MULTIPLE MALIGNANCIES AMONGST CANCER SURVIVORS IN THE NETHERLANDS SINCE 1989

-Implications for surveillance

Lifang Liu

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Multiple malignancies amongst cancer survivors in the Netherlands since 1989-implications for surveillance

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Multiple Malignancies amongst Cancer Survivors in the Netherlands since 1989

-Implications for Surveillance

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-implicaties voor surveillance

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Dedicate to papa, mama, brother

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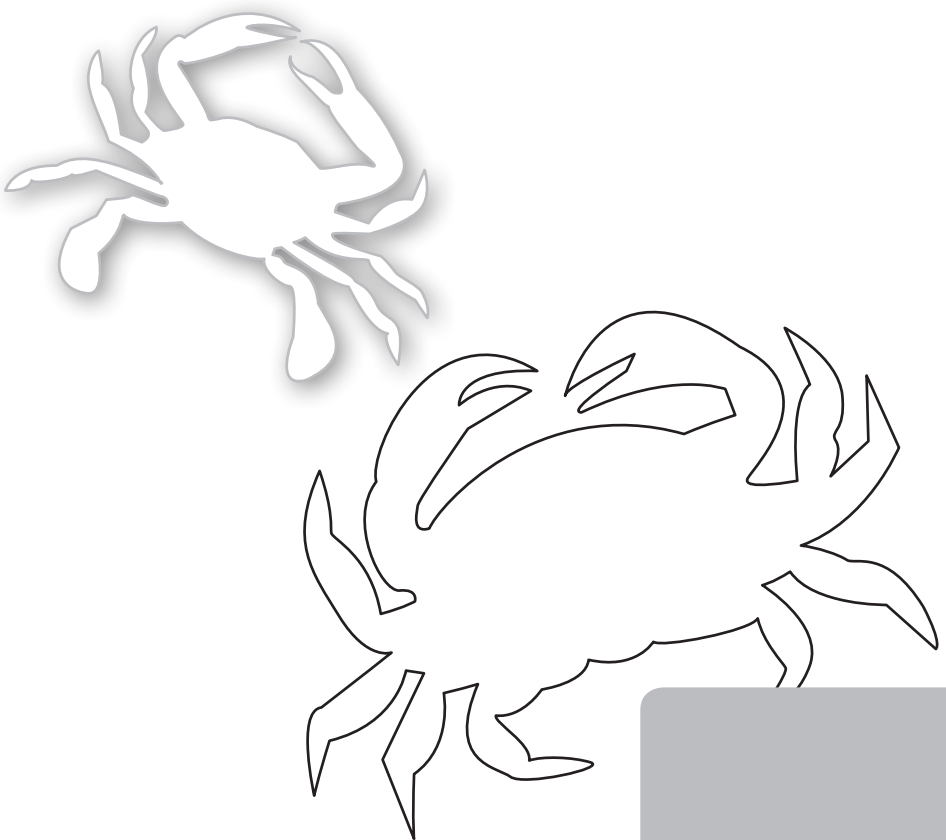
CHAPTER 1

Introduction



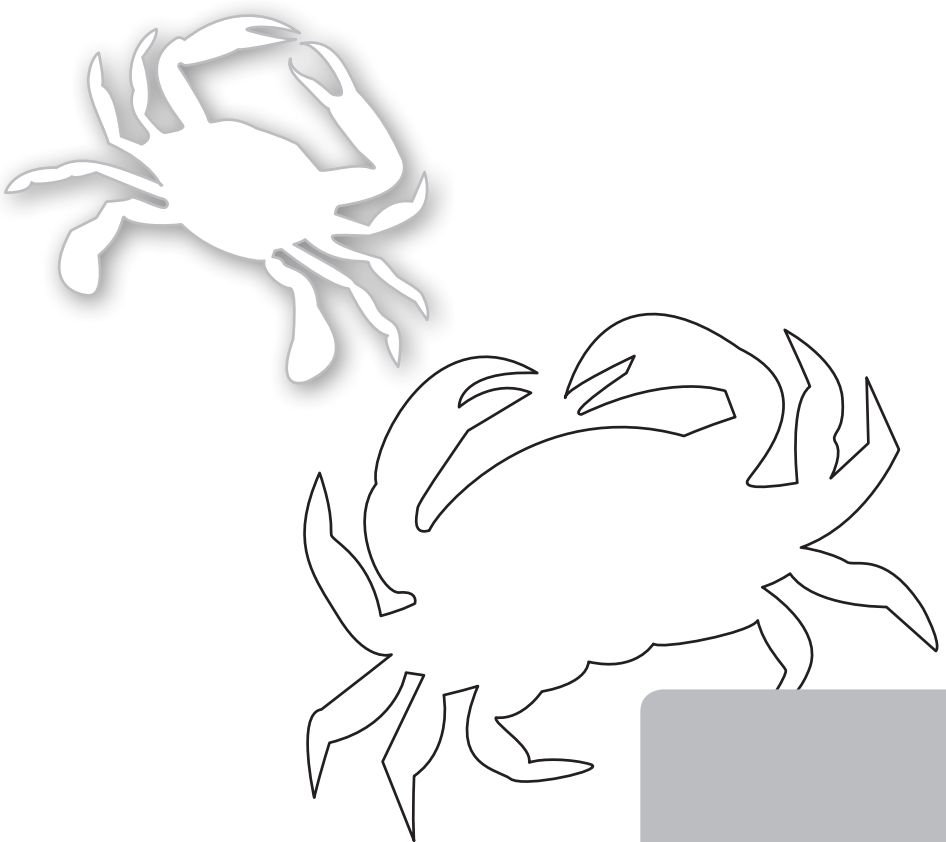
This chapter consists of two parts:

