoplasms after diagnosis of skin cancer [18]. We compared the incidence of prostate cancer as a second tumour among patients with a diagnosis of skin cancer (the observed incidence) with the prostate cancer incidence in the reference population (the expected incidence), the reference population being the population served by the Eindhoven Cancer Registry. We took into account the amount of time that had passed between the diagnosis of the first and second tumour, adjusting for age (in 5-year categories) and calendar period of the skin cancer diagnosis. Through the adjusted person-years obtained, we calculated the expected subsequent relative risk for prostate cancer for the general male population. The observed and expected numbers were compared in order to determine the standardised incidence ratio (SIR). Statistical significance and 95% confidence intervals (CI) were calculated using exact Poisson probability [19]. Risk estimates were calculated for the total study population and sub-analyses were performed for incidence of skin cancer in the head and neck area (chronically sun-exposed) and the other body sites (intermittently exposed), for age at diagnosis of skin cancer (age <60 vs ≥60 years) and for incidence of prostate cancer by stage (I & II compared to III & IV). Patients with missing information on body site were excluded from analysis (unknown location SCC: N=11, BCC: N=32, CM: N=69, this exclusion did not significantly influence results).

In the first years after a skin cancer diagnosis, patients are likely to decrease their sun exposure. If the hypothesized protective effect of sun exposure would be effective on the short term, one would therefore expect a more markedly decreased risk of second prostate cancer among skin cancer patients shortly after their initial diagnosis than at a longer follow-up time. Therefore we performed an additional analysis, calculating SIRs for prostate cancer incidence by time since skin cancer diagnosis divided in 6 periods; 0-1 year, 1-2, 2-3, 3-4, 4-5 and 5 or more years since skin cancer diagnosis.

12. 3. Results

We included 13,541 skin cancer cases eligible for analysis, with a total of 75,047 person-years. Table 12.1 gives the results of the analyses. Average age at diagnosis of SCC was 73, of BCC 66 and of melanoma 53 years; the average follow-up time was 5.0, 5.6 and 6.0 years, respectively.

Table 12.1. Subsequent prostate cancers observed in a cohort of skin cancer patients diagnosed in 1972-2002, Eindhoven Cancer Registry Area, the Netherlands

	N Cases	Median age (yrs) at diagnosis of		PY†	Obs‡	Exp§	SIR#	95% CI
		Skin cancer	Prostate cancer					
All skin cancers	13541	66.4	69.3	75,047	272	307	0.89	0.78, 0.99
Non-melanoma skin cancers	12121	67.4	74.2	66,564	253	291	0.87	0.77, 0.98
Melanoma	1420	52.7	68.3	8,483	19	16	1.16	0.71, 1.85
SCC	2620	73.2	77.0	13,204	56	66	0.84	0.64, 1.10
BCC	9501	65.7	73.0	53,360	197	224	0.88	0.76, 1.01
All skin cancers								
Age at diagnosis								
< 60 years	4650	51.2	61.6	31,886	42	38	1.10	0.80, 1.50
≥ 60 years	8891	72.5	75.2	43,182	230	269	0.86	0.75, 0.97
Location								
Head & Neck	9461	68.6	74.8	51,293	197	235	0.84	0.73, 0.97
Others	3968	59.8	71.4	23,357	75	71	0.85	0.64, 1.10
Prostate cancer stage								
1 & 2	13541	67.7	72.7	75,047	188	199	0.94	0.81, 1.09
3 & 4	13541	70.6	74.9	75,047	61	84	0.73	0.56, 0.94
Unknown	13541	75.6	76.6	75,047	23	24	0.95	0.60, 1.42
Non melanoma skin cancers								
Age at diagnosis								
< 60 years	3719	52.1	62.3	25,401	37	33	1.12	0.79, 1.55
≥ 60 years	8402	72.6	75.4	41,164	216	258	0.84	0.73, 0.96
Location of NMSC								
Head & Neck	9197	68.7	74.8	49,871	19	230	0.85	0.73, 0.98
Others	2881	63.1	71.9	16,426	58	59	0.98	0.74, 1.27
Prostate cancer stage								
1 & 2	12121	68.3	72.9	66,564	174	188	0.92	0.79, 1.07
3 & 4	12121	70.6	75.0	66,564	58	79	0.73	0.56, 0.95
Unknown	12121	75.6	76.6	66,564	21	23	0.92	0.57, 1.40
Melanoma								
Age at diagnosis								
< 60 years	931	45.4	58.7	6,465	5	5	1.01	0.33, 2.37
≥ 60 years	489	69.8	72.1	2,018	14	11	1.23	0.67, 2.06
Location of melanoma								
Head & Neck	264	65.1	75.0	1,422	2	4	0.46	0.06, 1.66
Others	1087	51.3	68.3	6,931	17	12	1.44	0.84, 2.34
Prostate cancer stage								
1 & 2	1420	63.3	67.7	8,483	14	11	1.31	0.72, 2.20
3 & 4	1420	53.7	60.3	8,483	3	4	0.69	0.14, 2.03
Unknown	1420	73.2	74.6	8,483	2	1	1.49	0.18-5.39

†: number of person-years of observation between date of diagnosis of skin cancer and date of diagnosis of prostate cancer
‡: observed number of prostate cancer patients
§: expected number of prostate cancer patients
#: Standardised Incidence Ratio

For all skin cancers combined, there was a decreased risk of subsequently developing prostate cancer (SIR 0.89, 95% CI: 0.78, 0.99). This risk was significantly decreased for patients with a previous diagnosis of non-melanoma skin cancer (NMSC) (SIR 0.87, 95% CI: 0.77, 0.98), but not for melanoma patients. All male skin cancer patients with a skin cancer

diagnosis after age 60 (SIR 0.86, 95% CI: 0.75, 0.97) and those with any skin cancer in the head and neck region (SIR 0.84, 95% CI: 0.73, 0.97) had a significantly decreased risk of subsequent prostate cancer incidence. Among skin cancer patients, advanced prostate cancer (stage 3&4) incidence rates were significantly decreased compared to the general population (SIR 0.73, 95% CI: 0.56, 0.94).

After analysing the cohorts separately for NMSC patients and patients diagnosed with a melanoma, risks remained significantly lower in the group of NMSC for those aged >60 at diagnosis (SIR 0.84 (95% CI: 0.73, 0.96) and those with a head and neck NMSC (SIR 0.85 (95% CI: 0.73, 0.98). Risk of developing an advanced prostate cancer was especially decreased (SIR 0.73 (95% CI: 0.56, 0.95). Melanoma was positively associated, though not significantly, with subsequent prostate cancer risk (SIR 1.16, 95% CI: 0.71, 1.85), except for head and neck melanomas (SIR 0.46, 95% CI: 0.06, 1.66) and advanced prostate cancer (SIR 0.69 (95% CI: 0.14, 2.03) for which point estimates were smaller than 1.

Table 12.2 describes the results of the analyses by period since diagnosis of NMSC, but not for melanoma due to small numbers of prostate cancer cases after an initial melanoma diagnosis. Though point estimates did not always reach statistical significance, the results clearly demonstrate that the risk of developing prostate cancer was lowest in the time period shortly after NMSC cancer diagnosis (during the first year: SIR=0.53, 95% CI 0.34, 0.78), gradually increasing with time (≥5 years after NMSC diagnosis: SIR=1.10, 95% CI 0.90, 1.34).

Table 12.2. Standardized Incident Ratio (SIR) with 95% confidence interval of second prostate cancer among non melanoma skin cancer patients diagnosed in the Eindhoven Cancer Registry in the South of the Netherlands

Time since skin cancer diagnosis	**BCC**		**SCC**		**Non-melanoma skin cancer**	
	SIR*	95% CI	SIR*	95% CI	SIR*	95% CI
0-1 year	0.51	0.30, 0.80	0.58	0.23, 1,20	0.53	0.34, 0.78
1-2 years	0.91	0.62, 1.29	0.66	0.26, 1,36	0.85	0.60, 1.17
2-3 years	0.65	0.40, 1.00	0.56	0.18, 1.30	0.63	0.41, 0.93
3-4 years	0.89	0.57, 1.32	0.97	0.39, 2.00	0.91	0.62, 1.29
4-5 years	1.01	0.64, 1.51	0.90	0.29, 2.09	0.99	0.66, 1.43
>= 5 years	1.10	0.87, 1.37	1.13	0.73, 1.66	1.10	0.90, 1.34

* SIR = Standardized Incidence Ratio

12.4. Discussion

Our results show that male NMSC patients are at a decreased risk of developing invasive prostate cancer. The decreased risk of developing prostate cancer was significant for skin cancers that are assumed to be related to chronic sun exposure: those occurring in the elderly and in the head and neck region. In patients with CM, which is assumed to be related to intermittent sun exposure [12, 13], a (non-significantly) increased risk of subsequent prostate cancer was exhibited, except for head and neck melanomas, which showed a (non-significantly) decreased risk. CMs in the head and neck area are, in contrast to other melanomas, assumed to be more related to chronic sun exposure [12, 13].

These observations are in line with the hypothesis that exposure to UVR protects against prostate cancer development and possibly against progression, as SIRs for advanced prostate cancer (stages 3&4) were lower than those for early (stage 1&2) disease.

Although we did not have individual information on UVR of the included cases, it is generally accepted that most skin cancer cases in predominantly Caucasian populations like in the South of the Netherlands are caused by high UVR exposure [9, 10]. This increased risk is mainly apparent for people with sun-sensitive skin. Other causes of non-melanoma skin cancer include immunosuppression [20], smoking [21] and exposure to pesticides [22]. Apart from some rare familial syndromes, little is known about non-solar risk factors for melanoma; effects of contraceptive use [23] and swimming in polluted water [24] have been postulated but not confirmed. All these non-solar factors are, to our knowledge, not associated with a decreased risk of prostate cancer and thus cannot explain our observations. Therefore, our findings are in line with the hypothesis that exposure to UVR would decrease the risk of prostate cancer development.

After their skin cancer diagnosis, skin cancer patients were likely to be under increased medical scrutiny and to reduce their sun exposure drastically, resulting in lower sun exposure shortly before the prostate cancer diagnosis. If short-term sun exposure were important in determining the risk of developing a prostate cancer, one would expect the lowest SIRs to occur shortly after skin cancer diagnosis, as observed in our analyses: SIRs were lowest in the first year, gradually increasing to reach levels of around 1 after ≥5 years of follow-up. Of interest is the 'drop' in SIR estimates during the 3rd year of follow up (2-3 years after diagnosis): possibly an effect of a decreasing intensity of medical surveillance. Due to the increased medical surveillance during the first years after skin cancer diagnosis, one would expect more (prostate) cancer cases to be detected in this period than in the average population – this may have artificially increased numbers of prostate cancer in our cohorts and diluted our results, but provides even stronger evidence for a 'real' decrease in risk shortly after prostate cancer diagnosis.