i) 1. 1 General introduction and problem definition: definition, risk and prognostic factors, as well as methods and statistical issues to estimate risk and prognosis of patients with MMs

ii) 1. 2 Prevalence of multiple malignancies on Jan 1 2007

CHAPTER 1.1

General introduction and problem definition



1.1 GENERAL INTRODUCTION AND PROBLEM DEFINITION

Early detection of cancer as well as advances in therapy and supportive care have resulted a prolonged survival period of time after cancer. In the Netherlands the 5-year relative survival for all types of cancers combined increased from 47% in 1989-1993 to 59% in 2004-2008[1]. Once patients have survived long enough (i.e. 10 years) since diagnosis of their cancer, their life expectancy usually becomes almost the same as people without a cancer (conditional 5-year relative survival>95%)[2]. A Netherlands Cancer scenario Report expected the prevalence of second cancer patients to increase from 14,000 in 1985 to 24,000 (excl. skin cancer) in 2000 when assuming an average increase of duration of survival by 1% per annum[3]. The Signallling report in 2004 from the Dutch Cancer Society estimated the prevalence of multiple malignancies (MMs) to reach around 100,000 cases in 2015 in the Netherlands due to a twofold number of cancer survivors since 2005[4]. Since a second cancer diagnosis may impair survival and is likely to affect quality of life amongst cancer survivors we should be interested in prevention and early detection and its undoubtedly more complex treatment[5-11].

MMs are defined as two or more primary cancers occurring in an individual that are neither an extension, nor a recurrence, nor a metastasis of the first tumor[12,13]. MMs can be differentiated into synchronous and metachronous cancers, based on the length of the **interval between the diagnosis of the first and second cancer**. Synchronous cancers occur within 6 months after the first cancer diagnosis, and metachronous cancers later (**Figure 1**). But this definition may vary depending on the specific research questions posed.

Source: Netherlands Cancer Registry

Figure 1. Definitions of second cancers diagnosis according to follow-up periods
Note: A localized, e.g. T1 synchronous, cancer is likely to be a prevalent cancer whose diagnosis is only made earlier but which otherwise have been detected later.

1.1.1 Etiology and risk

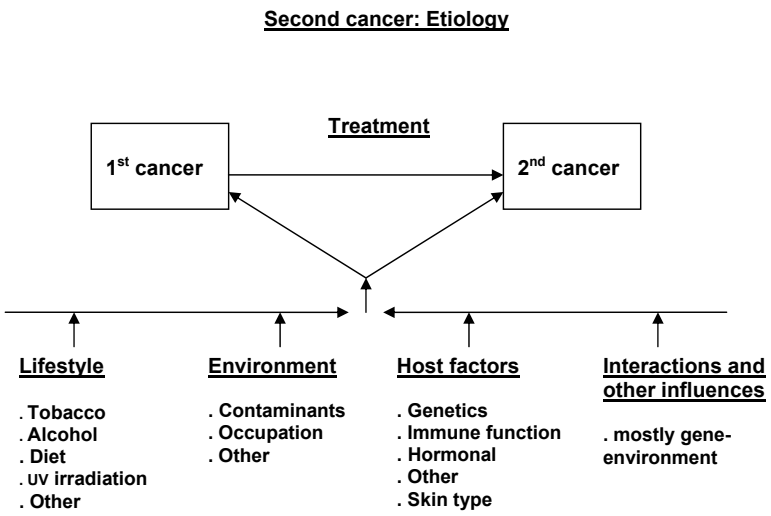
On average, cancer patients have a two-fold increased risk to develop another cancer as compared with the general population[14,15]. But this risk is very unevenly divided over cancer types, because it can be due to (**Figure 2**):

i) Shared lifestyle risk factors in the same patient with an initial cancer i.e. related to smoking, alcohol, obesity, UV and infection. For instance, amongst survivors of head and neck cancer, a higher risk (i.e., SIR>1) for lung cancer is observed, likely due to smoking[16]; amongst women with cervical cancer, a higher risk of cancers of the vagina, vulva, and anus are observed, likely related to Human Papilloma Virus (HPV) as a common cause[17-19].

ii) Side effects from the treatment of the first cancer, e.g. radiotherapy, chemotherapy or hormonal therapy, or a combination of effects of more than one of these modalities. Second cancers related to radiotherapy usually occur 10 years after diagnosis and their risk is higher amongst patients who received radiotherapy[20,21]. Second primary breast cancer might be the late adverse effect of initial radiotherapy in patients with a prior Hodgkin's lymphoma[22-24]. The lag-time between treatment and hematological cancers is generally shorter as compared to solid tumors. For instance, myelomonocytic or monocytic leukaemia, often occur shortly (i.e. within 1 year) after chemotherapy has been administered, whereas alkylating agent-related acute myeloid leukemia (AML) become most common 5-10 years after the initial cancer diagnosis[25-29]. However sometimes therapy may have a protect effect. For instance, endocrine therapy with Tamoxifen for breast cancer has been shown to have a protective effect against contralateral breast cancer[30].

iii) Immune-suppression.Impairment of the immune system, resulting in a lack of control of oncogenic viruses greatly elevates the risk of infection-related cancers. Patients with Human Immunodeficiency Virus (HIV) or with organ transplants are at very high risk of non-Hodgkin's disease (NHL) or Kaposi sarcoma (KS) and also have a substantially increased risk of Hodgkin's disease (HD), cervical cancer and skin cancer. Impaired immune function is thought to (partly) explain the increased risk of multiple malignancies amongst cancer survivors of NHL, KS and skin melanoma[31-34].

iv) Genetic predisposition e.g. BRCAI/II and HNPCC. Women with BRCAI/II mutations have a high cumulative risk of developing breast cancers by age of 70 years (35-84%) and ovary (10-50%)[35]. Patients with hereditary non-polyposis colorectal cancer (HNPCC, Lynch syndrome) are at increased risk for cancers in breast, ovary, and skin (melanoma)[25,36,37]. Multiple cancers associated to a genetic predisposition often occur at younger ages of onset compared with sporadic cancers.



Source: Netherlands Cancer Registry

Figure 2 Determinants of risk of subsequent primary cancers
Adapted from Travis, L.B. Acta Oncologica 2002; 41:323-333[38].

1.1.2 Prognosis of patients after a second cancer diagnosis

Generally the occurrence of a second cancer has been reported to be associated with lower survival: this was observed for most cancer sites when second primary cancers were included in the analyses[5,39]. Amongst patients with colorectal cancer, a history of previous cancer diagnosis alters the cancer treatment and impairs prognosis[40,41]. Women with contralateral breast cancer experienced worsened survival than women with a unilateral cancer, irrespective of stage at initial cancer[11]. Chemotherapy-related acute myeloid leukaemia (AML) has been shown to shorten survival time of cancer patients[42].

Better survival was observed amongst patients with multiple colorectal cancers because multiple colorectal cancers might have a different carcinogenesis pathway (e.g. microsatellite instability, MSI) and react better to chemotherapy[43-45].

1.1.3 Current state of multiple malignancies in the Netherlands and methodological challenges

An increasing and often diverse group of patients who needs more attention- As in many other industrialized countries the prevalence of cancer in the Netherlands has risen markedly, and has been predicted to continue to increase from 366,000 (2%) in 2000 to 692,000 (4%) in 2015[4]. The combination of higher survival of patients with a first primary due to earlier detection and improved treatment as well as aging of the population drives up the number of patients with more than one cancer. However updated and tumor-specific estimations are lacking related to first primary of the increasing present and future size of the problem, hampering prioritization of prevention and surveillance. In the 2007 report of the Health Council on optimal long-term surveillance of cancer patients comprehensive discussions for the detection of multiple cancers were missing[46].

Methodological challenges- Risks of second cancer amongst breast and testicular cancer as well as lymphoma patients have been explored in the Netherlands[8,29,47-57]. Recent reports from the US and Australian cancer registries provide an overview of the size and nature of multiple cancer, but analyses were based on < 20% of the national populations[14,15]. Worldwide, researchers of second primary cancer usually have focused on the relative risks compared to general population but often they did not examine the – generally rising time trends of various second malignancies because of small number of cases or a short length of follow-up periods of available data[58].

1.1.4 Methods and statistical analysis

In this thesis, several methods were applied to estimate the occurrence and prognosis of MMs[59]. They are summarized in **Table 1** In short:

(1) To assess the burden of multiple cancers:

i) *Point prevalence* of MMs is the proportion/number of people alive with more than one cancer diagnosis at a certain point in time (e.g. Jan 1 2007), disregarding the moment of onset of disease between 1989 and 2006;

ii) 20-year *Cumulative incidence (CI)* of second cancers, of a certain type of second primary cancer is the cumulative proportion of patients who had this cancer diagnosis over a period of time (e.g. 20 years). When estimating CI for a certain cancer, competing risks for other type of second cancers and death was taken into consideration[60]. For instance, when estimating CI for a second breast cancer, death, and second other cancers (rather than breast cancer) are treated as competing risks.

iii) *Absolute excess risk (AER)* from the occurrence of second cancers as compared to general population. It is defined as the difference between the observed and the expected number of patients with second primary cancer, divided by the number of person years at risk, usually expressed per 10,000.