A few studies have previously looked at incidence of tumours, amongst which prostate cancer, after skin cancer diagnosis [25-33](Table 12.3). Most of these did not find a significant association between skin cancer diagnosis and prostate cancer [26, 27, 29, 30], and did not investigate the effect of body site or the age at diagnosis of the skin cancer cases. Very few gave information on mean or median age at diagnosis and/or mean years of follow-up or person-years at risk. None of these studies investigated associations with prostate cancer

stage, and most suffered a problem of small numbers, like we did when only considering SCC or melanoma, causing a lack of power to show any statistically significant effects [25-29, 33]. One large study investigating prostate cancer incidence after BCC found an increased risk [31]. This study had accumulated a mean follow-up time of about 9 years, against 5.6 years in our BCC cohort. As the SIRs tended to increase with time since skin cancer diagnosis, this possibly explains the observed increased risk in this study [31]. Another study, which did not mention mean follow-up time, found a decreased risk, with estimates very similar to ours [32]; the other two studies did not find any significant association [26, 29]. None of the studies on BCC gave an indication of the completeness of their registry of (first primary) BCCs. In many countries BCCs are not routinely registered, therefore some of the populations of BCC patients may have been biased towards the clinically more complicated cases. As was the case in our study, all previous studies reporting the incidence of prostate cancer after SCC [28, 30, 33] and CM [25, 27] had too low numbers to make reliable estimates. One Danish study observed a non-significantly decreased risk of prostate cancer after SCC with a SIR very similar to that observed in our study [33]. One study found an increased risk of prostate cancer after a diagnosis of CM [27], another found an increased risk after CM for patients younger than 51, and a decreased risk for patients diagnosed after age 50 [25].

Table 12.3. Results of other studies reporting incidence of prostate cancer after skin cancer diagnosis

Country, registry (ref nr)	Localisation, age of skin cancer	Number of (male) skin cancer patients	Age at diagnosis of skin cancer	Mean yrs of follow-up	Observed number of prostate cancer cases	SIR†	95% CI
BCC							
Finland, Finnish Cancer Registry [31]	All BCC	29727	‡	±9	1121	1.2	1.2, 1.3
	Head & neck only	20796	‡	‡	839	1.2	1.2, 1.3
Switzerland, Vaud & Neuchatel cancer registry [29]	BCC	5947	60-69	‡	155	1.1	0.9, 1.3
USA, Kaiser Permanente Medical Care Program [26]	BCC	1648	45-64	11.3	108	1.1	0.9, 1.4
UK, South&West Cancer Registry [32]	BCC	13961*	‡	‡	177	0.85	0.73, 0.99
SCC							
UK, Thames Cancer Registry [30]	SCC	16962	‡	‡	389	1.0	0.9, 1.1
Switzerland, Vaud & Neuchatel cancer registry [28]	SCC	2529	60-69	‡	74	1.1	0.9, 1.4
Danish Cancer Registry [33]	SCC	3306	‡	‡	49	0.8	0.6, 1.1
CMM							
Switzerland, Vaud & Neuchatel cancer registry [27]	CMM	782	60-69	‡.	16	2.1	1.2, 3.4
USA, Hospital based [25]	CMM≤50	298 <150	Median: 43	6.5	1	1.8	0.0, 7.0
	CMM>50		‡	‡	1	0.2	0.0, 0.9

* No separate numbers for males and females were given, prostate risk was separately calculated within cohort of men skin cancer patients only

†: Standardized Incidence Ratio

‡: not available

Unlike the situation in most cancer registries, reporting of both NMSC and CM to the Eindhoven Cancer Registry occurs routinely [14]. A small degree of underreporting cannot be excluded since a high proportion of NMSC are treated in office settings where maybe not all tumour material will be sent for pathology review. However, material of all first primary BCCs and SCCs will be sent for pathology, and it is therefore unlikely that this cohort of patients

will have been subject to selection. As NMSC generally has a good prognosis, there are no severe biases expected based on survival time.

The significantly decreased prostate cancer incidence in the group of BCC patients can hardly be explained by bias: patients with a cancer diagnosis are more intensely checked for subsequent tumours and might be regarded as being vulnerable for tumour development. If such higher vulnerability and/or stronger surveillance would play a role, this would have increased the level of prostate cancer detection, especially during the first years after skin cancer diagnosis, and would have diluted our results. In the Netherlands, there is no population-based prostate cancer-screening programme; voluntary PSA-screening in this population was quite low and even completely absent in the earlier years of follow-up. However, should skin cancer patients have been under a more frequent and closer medical scrutiny, then diagnosis of a subsequent prostate cancer would more likely have occurred at an earlier stage. Since the levels of PSA-screening were low in this population during the years of follow-up, any such effect would be minimal. Moreover, if this were true this would suggest a bias for more medical screening in skin cancer patients and a higher detection rate of prostate cancer in general, which was not the case.

Although biases are unlikely to have caused the observed association, there is some potential for confounding, for example by physical exercise and/or selenium supplementation. Exercise might be associated with skin cancer through enhancing exposure to UVR and might also be associated with reduced prostate cancer risk. Similarly, selenium supplementation has been found to (non-significantly) increase the risk of recurrent skin cancer, while reducing prostate cancer occurrence [34].

A growing body of evidence, including our findings, supports the hypothesis that UVR protects against the development of prostate cancer, possibly through the formation of vitamin D3 [1-8], although some plasma studies do not clearly suggest a benefit of vitamin D levels on prostate cancer risk [35, 36]. If the hypothesis of UVR having a protective effect against prostate cancer, and possibly other tumours and also some auto-immune diseases is confirmed [37], it will be important to modify public health messages regarding UVR exposure: levels of UVR that do not result in increased risk of skin cancers should be defined. Additionally, if indeed vitamin D is relevant, then recommendations to increase oral intake of vitamin D through supplementation and/or fortification should be made.

References

1. Hanchette CL, Schwartz GG. Geographic patterns of prostate cancer mortality. Evidence for a protective effect of ultraviolet radiation. *Cancer*. 1992;70:2861-2869.
2. Grant WB. An estimate of premature cancer mortality in the u.S. Due to inadequate doses of solar ultraviolet-b radiation. *Cancer*. 2002;94:1867-1875
3. Freedman DM, Dosemeci M, McGlynn K. Sunlight and mortality from breast, ovarian, colon, prostate, and non-melanoma skin cancer: A composite death certificate based case-control study. *Occup Environ Med*. 2002;59:257-262
4. Grant WB. A multicountry ecologic study of risk and risk reduction factors for prostate cancer mortality. *Eur Urol*. 2004;45:271-279
5. Luscombe CJ, Fryer AA, French ME, Liu S, Saxby MF, Jones PW, Strange RC. Exposure to ultraviolet radiation: Association with susceptibility and age at presentation with prostate cancer. *Lancet*. 2001;358:641-642.
6. Bodiwala D, Luscombe CJ, French ME, Liu S, Saxby MF, Jones PW, Fryer AA, Strange RC. Associations between prostate cancer susceptibility and parameters of exposure to ultraviolet radiation. *Cancer Lett*. 2003;200:141-148
7. John EM, Schwartz GG, Koo J, Van Den Berg D, Ingles SA. Sun exposure, vitamin d receptor gene polymorphisms, and risk of advanced prostate cancer. *Cancer Res*. 2005;65:5470-5479
8. John EM, Dreon DM, Koo J, Schwartz GG. Residential sunlight exposure is associated with a decreased risk of prostate cancer. *J Steroid Biochem Mol Biol*. 2004;89-90:549-552
9. Kricker A, Armstrong BK, English DR, Heenan PJ. A dose-response curve for sun exposure and basal cell carcinoma. *Int J Cancer*. 1995;60:482-488
10. International Agency for Research on Cancer. Solar and ultraviolet radiation. *IARC Monographs on the evaluation of carcinogenic risks to humans, Vol. 55*. 1992
11. Armstrong BK, Kricker A. The epidemiology of uv induced skin cancer. *J Photochem Photobiol B*. 2001;63:8-18
12. Whiteman DC, Watt P, Purdie DM, Hughes MC, Hayward NK, Green AC. Melanocytic nevi, solar keratoses, and divergent pathways to cutaneous melanoma. *J Natl Cancer Inst*. 2003;95:806-812
13. Elwood JM, Gallagher RP. Body site distribution of cutaneous malignant melanoma in relationship to patterns of sun exposure. *Int J Cancer*. 1998;78:276-280
14. de Vries E, Louwman M, Bastiaens M, de Gruijl F, Coebergh JW. Rapid and continuous increases in incidence rates of basal cell carcinoma in the southeast netherlands since 1973. *J Invest Dermatol*. 2004;123:634-638
15. de Vries E, van de Poll-Franse LV, Louwman WJ, de Gruijl FR, Coebergh JW. Predictions of skin cancer incidence in the netherlands up to 2015. *Br J Dermatol*. 2005;152:481-488
16. International Agency for Research on Cancer (WHO), International Association of Cancer Registries, European Network of Cancer Registries. International rules for multiple primary cancers (icd-o third edition). 2004
17. UICC. *Tnm atlas illustrated guide to the tnm/ptnm classification of malignant tumours. 4th edn, 2nd revision.* Berlin: SpringerVerlag; 1992.
18. Soerjomataram I, Louwman WJ, de Vries E, Lemmens VE, Klokman WJ, Coebergh JW. Primary malignancy after primary female breast cancer in the south of the netherlands, 1972-2001. *Breast Cancer Res Treat*. 2005;93:91-95
19. Breslow N, Day N. *Statistical methods in cancer research. The design and analysis of cohort studies.* Lyon, France: IARC Scientific Publishers; 1987.
20. Hampton T. Skin cancer's ranks rise: Immunosuppression to blame. *Jama*. 2005;294:1476-1480
21. De Hertog SA, Wensveen CA, Bastiaens MT, Kielich CJ, Berkhout MJ, Westendorp RG, Vermeer BJ, Bouwes Bavinck JN. Relation between smoking and skin cancer. *J Clin Oncol*. 2001;19:231-238
22. Spiewak R. Pesticides as a cause of occupational skin diseases in farmers. *Ann Agric Environ Med*. 2001;8:1-5
23. Feskanich D, Hunter DJ, Willett WC, Spiegelman D, Stampfer MJ, Speizer FE, Colditz GA. Oral contraceptive use and risk of melanoma in premenopausal women. *Br J Cancer*. 1999;81:918-923
24. Nelemans PJ, Rampen FH, Groenendal H, Kiemeney LA, Ruiter DJ, Verbeek AL. Swimming and the risk of cutaneous melanoma. *Melanoma Res*. 1994;4:281-286.
25. Bhatia S, Estrada-Batres L, Maryon T, Bogue M, Chu D. Second primary tumors in patients with cutaneous malignant melanoma. *Cancer*. 1999;86:2014-2020

26. Friedman GD, Tekawa IS. Association of basal cell skin cancers with other cancers (united states). *Cancer Causes Control*. 2000;11:891-897
27. Levi F, La Vecchia C, Randimbison L, Te VC, Erler G. Incidence of invasive cancers following cutaneous malignant melanoma. *Int J Cancer*. 1997;72:776-779
28. Levi F, Randimbison L, La Vecchia C, Erler G, Te VC. Incidence of invasive cancers following squamous cell skin cancer. *Am J Epidemiol*. 1997;146:734-739
29. Levi F, La Vecchia C, Te VC, Randimbison L, Erler G. Incidence of invasive cancers following basal cell skin cancer. *Am J Epidemiol*. 1998;147:722-726
30. Maitra SK, Gallo H, Rowland-Payne C, Robinson D, Moller H. Second primary cancers in patients with squamous cell carcinoma of the skin. *Br J Cancer*. 2005;92:570-571
31. Milan T, Pukkala E, Verkasalo PK, Kaprio J, Jansen CT, Koskenvuo M, Teppo L. Subsequent primary cancers after basal-cell carcinoma: A nationwide study in finland from 1953 to 1995. *Int J Cancer*. 2000;87:283-288
32. Bower CP, Lear JT, Bygrave S, Etherington D, Harvey I, Archer CB. Basal cell carcinoma and risk of subsequent malignancies: A cancer registry-based study in southwest england. *J Am Acad Dermatol*. 2000;42:988-991
33. Frisch M, Melbye M. New primary cancers after squamous cell skin cancer. *Am J Epidemiol*. 1995;141:916-922
34. Duffield-Lillico AJ, Reid ME, Turnbull BW, Combs GF, Jr., Slate EH, Fischbach LA, Marshall JR, Clark LC. Baseline characteristics and the effect of selenium supplementation on cancer incidence in a randomized clinical trial: A summary report of the nutritional prevention of cancer trial. *Cancer Epidemiol Biomarkers Prev*. 2002;11:630-639
35. Platz EA, Leitzmann MF, Hollis BW, Willett WC, Giovannucci E. Plasma 1,25-dihydroxy- and 25-hydroxyvitamin d and subsequent risk of prostate cancer. *Cancer Causes Control*. 2004;15:255-265
36. Jacobs ET, Giuliano AR, Martinez ME, Hollis BW, Reid ME, Marshall JR. Plasma levels of 25-hydroxyvitamin d, 1,25-dihydroxyvitamin d and the risk of prostate cancer. *J Steroid Biochem Mol Biol*. 2004;89-90:533-537
37. Holick MF. Sunlight and vitamin d for bone health and prevention of autoimmune diseases, cancers, and cardiovascular disease. *Am J Clin Nutr*. 2004;80:1678S-1688S

PART V

General discussion and conclusion

Chapter 13

Discussion and conclusion

The problem of multiple cancers is increasing in magnitude. Currently about 10% of patients with cancer are expected to develop a second cancer. The numbers of people at elevated risk of multiple malignancies, i.e. the elderly and cancer survivors, are rising. Thus, in absolute terms, the number of patients with multiple primary cancers is expected to continue rising. Furthermore, due to intensified cancer detection efforts through screening and the increased awareness among patients and doctors towards cancer, the relative risk of multiple cancers has been increasing as well. In this work, our aim was to examine the risk of second malignancies among cancer survivors, in particular among those who were diagnosed with breast and skin cancer. We used data from a long-standing cancer registry in southern Netherlands. In this discussion, the main findings and their interpretation will be first summarized. This will be followed by a discussion of the drawbacks and biases in relation to interpretation of results. The third section of this chapter discusses the clinical and etiological implications of our studies. This part ends with recommendations for future research.

13.1. Summary and interpretation of findings

Risk of second cancer among patients previously diagnosed with primary breast cancer

Determinants of breast cancer incidence

The risk of developing a second primary malignancy may partly be attributable to the same factors that underlie the development of a first cancer. Therefore, it is important to shortly review the risk factors for breast cancer, as done in chapter 3 and 4. Increased risk of breast cancer has been related to the following risk factors:(1) family history of breast cancer or germline mutation of a cancer susceptibility gene; (2) reproductive history and hormonal factors, e.g. older age at first child, lower parity, and post-menopausal hormone intake; (3) physical characteristics, e.g. dense breast tissue, post-menopausal obesity or tall stature; and (4) nutritional factors, e.g. excess alcohol consumption and fat/energy intake[1, 2]. In an ecological study, we showed that there is a strong correlation between the overall excess incidence of breast cancer in 2002 and the average age of the mother at first birth in 1972-2002. Both current and past average age at first childbirth were associated with recent excess risk of breast cancer. However, risk factors for breast cancer such as younger age at menarche, lower parity, higher obesity and use of post-menopausal hormones therapy, are also generally more frequent in countries with a high incidence of breast cancer. Besides being directly linked to an increased risk of breast cancer, older age at first child delivery is probably also a risk indicator of clustering of risk factors in western populations.

Impact of a second cancer on the survival of breast cancer survivors

A diagnosis of a new cancer among breast cancer survivors impairs their survival. An increased risk of second primary cancers among breast cancer patients remain even decades after the first diagnosis[3]. Therefore, we examined the impact of a second cancer diagnosis among patients with breast cancer surviving more than 10 years. We observed a better overall survival for women without second primary tumours as compared to women who developed a new primary cancer. In addition, based on our review, we concluded that conventional prognostic factors for survival such as tumour size, nodal status and grade

remain the most important factors for long-term survival, though their role decreases over time since diagnosis.

Has the incidence of breast cancer among female cancer survivors changed?
In the southern Netherlands a 20% increased in incidence of first primary breast cancer between 1975 and 1990 was reported[4]. To examine whether this pattern is also evident among female cancer survivors, we examined their incidence rate of breast cancer. We found that over a period of 20 years, the incidence of breast cancer among female cancer survivors has doubled. Population aging contributed to approximately 36% of this increased trend. The highest increase in incidence occurred among the elderly survivors (ages 75+), which increased by a factor of four over the study period.

Female cancer survivors undergo higher surveillance and are probably more aware of breast cancer. Thus, we expected the stage distribution to be more favourable among second cancer patients as compared with first cancer patients. Unexpectedly, our results suggest that almost half of breast cancer survivors are stage II patients, whereas previous research shows that the majority of first cancer cases are stage I. This is particularly evident among survivors of non-breast malignancies (on study implication please see section 13.3).

Risk of second cancer among patients with breast cancer
During the 30 years of follow-up, 13% of breast cancer patients in our cohort were diagnosed with a second primary cancer. In contrast to the general population, patients with malignant breast cancer experienced a 2-fold increase risk of a new primary cancer. The most pronounced risks were found for a second breast, salivary gland and connective tissue cancer, approximately 3 times higher than that of general female population. Risks for cancer of colon, ovary, skin (melanoma) and bladder were also elevated though of a lower magnitude. Risk was especially high for those who were younger at first breast cancer diagnosis.
Which risk factors may explain this pattern of increased cancer risk? Multiple cancer occurrences in younger patients are commonly linked to genetic predisposition to cancer.[5] In our study, this is probably the case for some cases of multiple breast and ovarian cancers as well as melanoma of the skin. About 6% of women who were diagnosed with a breast cancer below the age of 50 had a BRCA1/2 mutation.[5] The majority of these patients would later in life be diagnosed with a second breast or ovarian cancer.[5] Besides the role of a single high penetrance gene mutation, a polygenic model probably explains part of the multiple cancers incidence.[6] This hypothesis is supported by studies showing an increased risk of second cancers among those without a familial history of cancer. In addition, genetic predisposition towards cancer may interact with external risk factors increasing the risk of a second cancer among breast cancer patients. For example, younger patients show a higher risk of second cancer after irradiation compared to older patients[7]. Beside the fact that tissue cells among young patients are more sensitive towards radiation, interaction between genetic predisposition and radiation might increase the risk of developing a second cancer in these women[7-10].

Studies have shown that the majority of multiple cancer cases lack a family history[6, 11]. Thus, a second possible explanation of our findings points at the role of non-genetic risk factors,

particularly those related to lifestyle. Nutrition, high body mass index, physical inactivity and reproductive factors[12-16] may be related to an increased risk of breast, colorectal and endometrium cancer in our cohort of breast cancer patients.

In our study, we found a (non-significantly) decreased cervical cancer risk among breast cancer patients as compared with the general population. Previous studies have reported similar results[17-19]. A possible explanation of these findings is that higher socioeconomic status is associated with higher breast cancer incidence[20] but lower cervical cancer incidence[20]. This may reflect antagonistic effects of risk factors related to socioeconomic status on breast and cervical cancer, which may in turn explain the lower risk of cervical cancer among breast cancer patients.

A third explanation of our findings points to the role of first cancer treatment. Unlike the general population, breast cancer patients are exposed to cancer treatments that are often carcinogenic. For example, we found that breast cancer patients exhibit an increased risk of sarcoma, esophageal and salivary cancer, which is probably related to irradiation as part of the first breast cancer therapy[9, 21-23]. We also found a higher risk of endometrial cancer in those receiving hormonal treatment as compared with those who only underwent surgery. Consistent with these findings, tamoxifen (the most common hormonal breast cancer treatment), has been proven to increase the risk of endometrial cancer[24, 25] On the other hand, we observed a lower risk of breast cancer among patients who received hormonal therapy as compared to those who received other type of cancer treatment.

Second cancer risk in patients with in situ breast cancer

During the last decade, a marked increased in the incidence of *in situ* breast cancer has been observed in the Netherlands, probably as a consequence of population-screening[26]. Therefore, we examined the risk of second cancer in patients with *in situ* breast cancer. Approximately 10% of these patients were subsequently diagnosed with a second cancer. We observed increased risks of second breast and skin cancer, 4- and 2-times higher than the general population, respectively. We found that this excess risk of second breast cancer is not explained by treatment choice (i.e. radiotherapy) for *in situ* breast cancer. This points to the role of a shared aetiology (lifestyle or hereditary) for both first and second cancer. Furthermore, we found that the pattern of increased cancer risk for patients with *in situ* breast cancer resembles that for patients with malignant breast cancer, as both groups of patients had an increased risk of colorectal, ovarium, lung and skin cancer as compared to the general population. Therefore, similar follow-up strategies may be required for patients with malignant breast cancer and patients with *in situ* breast cancer.