Table 1 Definitions and formulas of indicators of risk of second primary cancers in this thesis

Measures	Definition	Formula
BURDEN		
Point Prevalence	The proportion of people alive with more than one cancer diagnosis at a certain point in time.	$\sum_{i=1}^{n} I_{j-i+0.5} \, S_{j-i+0.5}^{\,(i-0.5)}$
Cumulative incidence (CI)	Cumulative proportion of patients who had this cancer diagnosis over a period of time (e.g. 20 years) taking competing risks into consideration[60].	$CI(t) = 1 - e^{-IR(t)*D}$
6-month CI	Cumulative proportion of patients who had this cancer diagnosis over a period of time (e.g. 6 months) taking competing risks into consideration[60].	$CI(t) = 1 - e^{-IR(t)*D}$
Absolute excess risk (AER)	Excess absolute incidence of a cancer amongst cancer patients as compared with general population	(O-E)/person years at risk *10,000
RISK		
Standardized incidence ratio (SIR)	Risk for a cancer amongst cancer patients as compared with general population	O/E
PROGNOSIS		
Crude survival	Cumulative survival on the function of time-Kaplan-Meier method	$\hat{S}(t) = \prod_{t_i<t} \frac{n_i - d_i}{n_i}$
Hazard Ratio	Mortality rate ratio in the group of patients with one and with 2 cancers. Equivalent to outcome in a time-matched nested case-control study design.	$\log h(t) = f(h_0(t), \alpha + \beta_1 X_1 + \cdots + \beta_k X_k)$

*O=Observed number, E=expected number (person years at risk*background incidence)*

(2) To assess relative risk for second cancers: we used standardized incidence ratio (SIR) as a relative risk for a certain cancer amongst cancer patients as compared to the general population. SIR expresses the excess incidence of a certain cancer amongst a cohort of cancer patients relative to the background incidence amongst the general population, that is the ratio between observed and expected number of patients with second primary cancer.

(3) To assess prognosis of patients with multiple cancers: We applied the Kaplan-Meier method to illustrate the crude (absolute) survival differences between patients with one cancer and those with two. Then the Cox proportional hazard (CPH) model (univariate) was used to find the important prognostic factors amongst patients with two cancers. Finally, multivariate CPH model with second cancer as time-dependent variable was used to obtain the hazard ratio (HR) between patients with one and with two cancers. Model fit was evaluated using residual-based graphical methods and goodness-of-fit test statistics. The proportional hazard assumption was evaluated via a test for a non-zero slope in a

generalized linear regression of the scaled Schoenfeld residuals on functions of time[61]. This method is equivalent to a time-matched cohort-nested case control study design. Until the moment in time that a second cancer is diagnosed, all patients are in the group of patients with one cancer - assuming they have the same mortality (HR=1). Upon the occurrence of the second cancer, patients moved to the 'MMs' group and their mortality can diverge from the group of people without a second cancer.

(4) To estimate time trend of SIR and AER for second cancers: The number of patients with a second cancer in a certain cohort will increase with longer follow-up time, simply because with the rise of age there is more time (chance) to develop another cancer. Therefore, if follow-up time differs substantially across cohorts, biased comparisons will occur. In order to circumvent this problem, I used fixed inception cohort designs for the analyses, ensuring comparability of follow-up time across period cohorts. When using fixed inception cohorts to examine trends of SIR/AER, one should avoid (too) much overlap in background incidence in two adjacent cohorts in order to avoid underestimation in trend analysis. Also an ample sample size and long-term follow-up for the data are essential to use this study design, which fortunately are both available in the Netherlands Cancer Registry data.

(5) To estimate surface-adjusted SIR and AER:
Second cancers cannot develop in tissues that have been resected during treatment of the first cancer, hence, when comparing risk in the remaining tissue with the risk in general population in possession of their full organ, lower risks are expected (i.e. SIR <1 and AER<0), although the underlying risk might be higher because of unfavorable etiological circumstances. SIR and AER resulting from this approach should be interpreted as 'relative/absolute' risk per unit surface in the patient population compared with the risk in the general population. This approach may also shed some light on etiology of cancers: similar surface-adjusted incidence rates between sub site of colon and rectum suggest similar etiology[51,62,63].

To compute the *expected numbers* in the AER and SIR, person years at risk for each of the sex-, age- (5-year band), and calendar year-specific (1-year band) strata were multiplied by the corresponding incidence rate in the general population and then summed across strata[64]. Person years at risk in the patient cohort was calculated by summing individual follow-up times at the date of first cancer diagnosis until the occurrence of the second cancer of interest, of other second cancer, end of study (December 31st 2008), or death, whichever came first. In our study, the maximum individual follow-up time was therefore 20 years and the minimum follow-up time was one day (tumors diagnosed with zero follow-up time being excluded).

Synchronous second cancers are often excluded in SIR and AER calculations instead a 6-month/1-year cumulative incidence is calculated.