Risk of colorectal, breast and prostate cancer among skin cancer patients: examining the protective role of sunlight

Sun exposure appears to have a beneficial effect on the initiation and progression of some cancers including breast, colon and prostate cancer. This effect might be mediated by the production of vitamin D.[27] On the other hand, solar radiation is a major risk factor for skin cancer.[28, 29] Thus in the context of studying multiple cancers, we examined the risk of breast, colorectal and prostate cancer among patients previously diagnosed with a skin cancer.

There are 3 major types of skin cancer characterised by a different history of sun exposure: (1) Squamous cell carcinoma (SCC) of the skin, related to chronic sun exposure; (2) Cutaneous melanoma (CM), mostly associated with intermittent sun exposure; and (3) basal cell carcinoma of the skin, which is the most common skin cancer type, and appears to be associated with both chronic and intermittent sun exposure. If sunlight protects against others cancers, there should be a reduced risk of developing these cancers among patients with SCC, because the latter should have the largest cumulative sun exposure.

Indeed, we found a decreased risk of colorectal and prostate cancer among male skin cancer patients, particularly among those with SCC. Furthermore, patients with SCC who were older than 60 at the time of diagnosis and who had the lesion in the head and neck area had the lowest risk of a second colorectal cancer. Older skin cancer patients have presumably been exposed to the sun longer than younger patients. In addition, skin cancer in the head and neck area is also associated to chronic sun exposure[30]. These findings are consistent with the sunlight hypothesis: the more chronic sun exposure the lower the risk of developing certain cancers.

Although not significant, for breast cancer after skin cancer diagnosis, we observed a similar pattern as that for colorectal cancer: SCC patients who were older than 60 at diagnosis with a lesion on the head and neck area had the lowest risk of breast cancer. For CM patients a higher risk of breast cancer as compared to the general population was found. In our previous study where we assessed the risk of second cancer among breast cancer patients, we also observed a higher risk of melanoma. This may reflect a higher socio-economic status, which is related to higher intermittent sun exposure, but to lower number of children, younger age at the first child's birth and probably higher awareness for breast cancer leading to higher attendance rate for screening. A small fraction of this risk may also be explained by genetic predisposition towards both CM and breast cancer.

We also found that the risk of colorectal or prostate cancer among skin cancer patients was lowest during the first year after skin cancer diagnosis, and increased gradually thereafter. Skin cancer patients may reduce their sun exposure soon after the skin cancer diagnosis. Thus, our findings may suggest that the protective effect of sun exposure diminished as soon as sun exposure was reduced. How is it possible that individuals who reduce their sun exposure experience a reduction in its protective in such a short period? Other studies have indicated that maintaining the Vitamin D level needed to effectively protect against cancers requires a continuous sun exposure. In a summer in Europe, level of Vitamin D is 50 % higher than in winter time[31]. Studies showing the seasonality in cancer survival, with improved survival among those diagnosed in summer and autumn as compared with those diagnosed in winter, further support the hypothesis of an immediate sunlight protective effect[32, 33]. Furthermore, incidence of melanoma also showed seasonal variation with highest incidence rates in the summer. This suggests an influence of recent sun exposure on melanoma risk, and possibly also on reducing the risk of other cancers[34].

13.2. Study limitations

Unavailability of individual exposure data

Our studies are primarily based on cancer registry data. This type of studies is population-based and provides a large number of cases. This allows detection of even a small increase in risk as well as providing a reference population. However, detailed data on risk factors are usually not available in registry data. Thus, we were not able to assess the role of prominent risk factors in the explanation of the increased risk of second cancer among breast cancer patients. A careful interpretation of results is thus warranted, because we did not adjust for potential confounding.

For instance in our skin cancer study: higher physical activity has been related to higher sun exposure and thus a higher risk of skin cancer.[35] Higher physical exercise is also known to lower the risk of colorectal cancer.[36] It could be that the reduced risk of colorectal cancer is caused through higher physical activity. However, physical activity is more related to melanoma of the skin[35] and among these patients no lower risk of colorectal cancer was observed. Thus, it is yet unlikely that that the reduced risk of colorectal cancer among patients with SCC or BCC is due to differences in physical activity.

Another example is our study on excess breast cancer risk and mean age at first child. We found a strong correlation between national excess of breast cancer cases and the national average age when women previously had their first childbirth. The observed correlations may be due to other risk factors such as parity or duration of hormonal contraception use, which are also related to breast cancer risk. However, studies have demonstrated that after correcting for other breast cancer risk factors such as oral contraceptive use and number of children[37], age at first birth remained an independent risk factor of breast cancer risk. On the other hand, that two thirds of the cross country difference is explained by the difference in the timing of first child seems to be an overestimation. Furthermore, though of a lower magnitude, there was also a correlation between age at first child in 2002 and excess breast cancer risk in the same period: women who had their first child in 2002 should not yet be at high risk of breast cancer, suggesting that this may simply be a spurious association. Ultimately, we concluded that although higher age at first childbirth is likely to be directly related to higher breast cancer risk, it is also associated with many other risk factors for cancer, which explains why such as high correlation is observed.

Differentiating a new primary cancer from cancer recurrence

A new primary cancer of the breast among patients with a previous breast cancer can be difficult to distinguish from a recurrence, in case of a synchronous ipsilateral breast cancer. A contralateral breast cancer seems to be correctly coded as a new primary cancer[38]. The IARC rules of multiple cancers of paired organs such as the breast request that only multicentric or cancers of different histology be considered as independent new tumors[39, 40]. Applying these rules, to some extent, reduces misclassification of recurrence and new primary cancer (please see 13.4 on future research).

Differentiating a new primary cancer from cancer metastasis

We might have misclassified primary second cancers and metastases of the initial cancer. This is probably more of a problem in our breast cancer cohort, where about 5% of all cases had distant metastasis.[41, 42] Skin cancer rarely metastasised except for approximately 11% of the melanoma cases,[43] though more than half of the distant metastasised cases would be again occurring on the skin.[44] We found little evidence of this problem, also because we did not observe increased risks of second cancers that are common metastasis sites of breast or skin cancer.

The most common sites of distant metastasis among breast cancer patients are[41, 45]:

- Bone (± 50%)
- Liver (± 20%)
- Brain (± 15%)
- Others (± 15%) including epidural, leptomeningeal, ocular and ovary

The most common sites of distant metastasis among cutaneous melanoma patients are[44]:

- Skin, subcutaneous tissues, and nonregional lymph nodes (± 60%)
- Lung (± 15-36%)
- Gastrointestinal tract (± 2-4%) mostly in the small bowel and less common in the colon and stomach
- Others including hepatobiliary system and spleen

13.3 Study implications

Surveillance

The increase of breast cancer incidence among female survivors was largest for patients with breast cancer stage II. In addition, those who were first diagnosed with a non-breast cancer in the end 1990s had a rather unfavorable stage distribution of second breast cancer with 44% of breast cancer stage II, and 18% of cancer stage III. Early diagnosis of a new breast cancer in (ex)-cancer patients might be more difficult due to their operated or radiated breast/chest, thus resulting in an increased incidence of stage II breast cancer. With respect to carcinogenesis, first cancer treatment may cause a more malignant cancer, thus leading to a higher proportion of stage II breast cancer.

Nonetheless, our findings highlight the need for more intensive follow-up, particularly for women previously diagnosed with a non-breast cancer, e.g. through biennial clinical breast examination in addition to the standard mammography. A previous study showed that a biennial clinical breast examination can reduce breast cancer mortality for women with a moderately increased risk of breast cancer.[46]

An important factor to be considered is the impact of increased surveillance on patients' quality of life. It has been demonstrated that women who undergo a more intensive examination e.g., with MRI, have a higher proportion of intense anxiety (10.2%) as compared to those who only have mammography (5.2%) or clinical breast examination

(1.8%)[47]. However an analysis of health-related quality of life did not show a relevant impact of more intense screening among women with higher- breast cancer risk[47]. Thus, it seems that intensified screening may bring more benefit than harm to female cancer survivors, as it contributes to detect a second breast cancer at an early stage.

We found that the risk of developing a new cancer among breast cancer patients is still increased even after 15 years, which stresses the need for long-term surveillance. However, we also showed that an increased risk of certain malignancies such as second salivary cancer (SIR: 5) does not always correlate with a high absolute excess risk (respective AER: 0.5) and population burden. Thus, surveillance should be directed to second cancers that have both high relative increased risk and absolute excess risk. Examples of these are second breast and ovarian cancers among women diagnosed before the age of 50. Among older breast cancer patients, awareness of second breast and colon cancer should be increased.

Cancer treatment and management

Treatment of breast cancer among patients with a previous cancer

As the proportion of elderly increases, so does the number of those with multiple primary cancers. Treatment of cancer among the elderly is complex due to the co-existence of other illnesses. Co-morbidity including a previous cancer diagnosis limits the possibilities for treatment, and may ultimately impair survival.[48] As compared to younger patients, older patients with breast cancer generally receive less aggressive treatment with less radiation and lymph node staging[48]. However, among older cancer patients, more aggressive treatment may cause more complications. Thus, whether applying a non-standard treatment is a good practice is questionable. Therefore, in particular for the elderly with a previous cancer diagnosis, treatment decisions need to balance between the achievement of the expected survival with 'good' quality of life, and the harm of a more aggressive treatment. Future studies are needed on this area (see section 13.4. for specific studies recommended)

Breast cancer among breast cancer survivors are likely to be less aggressive than first cancer tumours, partly because breast cancer patients are subject to higher surveillance, with annual mammography until the age of 60 followed with a biennial mammography up to the age of 74[49]. Screen-detected breast cancers are more commonly slow-growing tumours that would otherwise have stayed longer in the pre-clinical phase if had not been detected[50]. Yet, current national guidelines for breast cancer treatment do not differentiate between treatment for a new primary breast cancer and for a recurrence and treatment[51]. Thus, although further research is required, patients with a second breast cancer may require a less aggressive treatment than patients with a first diagnosis or recurrent cancer.

Reducing the risk of major second or first primary cancers

Risk of second cancer among breast cancer patients has been related to lifestyle factors including body mass index. Obese breast cancer patients have approximately 2-fold greater hazard of contralateral breast tumours relative to women with normal-weight women.[12-14] Likewise, obesity and/or adult weight gain increases the risk of other second primary cancers including endometrial and colon cancer risk.[12-14] Thus, modification towards a

healthier lifestyle may decrease the risk of a second cancer. Furthermore, overall survival can be improved through promotion of a healthier lifestyle among patients.

A growing body of evidence[27], including findings from our study, supports the hypothesis that sunlight protects against the development of colorectal and prostate cancer, possibly through the formation of vitamin D3. For breast cancer, our findings were less clear, but a similar pattern as observed for skin cancer patients with a second colorectal cancer was shown: skin cancer patients who theoretically had higher sun exposure had the largest risk reduction of breast cancer. If sunlight has a protective effect against colorectal and prostate cancer, it is important to balance the positive and negative effects of sun exposure in public health messages. Furthermore, sunlight may also protect against other malignancies such as ovarian and non-hodgkin lymphoma, as well against immune diseases such as multiple sclerosis.[52] The level of sun exposure that does not result in increased risk of skin cancers should be defined. Additionally, if indeed vitamin D reduces the risk of colorectal, prostate and possibly breast cancer, recommendations to increase oral intake of vitamin D through supplementation and/or fortification should be developed.

13.4. Recommendations for future research

Improvements in early detection, diagnosis and treatment of cancer have increased survival of patients with many types of cancer including breast cancer. However, such improvements have also led to a major increase in the number of individuals with multiple malignancies. This problem will continue to grow dramatically in industrialized societies where the proportion of elderly continues to rise. Research action in several fronts is needed to tackle these increasing trends:

Public health – prevention research

Firstly, studies assessing the role of changing lifestyle after a cancer diagnosis are scarce, and therefore are needed. Current studies on lifestyle and the risk of a second primary are mostly based on lifestyle before or at cancer diagnosis. The type of intervention effective to gain a healthier lifestyle and ultimately decreased risk of second cancer is warranted. Secondly, the optimal strategies to follow cancer survivors and thus improve early detection of new cancer need to be better defined. Cost-effectiveness study of more intensive breast cancer screening among female cancer survivors especially those who had a non-breast cancer as first cancer should be considered, e.g., by including a clinical breast examination or a breast self-examination.

Further studies comprising data on sun exposure and vitamin D blood levels are required to establish the role of sunlight in reducing the risk of colorectal, prostate or breast cancer. Within the cancer registry, a nested case-control study using questionnaires on lifestyle including sun exposure, eating habits and other risk factors of the corresponding cancer may shed light on the protective role of sunlight. Other studies could examine the risk of cancer before the occurrence of skin cancer and thus indirectly test the sunlight hypothesis. If sunlight does reduce the risk of some cancers, the incidence of these malignances should also be lower before the diagnosis of a skin cancer. Furthermore studies have reported a higher survival rate among colorectal, breast and prostate cancer patients who were diagnosed in the late summer. Thus suggests that more intensive sun exposure, and thus

higher vitamin D level, may improve disease prognosis. In population-based registries, studies could compare survival of colorectal, breast or prostate cancer among patients previously diagnosed with skin cancer, with survival among patients not diagnosed with skin cancer. If the sunlight hypothesis were true, we should observe a survival benefit mostly for those who were previously diagnosed with SCC, gradually decreasing for those who were previously diagnosed with melanoma.

Clinical research

Further research could be done in a number of different areas. Firstly, in particular among the elderly, descriptive studies are required on variation of treatment practices of a second cancer and its impact on survival. Population- or hospital-based registry studies can serve as basis for future clinical trials of optimal treatment of the elderly. Secondly, future studies that retrieve more detailed data from medical records e.g. detailed treatment choice and patients characteristics accompanied by examination of cause-specific death, will surely add much to our current knowledge on treatment of the elderly with multiple malignancies and its impact on survival. This will be the base of a case control study assessing the disease process including recurrences, metastases[42], second cancer, other illness such as cardiovascular disease[53], and ultimately cause of death[3, 54]. If possible, biological matters from patients should be collected and preserved in a biobank. Biomarkers assessment of the first primary cancer and the host themselves might help to improve early detection of multiple cancers or morbidity from other disease. Furthermore it will also add our knowledge on the pathogenesis of multiple cancers in general. Finally, qualitative research is warranted on the decision-making process for individual patients, including analysis of patients' treatment preference, particularly among the elderly.[55]

Patient perspective has long been taken care of more or less explicitly by the various medical doctors, as well as epidemiologists. But, more recently more attention was directed towards understanding of their concerns and quality of life. However, studies are still lacking examining quality of life among patients with multiple cancers, their relationships with the family, infertility problems, with chronic pain the assumed beneficial role of a healthier lifestyle or scalp cooling to reduce alopecia. Finally study findings need to be communicated to the patients, thus their involvement in clinical decision-making can be increased.

In this thesis, we have focused our studies among breast and skin cancer patients. Future studies should also examine risks in other cancer patients, e.g. colorectal, lung, lymphomas, head and neck cancer, kidney and bladder cancers. Studies on the occurrence and course of multiple malignancies can improve our insight of the aetiology and genesis of cancer in general. Furthermore, cancer treatment will continue to improve possibly through emerging new therapies, which highlights the need for continuous surveillance. In addition, identifying those at risk of multiple cancers will provide input on detection strategies through which survival can be improved. Population-based registries can significantly contribute to improve monitoring and increase understanding of the causes and pattern of second cancer.

References

1. SignaleringscommissieKanker. De rol van voeding bij het ontsaan van kanker. 2004
2. Veronesi U, Boyle P, Goldhirsch A, Orecchia R, Viale G. Breast cancer. Lancet. 2005;365:1727-1741
3. Hooning MJ, Aleman BM, van Rosmalen AJ, Kuenen MA, Klijn JG, van Leeuwen FE. Cause-specific mortality in long-term survivors of breast cancer: A 25-year follow-up study. Int J Radiat Oncol Biol Phys. 2006;64:1081-1091
4. Louwman M, Voogd AC, van Dijck JAAM, Nieuwenhuijzen GAP, Ribot JG, Pruijt JFM, Coebergh JW. On the rising trends of incidence and prognosis for breast cancer patients diagnosed 1975-2004: A long-term population-based study in southeastern netherlands. 2007:37-52
5. Peto J, Collins N, Barfoot R, Seal S, Warren W, Rahman N, Easton DF, Evans C, Deacon J, Stratton MR. Prevalence of brca1 and brca2 gene mutations in patients with early-onset breast cancer. J Natl Cancer Inst. 1999;91:943-949
6. Hemminki K, Ji J, Forsti A. Risks for familial and contralateral breast cancer interact multiplicatively and cause a high risk. Cancer Res. 2007;67:868-870
7. Gao X, Fisher SG, Emami B. Risk of second primary cancer in the contralateral breast in women treated for early-stage breast cancer: A population-based study. Int J Radiat Oncol Biol Phys. 2003;56:1038-1045
8. Boice JD. Ionizing radiation. New York: Oxford University Press.
9. Curtis R, Ron E, Hankey BF, Hoover RN. New malignancies following breast cancer. In: Curtis R, Freedman DM, Ron E, Ries LAG, Hacker DG, Edwards BK, Tucker MA, Fraumeni JFJ, eds. New malignancies among cancer survivors: Seer registries, 1973-2000. Bethesda, MD: National Cancer Institute; 2006:181-205.
10. van Leeuwen FE, Travis LB. Second cancers. Philadelphia: Lippincott Williams and Wilkins; 2005.
11. Dong C, Hemminki K. Multiple primary cancers of the colon, breast and skin (melanoma) as models for polygenic cancers. Int J Cancer. 2001;92:883-887
12. Dignam JJ, Wieand K, Johnson KA, Fisher B, Xu L, Mamounas EP. Obesity, tamoxifen use, and outcomes in women with estrogen receptor-positive early-stage breast cancer. J Natl Cancer Inst. 2003;95:1467-1476
13. Dignam JJ, Wieand K, Johnson KA, Raich P, Anderson SJ, Somkin C, Wickerham DL. Effects of obesity and race on prognosis in lymph node-negative, estrogen receptor-negative breast cancer. Breast Cancer Res Treat. 2006;97:245-254
14. Trentham-Dietz A, Newcomb PA, Nichols HB, Hampton JM. Breast cancer risk factors and second primary malignancies among women with breast cancer. Breast Cancer Res Treat. 2006
15. Chen Y, Thompson W, Semenciw R, Mao Y. Epidemiology of contralateral breast cancer. Cancer Epidemiol Biomarkers Prev. 1999;8:855-861
16. Vaittinen P, Hemminki K. Risk factors and age-incidence relationships for contralateral breast cancer. Int J Cancer. 2000;88:998-1002
17. Levi F, Randimbison L, Te VC, La Vecchia C. Second primary cancers in breast cancer patients in vaud, switzerland. Cancer Causes Control. 1998;9:463-464; discussion 465
18. Brenner H, Siegle S, Stegmaier C, Ziegler H. Second primary neoplasms following breast cancer in saarland, germany, 1968-1987. Eur J Cancer. 1993;29A:1410-1414
19. Adami HO, Bergkvist L, Krusemo U, Persson I. Breast cancer as a risk factor for other primary malignant diseases. A nationwide cohort study. J Natl Cancer Inst. 1984;73:1049-1055
20. Social inequalities and cancer. IARC Sci Publ. 1997:1-15
21. Mellemkjaer L, Friis S, Olsen JH, Scelo G, Hemminki K, Tracey E, Andersen A, Brewster DH, Pukkala E, McBride ML, Kliewer EV, Tonita JM, Kee-Seng C, Pompe-Kirn V, Martos C, Jonasson JG, Boffetta P, Brennan P. Risk of second cancer among women with breast cancer. Int J Cancer. 2006;118:2285-2292
22. Salminen EK, Pukkala E, Kiel KD, Hakulinen TT. Impact of radiotherapy in the risk of esophageal cancer as subsequent primary cancer after breast cancer. Int J Radiat Oncol Biol Phys. 2006;65:699-704
23. Rubino C, Shamsaldin A, Le MG, Labbe M, Guinebretiere JM, Chavaudra J, de Vathaire F. Radiation dose and risk of soft tissue and bone sarcoma after breast cancer treatment. Breast Cancer Res Treat. 2005;89:277-288
24. Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: An overview of the randomised trials. Lancet. 2005;365:1687-1717
25. Swerdlow AJ, Jones ME. Tamoxifen treatment for breast cancer and risk of endometrial cancer: A case-control study. J Natl Cancer Inst. 2005;97:375-384
26. Fracheboud J, Otto SJ, van Dijck JA, Broeders MJ, Verbeek AL, de Koning HJ. Decreased rates of advanced breast cancer due to mammography screening in the netherlands. Br J Cancer. 2004;91:861-867
27. van der Rhee HJ, de Vries E, Coebergh JW. Does sunlight prevent cancer? A systematic review. Eur J Cancer. 2006;42:2222-2232
28. de Vries E, Coebergh JW. Cutaneous malignant melanoma in europe. Eur J Cancer. 2004;40:2355-2366
29. de Vries E, Louwman M, Bastiaens M, de Gruijl F, Coebergh JW. Rapid and continuous increases in incidence rates of basal cell carcinoma in the southeast netherlands since 1973. J Invest Dermatol. 2004;123:634-638
30. Armstrong BK, Kricker A. The epidemiology of uv induced skin cancer. J Photochem Photobiol B. 2001;63:8-18
31. Moan J, Porojnicu AC, Robsahm TE, Dahlback A, Juzeniene A, Tretli S, Grant W. Solar radiation, vitamin d and survival rate of colon cancer in norway. J Photochem Photobiol B. 2005;78:189-193