1.1.5 Study population: Netherlands Cancer Registry between 1989 and 2008

Since 1989 the Dutch population was covered by nine regional cancer registries (eight from 2008, culminating into two from 2011), which established the Netherlands Cancer Registry (NCR), providing national coverage.

The cancer registration process in the Netherlands works as follows:

The registries receive notifications of all newly diagnosed malignancies through the 60 laboratories that are part of the national automated pathology archive (PALGA)[65]. Additional sources are the national registry of hospital discharge, haematology laboratories and radiotherapy institutes. Incompleteness has been estimated to be at most 5%, occurring mostly amongst older outpatients with a clinical, (e.g. radiological) diagnosis only [66] and which might indeed affect second cancers as well. Trained registration clerks actively collect data on diagnosis, topography, histology, stage, and information about initial treatment (delivered within 6 months from diagnosis) from hospital medical records. The medical record is generally regarded as the most complete source of information on the patient's past and current health status[67]. Information on the vital status of the patients was initially obtained from the municipal registries and since 1995 from their nationwide network (GBA). These municipal registries provide virtually complete coverage of all deceased citizens in the Netherlands.

The NCR registers all new cancers (excl. basal cell carcinoma of the skin which is only registered at the Eindhoven cancer registry)[68,69] and applies International Association for Cancer Registry (IACR) rules for coding second primary cancers[12,13].

1.1.6 Main research questions

In this thesis, I aimed to answer the following main research questions:

i) What is the prevalence of multiple malignancies in the Netherlands?
- What types of cancers more or less often coexisted within one patient?
- What are the characteristics of tumors and patients with multiple malignancies?

ii) Are there any striking risk patterns with increased or decreased relative and absolute risks amongst cancer patients compared to the general population (i.e. people without a history of cancer)? Can these risk patterns inform us on potential underlying risk factors for the co-occurrence of certain types of cancer within one patient?

iii) Are there any amenable prognostic consequences of the diagnosis of a second cancer?

Outline of this thesis

The work in this thesis is based on a large research project funded by the Dutch Cancer Society named 'The increasing burden of second primary cancers in the Netherlands: trend in incidence, survival and causes-of-death since 1970 (EMCR 2008-4132) in which a large variety of combinations of cancers has been studied and also a methodology was developed for these type of analyses. Most of these analyses were made with epidemiologists from the various Comprensive Cancer Center (CCC's) and junior and senior specialized clinicians.

In this **Chapter 1.1 (Introduction**) we present definitions used throughout this thesis, potential risk factors and indicators, prognostic factors and indicators, as well as methods and statistical issues to estimate risk and prognosis of patients with MMs. In order to illustrate order of magnitude of MMs, point prevalence of patients with MMs as of 2007 are described in **Chapter 1.2**.

In the framework of the thesis, I select the most common second cancers for detailed analysis on risk and survival. They are: colorectal cancer, breast cancer, prostate cancer, melanoma of the skin, and well as chronic lymphocytic leukemia (CLL).

Chapter 2 focuses on risk patterns of second cancers. In **Chapter 2.1** risk patterns for second cancers at the sub sites of colon and rectum are analyzed amongst survivors of colorectal cancer. In **Chapter 2.2,** the risk for a subsequent melanoma of the skin is estimated amongst survivors with a cutaneous melanoma. Three studies are performed in attempt to shed light on etiological and anatomical associations between the initial and subsequent cancers, while taking treatment of the initial cancer into consideration. **Chapter 2.3** analyzes the risk for non-breast cancer amongst women with a contralateral cancer. **Chapter 2.4** focused on the risk of detecting prostate cancer amongst all cancer survivors; and **in Chapter 2.5** detection of chronic lymphocytic leukemia (CLL)-is estimated in patients with cancer.

Time trends in incidence of second melanoma of the skin occurring after any cancer type are described between 1989 and 2008, using fixed-inception cohorts **(Chapter 2.5)**.

Prognosis after a second cancer is investigated amongst survivors of colon cancer and amongst women with breast cancer **(Chapter 3.1-3.2).**

A general discussion on main findings, implications and future research is presented in **Chapter 4.**