32. Lim HS, Roychoudhuri R, Peto J, Schwartz G, Baade P, Moller H. Cancer survival is dependent on season of diagnosis and sunlight exposure. Int J Cancer. 2006;119:1530-1536
33. Robsahm TE, Tretli S, Dahlback A, Moan J. Vitamin d3 from sunlight may improve the prognosis of breast-, colon- and prostate cancer (norway). Cancer Causes Control. 2004;15:149-158
34. Boniol M, De Vries E, Coebergh JW, Dore JF. Seasonal variation in the occurrence of cutaneous melanoma in europe: Influence of latitude. An analysis using the eurocare group of registries. Eur J Cancer. 2005;41:126-132
35. Schnohr P, Gronbaek M, Petersen L, Hein HO, Sorensen TI. Physical activity in leisure-time and risk of cancer: 14-year follow-up of 28,000 danish men and women. Scand J Public Health. 2005;33:244-249
36. Samad AK, Taylor RS, Marshall T, Chapman MA. A meta-analysis of the association of physical activity with reduced risk of colorectal cancer. Colorectal Dis. 2005;7:204-213
37. Chie WC, Hsieh C, Newcomb PA, Longnecker MP, Mittendorf R, Greenberg ER, Clapp RW, Burke KP, Titus-Ernstoff L, Trentham-Dietz A, MacMahon B. Age at any full-term pregnancy and breast cancer risk. Am J Epidemiol. 2000;151:715-722
38. Howe HL. A review of the definition for multiple primary cancers in the united states. Workshop proceedings from december 4-6, 2002, in princeton, new jersey. 2003
39. Hotes JL, Ellison LF, Howe HL, Friesen I, Kohler B. Variation in breast cancer counts using seer and iarc multiple primary coding rules. Cancer Causes Control. 2004;15:185-191
40. International rules for multiple primary cancers (icd-0 third edition). Eur J Cancer Prev. 2005;14:307-308
41. Steeg PS. Control of invasion and metastases. In: Harris JR, Lippman ME, Morrow M, Osborne CK, eds. Diseases of the breast. Philadelphia: Lippincott Williams & Wilkins 2004:459-472.
42. Engel J, Eckel R, Kerr J, Schmidt M, Furstenberger G, Richter R, Sauer H, Senn HJ, Holzel D. The process of metastasisation for breast cancer. Eur J Cancer. 2003;39:1794-1806
43. de Vries E, Bray FI, Eggermont AM, Coebergh JW. Monitoring stage-specific trends in melanoma incidence across europe reveals the need for more complete information on diagnostic characteristics. Eur J Cancer Prev. 2004;13:387-395
44. Spanknebel K, Kaufman HL. Surgical treatment of stage iv melanoma. Clin Dermatol. 2004;22:240-250
45. Solomayer EF, Diel IJ, Meyberg GC, Gollan C, Bastert G. Metastatic breast cancer: Clinical course, prognosis and therapy related to the first site of metastasis. Breast Cancer Res Treat. 2000;59:271-278
46. Rijnsburger AJ, van Oortmarssen GJ, Boer R, Baines CJ, Miller AB, De Koning HJ. Clinical breast exams as a screening tool: Cost-effectiveness. . 2005:94-107
47. Rijnsburger AJ, Essink-Bot ML, van Dooren S, Borsboom GJ, Seynaeve C, Bartels CC, Klijn JG, Tibben A, de Koning HJ. Impact of screening for breast cancer in high-risk women on health-related quality of life. Br J Cancer. 2004;91:69-76
48. Louwman WJ, Janssen-Heijnen ML, Houterman S, Voogd AC, van der Sangen MJ, Nieuwenhuijzen GA, Coebergh JW. Less extensive treatment and inferior prognosis for breast cancer patient with comorbidity: A population-based study. Eur J Cancer. 2005;41:779-785
49. Verbeek AL, Broeders MJ. Evaluation of the netherlands breast cancer screening programme. Ann Oncol. 2003;14:1203-1205
50. Moody-Ayers SY, Wells CK, Feinstein AR. "Benign" Tumors and "Early detection" In mammography-screened patients of a natural cohort with breast cancer. Arch Intern Med. 2000;160:1109-1115
51. Richtlijn: Behandeling van het mammacarcinoom. 2004;2005
52. van der Rhee HJ, de Vries E, Coebergh JW. [favourable and unfavourable effects of exposure to sunlight] gunstige en ongunstige effecten van zonlichtexpositie. Ned Tijdschr Geneeskd. 2007;151:118-122
53. Hooning MJ, Botma A, Aleman BM, Baaijens MH, Bartelink H, Klijn JG, Taylor CW, van Leeuwen FE. Long-term risk of cardiovascular disease in 10-year survivors of breast cancer. J Natl Cancer Inst. 2007;99:365-375
54. Louwman WJ, Klokman WJ, Coebergh JW. Excess mortality from breast cancer 20 years after diagnosis when life expectancy is normal. Br J Cancer. 2001;84:700-703
55. Louwman M, Vulto AJCM, Verhoeven RHA, Nieuwenhuijzen GAP, Coebergh JW, Voogd AC. Clinical epidemiology of breast cancer in the elderly. European Journal of Cancer. 2007;in press

Summary

Summary

The number of cancer survivors has been increasing with about 5% per year and is expected to grow in the near future due to rising detection and survival rates. Individuals who suffered from cancer exhibited a 20% higher risk of subsequent primary malignancies, possibly increasing over time (**chapter 1**). Thus studying multiple cancers has become of utmost importance, also because it currently comprises about 10% of all new cancer cases in most industrialized countries.

The aim of this thesis is two-fold, firstly to assess the clinical aspect of cancer survivorship using a cohort of female cancer survivors with focus on breast cancer survivors and secondly exploring the use of multiple cancer studies in an etiological context using a cohort of patients with skin cancer.

This thesis began with a review (**chapter 2**) on the epidemiology of multiple cancers, discussing the pattern and trends of multiple cancers as well as their possible determinants, which is also related to study design used. The determinants include an inherited predisposition to cancer, the usual carcinogenic and cancer promoting aspects of lifestyle, hormonal use and limited role of environmental factors, the major role of irradiation and systemic treatment of the previous primary cancer; last but not least there is the role of generally increased surveillance of cancer survivors.

This thesis is divided into two sections each focusing on two major cancers: breast and skin.

In chapter 3-5 general epidemiological aspects of breast cancer were discussed. Firstly, in an ecological study (**chapter 3**), we showed a very strong correlation between the overall excess incidence of breast cancer in 2002 and the average age of the mother at first birth in 1972, 1982 and 1992, which seemed to persist in 2002. Both past and current average age at first childbirth at population-level were very strongly associated with recent excess risk of breast cancer. The association may be so strong, because risk factors for breast cancer such as younger age at menarche, lower parity, obesity and use of post-menopausal hormones, also generally cluster in populations with a high incidence of breast cancer. Besides being directly linked to an increased risk of breast cancer, older age at first child delivery can also be considered as a risk indicator of clustering of risk factors in western populations. Thus, this indicator might therefore a good tool in estimations of future incidence of breast cancer.

In **chapter 4** we described the recent trend in breast cancer incidence in women aged 50-69 in the Netherlands compared to the USA. Recent trend has shown a decreased incidence of breast cancer in this age group attributable to reduced use of hormonal replacement therapy (HRT). However due to the smaller proportion of women using (HRT) in the Netherlands (only 13%), we only observed a flattening of the ever rising curves since the 50's but did not (yet) observe a substantial reduction in the incidence of breast cancer at age 50-69 years. In the following chapter (**chapter 5**) we examined the prognostic factors for survival among patients with breast cancer surviving more than 10 years. Among others, the impact of a second cancer diagnosis among these patients was assessed: a better overall survival for

women without second primary tumours as compared to women who developed a new primary cancer. In addition, tumor size, nodal status and grade remained the most important prognostic factors for long-term survival, although their role decreased over time. Most studies agreed on the long-term prognostic values of MI (mitotic index), LVI (lymphovascular invasion), Her2-positivity, gene profiling and co-morbidity for either all patients or a subgroup (node-positive or negative).

Trends in the incidence of a second breast cancer among female cancer survivors were examined in **chapter 6**. We found that over a period of 20 years, the incidence of breast cancer among female cancer survivors has doubled. Population aging contributed approximately 36% to this increased trend. The highest increase in incidence occurred among older survivors (age 75+), those diagnosed with a non-breast cancer and most of the increase was detected in stage 2, thus rendering a detection effect unlikely. Our findings warrant confirmation in other datasets and close exploration of a better follow-up strategy for female cancer survivors to detect subsequent breast cancer at an early stage.

During the last decades, we found a 50% increased incidence of second breast cancer among the breast cancer survivors. Among the general female Dutch population a marked increase in the incidence of breast cancer has also been reported. Thus, we compared the incidence of second cancer among breast cancer survivors to that of the general population in the following 3 chapters (**chapter 7-9**). During 30 years of follow-up, 13% of breast cancer patients in our cohort were diagnosed with a second primary cancer. Compared with the general population, patients with malignant breast cancer experienced a 2-fold increased risk of another (new) primary cancer. Most pronounced is the risk of developing another breast, salivary gland and connective tissue cancer, approximately 3 times higher than that of general female population. Also elevated, albeit to a lesser extent, were the risks for cancer of colon, ovary, skin (melanoma) and bladder. Closer monitoring of breast cancer patients seems warranted for second breast cancer and for ovarian cancer in women diagnosed with breast cancer before menopause and for colon cancer in breast cancer patients diagnosed after age 50. **Chapter 8** focused on the risk of second cancer among women with *in-situ* breast cancer. This was done because of the tremendously increased incidence of *in-situ* breast cancers during the last decade following mass mammography screening. Approximately 10% of these patients were subsequently diagnosed with a second cancer during a follow-up period of 30 years. Most evident, we observed an increased risk of second breast and skin cancer, 4- and 2-times higher than the general population, respectively. Furthermore, we found that the pattern of increased cancer risk for patients with *in-situ* breast cancer resembles that for patients with malignant breast cancer, as both groups of patients have an increased risk of colorectal, ovarian, lung and skin cancer as compared to the general population. Therefore, similar follow-up strategies may be required for patients with malignant breast cancer and patients with *in-situ* breast cancer.

The following chapters (**chapter 10-12**) studied multiple cancers among patients with skin cancer. **Chapter 10** shortly described the skin cancer cohort as well as the potential impact of its major risk factor, solar radiation in relation to the 3 types of skin cancer: BCC (Basal Cell Carcinoma), SCC (Squamous Cell Carcinoma) and CM (Cutaneous Melanoma). On the other hand, sun exposure might have a protective effect on the initiation and progression of

some cancers including breast, colon and prostate cancer, mediated by the production of vitamin D. Thus in the context of studying multiple cancers, we examined the risk of breast, colorectal (**chapter 11**) and prostate cancer (**chapter 12**) among patients previously diagnosed with a skin cancer. And indeed, we found a decreased risk of colorectal and prostate cancer among male skin cancer patients, particularly among those with SCC. Furthermore, patients with SCC, especially those who were older than 60 at the time of diagnosis; those with the lesion on the head and neck area had the lowest risk of a second colorectal cancer. Older skin cancer patients have supposedly been exposed to the sun longer than younger patients. In addition, skin cancer in the head and neck area is also associated to chronic sun exposure. These findings are consistent with the hypothesis: the more chronic sun exposure, the lower the risk of developing colorectal and prostate cancer. We also found that the risk of colorectal or prostate cancer among skin cancer patients was lowest during the first year after skin cancer diagnosis, and increased gradually thereafter. Skin cancer patients may reduce their sun exposure soon after the skin cancer diagnosis. Thus, our findings suggest that the protective effect of sun exposure is on progression and diminishes as soon as sun exposure was reduced.

Although not statistically significant, for breast cancer after skin cancer diagnosis, we observed a similar pattern as that for colorectal cancer: SCC patients who were older than 60 at diagnosis with a lesion on the head and neck area had the lowest risk of breast cancer. For CM patients a higher risk of breast cancer as compared to the general population was found. In our previous study where we assessed the risk of second cancer among breast cancer patients, we also observed a higher risk of melanoma. There are several explanations for this. This may reflect a higher socio-economic status, which is related to higher intermittent sun exposure, but to lower number of children, younger age at the first child's birth and probably higher awareness for breast cancer leading to higher attendance rate for screening. A small fraction of this risk may also be explained by genetic predisposition towards both CM and breast cancer e.g mutation in BRCA2.

In conclusion (**chapter 13**), our findings highlight the need for more intensive follow-up, particularly for women previously diagnosed with a non-breast cancer, e.g. through biennial clinical breast examination in addition to the standard mammography in women older than 50 years. Furthermore, our study showed the long-term increased risk of second cancer among breast cancer patients, which stresses the need for long-term surveillance. As for treatment decisions, a high proportion of multiple cancer patients is of advanced age, thus treatment needs to balance between the achievement of the expected survival with ‘good’ quality of life, and the harm of a more aggressive treatment. Second breast cancer among breast cancer survivors is likely to be less aggressive than first tumours, partly because of earlier detection by more intensive surveillance. Thus, future research is required to assess the effectiveness of a less aggressive treatment in this group of patients. Finally in the framework of patient management, the proportion of cancer survivors who will be affected by a second cancer is increasing, thus raising awareness and the need for more knowledge on an effective preventive strategy. Lifestyle modification after cancer diagnosis may decrease the risk of a second cancer, although such studies are still lacking.

As for the beneficial role of sunlight, our findings in skin cancer survivors who were most exposed to chronic UV-exposure support the hypothesis that sunlight protects against the development of colorectal and prostate cancer, possibly through the formation of vitamin D. If sunlight has indeed a protective effect against colorectal and prostate cancer, it is important to balance the positive and negative effects of sun exposure in public health messages. The levels of sun exposure that does not result in increased risk of skin cancers in the various groups of skin types should be defined. Additionally, if indeed vitamin D reduces the risk of colorectal, prostate and possibly advanced breast cancer, recommendations to increase various forms of intake of vitamin D, including orally, through supplementation and/or fortification should be implemented.

Future studies may be warranted that retrieve more detailed data from medical records on e.g. treatment choice and patient characteristics and finally examination of cause-specific death. International collaborations would be of increasing value for such studies (nested case-control studies), not only by increasing the number of study subjects, but also by enhancing the generalizability of the results.

We have to realize that we are, in a sense, the fortunate victims of our own success in the area of multiple cancers. Improved early detection of cancer and oncologic therapy have led to prolonged survival, and the risk of secondary malignancies has consequently increased. Therefore, the time may have come to take some counteraction against this increasing problem. Although it is widely known that lifestyle factors have a significant influence on the risk of developing a primary cancer, the influence of such changes on the risk of developing second cancers is largely unknown. Finally, as the numbers of patients with second cancers are increasing, further studies are warranted directed at various clinical and psycho-social aspects of these patients, including their survival and quality of life. The latter is also considered of major importance from the point of view of patients.

Samenvatting

Samenvatting

Het aantal mensen dat kanker overleeft is drastisch toegenomen en de verwachting is dat die groei nog verder zal toenemen in de nabije toekomst. Elke 10-jaar treedt ongeveer een verdubbeling op. Patiënten die ooit kanker hebben gehad, hebben een 20% hoger risico om nogmaals een vorm van kanker te krijgen. Dus het bestuderen van meervoudige tumoren is zeer belangrijk al was het alleen uit preventieve overwegingen. Het doel van dit proefschrift is tweeledig: ten eerste het in kaart brengen van de klinische aspecten van het overleven van kanker, gebruikmakend van een cohort van vrouwelijke (ex-)kankerpatiënten vooral (ex-)borstkankerpatiënten, en ten tweede het verkennende gebruik van studies naar meervoudige tumoren in een etiologische context, gebruikmakend van een cohort van (ex-) huidkankerpatiënten.

In **hoofdstuk 2** wordt de epidemiologie van meervoudige tumoren beschreven. Hierbij spelen de volgende factoren een belangrijke rol. De erfelijke gevoeligheid voor het ontwikkelen van kanker, gedeelde risicofactoren (carcinogenen), hormonale en omgevingsfactoren, behandeling van de eerste tumor, en de toegenomen overleving van bepaalde groepen kankerpatiënten. Inmiddels maken meervoudige tumoren wel 10% uit van alle nieuwe tumoren.

Hoofdstuk 3 t/m 5 gaan over de algemene epidemiologie van borstkanker. In een ecologische studie (**hoofdstuk 3**) blijkt er een sterke correlatie te bestaan tussen een verhoogde kans op borstkanker in 2002 en de gemiddelde leeftijd waarop vrouwen hun eerste kind kregen in de periode 1972-2002. Bekend is dat de lengte van het interval in de periode tussen eerste menstruatie en het eerste kind er toe doet. Andere risicofactoren voor borstkanker, zoals een lagere menarche leeftijd, minder kinderen per vrouw, meer overgewicht en het gebruik van hormoonsuppletie therapie, komen ook vaker voor in landen met een hogere borstkankerincidentie. Naast een direct verband tussen de hogere leeftijd bij de geboorte van het eerste kind, is die leeftijd ook een indicator van een langer interval waarin deze risicofactoren in de westerse bevolking clusteren.

In **hoofdstuk 4** wordt de trend in borstkanker incidentie bij vrouwen tussen 50 en 69 jaar in Nederland vergeleken met die in de Verenigde Staten. Recentelijk werd daar sinds 2002 een afname geconstateerd in borstkankerincidentie die toegeschreven werd aan de vermindering van het gebruik van post-menopausale hormoonsuppletie. Deze reductie werd in Nederland in mindere mate waargenomen, waarschijnlijk omdat hormoonsuppletie hier veel minder frequent en korter van duur was dan in de Verenigde Staten (13% versus 38%). Inmiddels worden de aanwijzingen steeds sterker dat hier wel degelijk sprake is van een belangrijke ontwikkeling.

De factoren die de prognose bepalen van borstkanker patiënten op de lange termijn (meer dan 10 jaar na diagnose) staan in **hoofdstuk 5**. Hierin werd een systematisch literatuuronderzoek verricht. Onder andere bleek de prognose van vrouwen met een nieuwe primaire tumor, na de eerste borstkanker diagnose, slechter te zijn dan van vrouwen zonder meervoudige tumoren.

De incidentie van borstkanker na een eerdere kwaadaardige tumor is in een periode van twintig jaar verdubbeld **(hoofdstuk 6)**. Deze stijging is voor circa 36% toe te schrijven aan het vaker voorkomen van borstkanker in de ouder wordende bevolking. De hoogste toename van de incidentie werd gezien bij vrouwen van 75 jaar en ouder, vrouwen met een andere vorm van kanker dan borstkanker; de tweede diagnose borstkanker bleek vaker stadium II te zijn ondanks verbeteringen in de screening. Dit benadrukt het belang van follow-up van kankerpatiënten om vroegtijdig nieuwe primaire tumoren op te kunnen sporen.

In een groep borstkanker patiënten die gedurende maximaal 30 jaar werden gevolgd (**hoofdstuk 7 t/m 9**), kreeg 13% opnieuw een primaire tumor. In vergelijking met de algemene bevolking hadden deze vrouwen een twee keer zo hoog risico om opnieuw kanker te krijgen. Met name het risico op een tumor in de andere borst, de speekselklieren en het bind- en spierweefsel waren ongeveer drie keer verhoogd. In iets mindere mate was ook het risico op darm-, eierstok-, huid-, en blaaskanker verhoogd. Een speciale follow-up van borstkankerpatiënten lijkt gerechtvaardigd gericht op tijdige opsporing van met name tweede mammacarcinoom en eierstokkanker bij premenopausale vrouwen en op dikkedarmkanker bij vrouwen ouder dan 50 lijkt gerechtvaardigd.

De introductie van het bevolkingsonderzoek naar borstkanker heeft geleid tot een enorme toename in het voorkomen van *in-situ* borstkanker. Ongeveer 10% van deze patiënten krijgt vervolgens een invasieve vorm van kanker (**hoofdstuk 8**). Met name het risico op een invasief mammacarcinoom en huidkanker zijn respectievelijk 4 en 2 maal zo hoog als in de algemene bevolking. Het patroon van risico op een tweede tumor na een *in-situ* borsttumor vertoont grote gelijkenis met dat na een eerste invasief mammacarcinoom, met name verhoogde risico's op dikkedarm-, ovarium-, long- en huidkanker. Daarom zou de surveillance gericht op andere kankers bij patiënten met een *in-situ* mammacarcinoom dezelfde moeten zijn aan de follow-up van een invasief mammacarcinoom.