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CHAPTER 1.2

Prevalence of multiple malignancies in the Netherlands in 2007

L. Liu, E. de Vries, M. Louwman, K. Aben, M. Janssen-Heijnen, M. Brink, J.W.W.Coebergh, I. Soerjomataram

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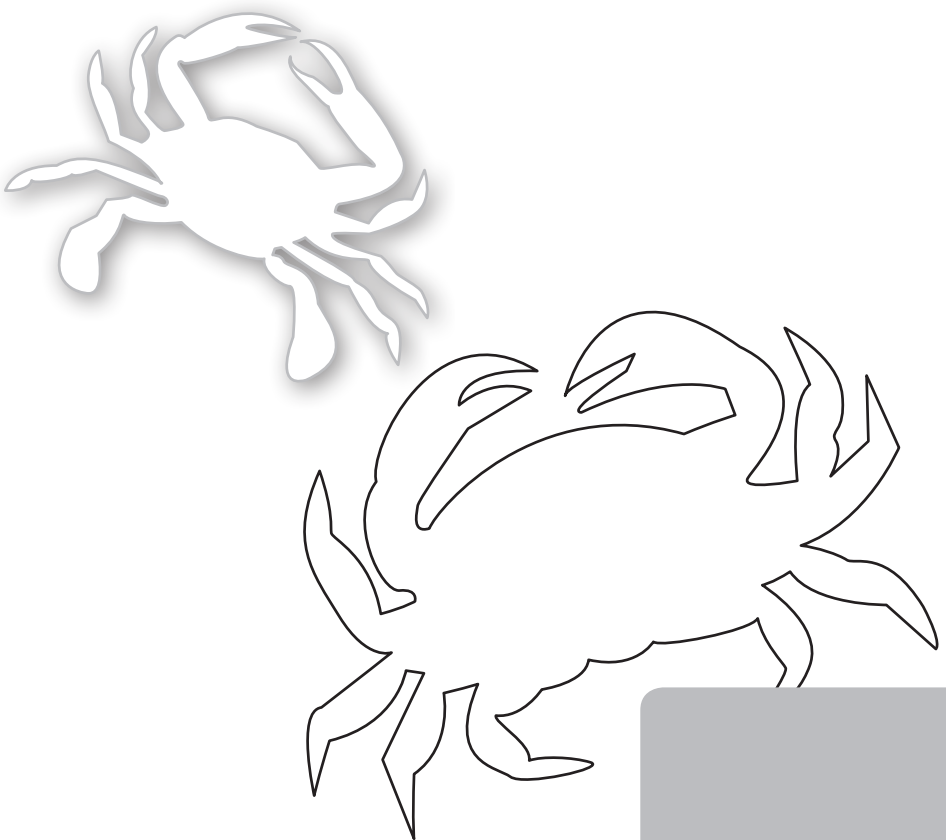

ABSTRACT

As the number of cancer survivors increases in the Netherlands, there is a concomitant increase in patients with multiple malignancies (MMs), the prevalence of which needs to be assessed to estimate care needs. This study analyzed incidence data on all malignant cancers diagnosed between 1989 and 2006 retrieved from the population-based Netherlands Cancer Registry. The point prevalence of MMs was determined on January 1 2007. Of all cancer survivors in 2007, 30,064 (7% of the total) were patients with MMs. Their median age was 74 (interquartile range 71-76) years. Ninety two percent (i.e. 27,660) of these patients had two cancer diagnoses. The most common subsequent cancers being squamous cell skin cancer (5,468), colorectal cancer (4,634) and breast cancer (3,959). High frequency of combinations included: 1) female breast and genital cancers (any order), 2) urinary tract and prostate cancers (any order), 3) Hodgkin's lymphoma and subsequent female breast cancer, and 4) non-Hodgkin's lymphoma and subsequent squamous cell skin cancer. As the number of cancer survivors continues to increase and their survival improves, MMs are becoming more important in the field of cancer surveillance.

INTRODUCTION

The number of cancer survivors is increasing due to improvements in early detection programs and treatment. In 2005 it was estimated that 400,000 people in the Netherlands had a previous cancer diagnosis which corresponds with 2.5% of the total population[1]. By 2015 the number of cancer survivors is predicted to increase by 38% to 692,000 individuals, representing 4% of the total Dutch population[2]. An additional cancer diagnosis is one of the main concerns in cancer survivors and therefore merits attention. In 2001, in the USA 8% of the prevalent cancer patients had had multiple malignancies (MMs) [3] and 1 of 6 (16%) newly diagnosed cases in 2004 had MMs[4]. The International Agency of Research on Cancer (IARC) has published a series of studies assessing the relative risk of developing second malignancies after a first cancer[5-12]. Similar studies have been performed in the Netherlands[13-17]. These sources show that cancer patients have an increased risk of developing a second cancer compared to the general population. Furthermore, compared to patients with a single malignancy, patients with MMs often exhibit a worse five-year relative survival following diagnosis of one or more secondary cancers[18, 19]. Moreover, the six aspects of quality of life (i.e. physical functioning, pain, general health perception, energy, social functioning, and role limitations due to emotional problems) have been shown to decrease significantly after a second breast cancer diagnosis[20]. Data on quality of lifeDue to the increasing number of cancer survivors, MMs will become an increasingly important topic in both cancer surveillance and epidemiology. A comprehensive description of patients with MMs would help to estimate care requirements and guide future research on MMs[21, 22].

The present study aimed to provide a comprehensive overview of the point-prevalence of MMs in the Netherlands in 2007.

MATERIAL AND METHODS

The population-based Netherlands Cancer Registry (NCR) provided incidence data on all malignant cancers, including MMs, diagnosed between 1989 and 2006. Information on vital status is updated through an annual linkage with the Dutch Municipality Register. This follow-up information is complete up since October 1994. Therefore, all patients diagnosed with a cancer before October 1994 who did not develop a subsequent cancer were censored at their last date of follow-up. If subsequent malignancies are diagnosed later, the follow-up of the patient can be reconstructed. Detailed description of NCR data can be found elsewhere[23]. The definition of multiple primaries in the Netherlands follows guidelines proposed by the international Association of Cancer Registries (IACR) and the International Agency for research on Cancer (IARC)[24]. According to these guidelines, a primary cancer is one that originates in a primary site or tissue and is thus neither an extension, nor a recurrence or a metastasis. The recognition of the existence of two or more primary cancers does not depend on time. Only one cancer can

be recognized as rising in an organ or pair of organs or tissue (as defined by the three-character category of the ICD or the topography of the ICD-O) unless the histology is different.

Definition of prevalence of multiple malignancies (MMs)

The point prevalence of cancer is defined as the proportion of people alive with cancer at a certain point in time, disregarding the moment of disease onset. We determined the point prevalence of patients with one cancer and patients with MMs on January 1 2007. Patients with MMs were defined as those with a primary invasive cancer followed by one or more additional cancers (invasive/in situ) between 1989 and 2006. These patients were classified as 'ever diagnosed patients with MMs' and were categorized into 3 groups according to the vital status: alive, deceased, and lost to follow-up (LFU). In the present study, those alive on January 1 2007 represent the prevalent cases of MMs. First primary invasive cancers were defined as first malignancies. Multiple primary cancers were defined according to international guidelines for multiple primary cancers[24]. We chose the presented first cancers based on the SEER data in the period from 1973 till 2002[25]. After a first cancer, if the 25-year cumulative incidence of the second cancers is larger than 10%, the first cancers were selected to be presented and were displayed in the following 13 anatomical sites/systems: mouth and pharynx, colorectal and anus, soft tissue, malignant melanoma of the skin, skin (squamous cell carcinoma), breast, female genital, male genital, prostate, kidney, urinary tract (renal pelvis, ureter, bladder, urethra), Hodgkin's and non-Hodgkin's lymphoma. All other first malignancies were grouped into a category 'other'. Ovarian carcinomas of borderline malignancy were excluded, as were basal cell carcinomas of the skin, which were only recorded in one regional registry[26].

Statistical analysis

Patients with MMs were described by gender, number, status on the last date of follow-up (alive, deceased and LFU), age on January 1 2007 (grouped into 6 age categories: 0-39, 40-49, 50-59, 60-69, 70-79, 80+) years and cancer types. Also calculated were: age at diagnosis of the first and subsequent cancers, and time intervals between cancer diagnoses. Age at each cancer diagnosis and time interval between diagnoses were presented as median and interquartile range (IQR). In addition, we calculated the proportion of survivors according to the number of cancer diagnoses (1, 2, 3 and 4 or more) and the period from the last diagnosis until the end of the study (<1 year, 1-2 years, 3-4 years and ≥5 years). Patients with MMs were grouped by site of first cancer. Statistical analyses were performed using SAS 9.0.

RESULTS

Between 1989 and 2006, a total of 1,351,621 individuals in the Netherlands were diagnosed with cancer (data not shown), 85,676 (6%) of whom were patients with MMs. In 2007, 424,340 of these patients were still alive, 7% (30,064) included patients with MMs. Ninety two percent of these patients (n = 27,660) had two cancers. Of all patients with multiple cancers diagnosed between 1989 and 2006, 58% (49,335) had died and 7% (6,277 patients) were LFU. Median age at first cancer diagnosis was 65 years (IQR: 62-67 years) and the median age on January 1 2007 was 74 years (IQR: 71-76 years). The period between two consecutive diagnoses ranged from 0.5 to 3 years (median, 1 year). As the number of cancers diagnosed per patient increased, the time interval between the diagnoses decreased (**Table 1**).

In 2007 there were no surviving patients with more than 5 cancer diagnoses. Men were more often diagnosed with MMs than women (8% vs. 6%, respectively). Most of the prevalent patients with MMs (42%, increasing from 25-30% for the 2nd cancer and 51-65% for the fourth or following cancers) were diagnosed within one year of their last cancer diagnosis (**Table 2**).

Table 1 Characteristics of patients with multiple malignancies among all those diagnosed with cancer in the period 1989-2006 in the Netherlands