Hoofdstuk 10 t/m 12 gaan over het optreden van meervoudige tumoren bij huidkankerpatiënten. **Hoofdstuk 10** bevat een beschrijving van het cohort en de belangrijkste risicofactor, te weten chronische en/of intermitterende blootstelling aan de zon. De gedachte is dat die blootstelling ook een beschermend effect kan hebben bij de initiatie en/of progressie van tumoren van sommige vormen van kanker, zoals borst-, colon- en prostaatkanker, door de invloed op de vitamine D productie. Het risico op borst-, dikkedarm- (**hoofdstuk 11)** en prostaatkanker (**hoofdstuk 12**) werd onderzocht bij patiënten die eerder huidkanker hadden. Inderdaad werd bij mannen een lager risico op dikkedarm- en prostaatkanker gevonden, vooral bij degenen met een plaveiselcelcarcinoom. Het risico op dikkedarmkanker was het laagst voor patiënten ouder dan 60 bij diagnose en waarbij het plaveiselcelcarcinoom in het hoofd-hals gebied was. Oudere patiënten zijn langer blootgesteld aan de zon en huidkanker in het hoofd-hals gebied is vooral gerelateerd aan langdurige zonblootstelling. Deze bevindingen komen overeen met de hypothese: bij meer chronische blootstelling aan de zon neemt de kans op sommige vormen van kanker af. Het risico op dikkedarm- en prostaatkanker bij huidkankerpatiënten was het laagst in het eerste jaar na de diagnose van de huidtumor en nam daarna geleidelijk toe. Mogelijk nam na het diagnosticeren van huidkanker de blootstelling aan de zon af en daarmee het beschermende effect. Eenzelfde patroon werd waargenomen voor borstkanker na

huidkanker, hoewel dit een zwakker verband bleek. Een verhoogd risico op borstkanker werd gevonden voor vrouwen met een voorafgaand melanoom van de huid. Dit kan gerelateerd zijn aan een hogere sociaal-economische status, die samenhangt met een hogere intermitterende zonblootstelling, maar ook aan een lager aantal kinderen, hogere leeftijd bij de geboorte van het eerste kind en een groter borstkanker-bewustzijn waardoor de kans op detectie groter is. Een klein deel van het risico is ook te verklaren door een gedeelde genetische aanleg voor zowel borstkanker als melanoom van de huid.

Uit de studies beschreven in dit proefschrift blijkt het belang van een intensieve follow-up van vrouwen met een eerdere vorm van kanker vooral vrouwen met een andere vorm van kanker dan borstkanker, dus een tweejaarlijks klinisch onderzoek van de borst, naast de standaard mammogram. Omdat het risico op een tweede tumor lang na diagnose van de eerste tumor aanhoudt, zou ook de termijn van follow-up voldoende lang moeten zijn.

Omdat een groot deel van de kankerpatiënten ouder is, moet de behandeling een balans zijn tussen het te behalen resultaat met een acceptabele kwaliteit van leven en de mogelijke schade van de behandeling. Meervoudige borsttumoren worden vaak minder agressief behandeld dan de eerste mammatumor, deels vanwege de meer intensieve follow-up. Vervolgonderzoek naar de effectiviteit van deze minder agressieve therapie is noodzakelijk. Bovendien moet benadrukt worden dat veranderen van de levensstijl het risico op een tweede tumor kan verminderen.

Onze bevindingen bevestigen het mogelijk beschermende effect van zonblootstelling, waarschijnlijk door de bijdrage aan de vorming van vitamine D. Het is dus belangrijk de positieve en negatieve effecten van blootstelling aan de zon zorgvuldig te communiceren naar de bevolking. Het niveau waarop geen schade aan de huid optreedt dient te worden vastgesteld. Bovendien zouden, indien de bescherming werkt via de verhoogde vitamine D productie, aanbevelingen voor grotere vitamine D inname met de voeding, via supplementen of door toevoeging aan voedingsmiddelen moeten worden overwogen. Die zouden eveneens osteoporose tegen kunnen gaan, hetgeen bij vele kankerpatiënten een probleem vormt.

Er is een behoefte aan studies met gedetailleerde gegevens uit medische dossiers, zoals behandelkeuze en patiëntgegevens, die ook informatie hebben over doodsoorzaken van de patiënten. Hierbij is wenselijk dat de patiënt verenigingen aan het CBS duidelijk maken dat deze gegevens ongehinderd ter beschikking komen van de kankerregistraties. Internationale samenwerkingsverbanden zijn in toenemende mate van belang voor dergelijke studies (ingebouwde ('nested') patiëntcontrole onderzoeken), niet alleen vanwege de grotere aantallen patiënten, maar ook om eventuele variatie op het spoor te komen dan wel tot generaliseerbare bevindingen te komen voor andere populaties. Benadrukt zij ook dat het optreden van meervoudige tumoren tot op zekere hoogte een teken is van succesvolle behandelingen en langdurige overleving mede door de verbeterde vroege opsporing van kanker. Door deze langere overlevingsduur is de kans om een tweede maligniteit te ontwikkelen soms echter wel verhoogd. Het is dan ook tijd om dit in omvang toenemende probleem aan te pakken vanuit een preventieve optiek. Als leefstijl factoren in belangrijke mate de kansen op het ontwikkelen van een eerste primaire tumor beïnvloeden, zou dit ook

het geval moeten zijn voor hierna optredende tumoren. Maar van de precieze effecten van leefstijl is niet zoveel bekend , en meer onderzoek op dit gebied is nodig.

Tot slot, aangezien de aantallen patiënten met meervoudige tumoren aanzienlijk toenemen, zijn nieuwe studies nodig en ook beter mogelijk gericht op de kwaliteit van leven van deze patiëntengroepen.

Dankwoord/
Acknowledgements

Dankwoord/Acknowledgements

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I love nonsense, it wakes up the brain cells. Fantasy is a necessary ingredient in living, It's a way of looking at life through the wrong end of a telescope, which enables you to laugh at life's realities

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Furthermore, another thing of working with Jan Willem, and this fits best to describe it.

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How did it get so late so soon? Its night before its afternoon.
December is here before its June.
My goodness how the time has flewn. How did it get so late so soon.

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Think they work you to hard..? Think of poor Ali Sard!
He has to mow grass in his uncle's backyard
And it's quick-growing grass, and it grows as he mows it.
The faster he mows it, the faster he grows it.

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And I'm so, so lucky, I am not Gucky Gown.
Who lives by himself, ninety miles out of town.

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Where they bumped. There they stood.
Foot to foot. Face to face.

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Be who you are and say what you feel because those who mind don't matter and those who matter don't mind.

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Curriculum Vitae

Curriculum Vitae

Isabelle Soerjomataram was born on 11 April 1977 in Innsbruck, Austria. She moved to Indonesia and finished her secondary school education there. In 1995 she went on to study Medicine at the University of Indonesia in Jakarta and got her medical degree in 2001. In January 2002 she worked as medical doctor coordinating mother and child health prevention program among the refugee in Madura, Indonesia. In the fall 2002 she was awarded a fellowship from the Dutch education centre in Jakarta for higher education for her postgraduate studies. She received a Master of Clinical Epidemiology from the Netherlands Institute for Health Sciences. Her dissertation examined the risk of second primary cancer among breast cancer patients using the data of the Eindhoven Cancer Registry. In the fall 2003 she started working as a researcher at the Epidemiology Department at the Medical University in Vienna, Austria. There she worked on the International Study on Asthma and Allergies in Childhood. In the mean time she continues to work with the Eindhoven cancer registry on the risk of multiple cancers. In the spring of 2004 she assisted the analysis for the Dutch Cancer Society report on trends, prognosis and implication in the Netherlands. Before starting to work in the Department of Public Health she spent the summer of 2005 following a course on cancer prevention in the National Cancer Institute, Bethesda, the USA. Since September 2005, she officially started her work at the Erasmus MC. She works on the Eurocadet project, a European Union funded project on prevention of cancer and its impact on future cancer incidence. Besides that she also works in the domain of cancer surveillance within the Netherlands and the Eindhoven cancer registry, continuing the project on the multiple primary cancers.

List of Publications

Peer reviewed journals

1. Soerjomataram I, Louwman M, Visser O, van Leeuwen FE, Coebergh JW. Does the decrease in hormone-replacement therapy also affect breast cancer risk in the Netherlands? ***Journal of Clinical Oncology*** (*in press*)
2. Soerjomataram I, de Vries E, Pukkala E, Coebergh JW. Excess of cancers in Europe: A study of eleven major cancers amenable to lifestyle change. ***Int J Cancer.*** 2007;120:1336-1343
3. Soerjomataram I, Coebergh JW. Should women be advised to have first childbirth at age <20 years to reduce breast cancer risk? ***J Cancer Res Clin Oncol.*** 2007;133(11):903
4. Soerjomataram I, Louwman MW, Ribot JG, Roukema JA, Coebergh JW. An overview of prognostic factors for long-term survivors of breast cancer. ***Breast Cancer Res Treat.*** March 2007.
5. de Vries E, Soerjomataram I, Houterman S, Louwman MW, Coebergh JW. Decreased risk of prostate cancer after skin cancer diagnosis: A protective role of ultraviolet radiation? ***Am J Epidemiol.*** 2007;165:966-972
6. Soerjomataram I, Pukkala E, Brenner H, Coebergh JW. On the avoidability of breast cancer in industrialized societies: older mean age at first birth as an indicator of excess breast cancer risk. ***Breast Cancer Res Treat.*** Oct 2007.
7. Soerjomataram I, Louwman WJ, van der Sangen MJ, Roumen RM, Coebergh JW. Increased risk of second malignancies after in situ breast carcinoma in a population-based registry. ***Br J Cancer.*** 2006;95:393-397
8. Soerjomataram I, Louwman WJ, de Vries E, Lemmens VE, Klokman WJ, Coebergh JW. Primary malignancy after primary female breast cancer in the south of the Netherlands, 1972-2001. ***Breast Cancer Res Treat.*** 2005;93:91-95
9. Soerjomataram I, Louwman WJ, Lemmens VE, de Vries E, Klokman WJ, Coebergh JW. Risks of second primary breast and urogenital cancer following female breast cancer in the south of the Netherlands, 1972-2001. ***Eur J Cancer.*** 2005;41:2331-2337

Book chapters

1. Soerjomataram I, Coebergh JWW. Multiple primary cancers. In: Mukesh V, ed. *Cancer Epidemiology*. Humana Press, New Jersey, USA, 2007.
2. [Workgroup in Prevalence of Cancer the Dutch Cancer Society. *Cancer in the Netherlands. Trends, prognosis and implication for Health Care*. Den Haag, Drukkerij van de Boogard, 2004.] *Dutch.*
3. [Vutuc C, Waldhör T, Soerjomataram I, Haidinger G. Basic Principles of Epidemiology. In Wittman, K.J., ed. *Human in the Environment, Family and Society*. Facultas Verlags- und Buchhandels AG Wien 122-148.] *German*.