	Male	Female	Total
Patients with multiple malignancies (MMs)			
No. of ever-diagnosed with MMs	51,009	34,667	85,676
No. of patients with MMs lost to follow-up	3,986 (8%)	2,291(7%)	6,277 (7%)
No. of patients with MMs who died before January 1 2007	31,824 (62%)	17,511(51%)	49,335 (58%)
No. of patients with MMs alive on January 1 2007(%)	15,199 (30%)	14,865 (43%)	30,064 (35%)
Survivors with MMs on January 1 2007			
Median age (years) (IQR)[1]			
at diagnosis of first cancer	67 (62;70)	62 (59;65)	65 (62;67)
at diagnosis of second cancer	71 (67;74)	67 (65;75)	70 (66;74)
at diagnosis of third cancer	73 (70;77)	71 (66;75)	72 (67;78)
at diagnosis of fourth cancer	73 (71;76)	71(68;76)	72 (68;75)
on January 1 2007	75 (72;80)	71 (66;78)	74 (71;76)
Median interval (years) (IQR)[1]			
Between first and the second diagnosis	3 (1;5)	3 (1;6)	3 (1;5)
Between second and the third diagnosis	1 (2;5)	2 (1;6)	2 (1;6)
Between third and the fourth diagnosis	1 (0;3)	1 (0;2)	1 (0;2)
Between fourth and the fifth diagnosis	0.5 (0;3)	0.5 (0;2)	0.5 (0;3)
Between first diagnosis and January 1 2007	7 (4;10)	8 (5;11)	8 (5;11)
Between last diagnosis and January 1 2007	2 (1;3)	2 (1;4)	2 (1;3)

[1]Interquartile range

Note: due to rounding off the total percentage may exceed 100%

Table 2 Overview of cancer survivors in the Netherlands diagnosed in the period 1989-2006 on January 1 2007

Period after the last diagnosis	<1 year	1-2 years	3-4 years	≥5 years	Total	% of cancer survivors
Number of cancers						
1						
Male	52,091 (30%)	35,345 (21%)	24,898 (15%)	59,263 (35%)	171,597 (100%)	93
Female	54,873 (25%)	41,247 (19%)	33,623 (15%)	92,936 (42%)	222,679 (100%)	
2						
Male	6,090 (44%)	3,095 (22%)	1,852 (13%)	2,753 (20%)	13,790 (100%)	6.5
Female	5,235 (38%)	3,059 (22%)	2,010 (14%)	3,566 (26%)	13,870 (100%)	
3						
Male	633 (50%)	262 (21%)	167 (13%)	173 (14%)	1,265(100%)	0.5
Female	445 (49%)	218 (24%)	104 (11%)	150 (16%)	917(100%)	
≥4						
Male	94 (65%)	28 (19%)	10 (7%)	12 (8%)	144(100%)	0.05
Female	40 (51%)	18 (23%)	9 (12%)	11 (14%)	78(100%)	
Total number of survivors with multiple malignancies						
Male	6,847 (45%)	3,385 (22%)	2,029 (13%)	2,938 (19%)	15,199(100%)	
Female	5,720 (38%)	3,295 (22%)	2,123 (14%)	3,727 (25%)	14,865(100%)	7
Total	**12,567 (42%)**	**6,680 (22%)**	**4,152 (14%)**	**6,665 (22%)**	**30,064**(100%)	
Total number of cancer survivors on January 1 2007						
	119,531 (28%)	**83,272 (20%)**	**62,673 (15%)**	**158,864 (37%)**	**424,340**(100%)	

Note: due to rounding off the total percentage may exceed 100%

MMs were most commonly observed among elderly patients (median 74 years), but MMs prevalence decreased among people aged 80 years or older. Less than 1% (274/30,064) of the MMs patients were younger than age 39 years (data not shown).

The youngest patients with MMs were survivors of Hodgkin's lymphoma (median age In 2007 55 years) and those with a first male genital cancer (97% testicular cancer; median age on January 1 2007 62 years) (**Table 3**). **Table 3** gives an overview of the distribution of subsequent cancers according to the type of the first and subsequent cancers. The shortest time interval between the first and second cancer was observed among survivors with a first urinary tract cancer (1 year), the longest time interval was found for those with Hodgkin's disease survivors (6 years). Overall, in 2007 the patients with MMs had lived with cancer (from the first diagnosis onwards) for 8 years (median), ranging from a median of 6 years for prostate cancer patients to a median of 11 years for survivors of Hodgkin's disease. The lowest proportion of subsequent cancers was found among first male genital cancers, being only 3%. The highest proportions were observed for urinary tract cancer (15%), mouth and pharynx cancer (12%), squamous cell carcinoma of the skin (10%) and colorectal cancer (9%).

In absolute terms, multiple cancers were most frequent among survivors of female breast cancer (n=5,774), colorectal (n=5,169) and prostate cancer (n=3,862).The most frequent combinations

Table 3 Prevalence of multiple malignancies by sites of first cancer diagnosed in the period 1989-2006 in the Netherlands on January 1 2007

	First cancer													
	Mouth and Pharynx	Colorectal	Soft tissues	Skin, melanoma	Skin, squamous skin cancer	Breast	Female Genital	Male Genital	Prostate	Kidney	Urinary system (renal pelvis, urinary bladder urethra)	Hodgkin's lymphoma	Non-Hodgkin's lymphoma	Other5
Total first cancer	15,227	55,879	3,734	27,304	28,104	107,037	28,354	8,446	54,139	8,762	12,331	4,146	14,075	56,802
First cancer only	13,463	51,114	3,492	25,477	25,319	101,589	26,155	8,230	50,570	7,994	10,435	3,968	13,090	53,380
Multiple tumors														
No. of the first cancer which developed Mms (%)[1]	1,764 (12%)	4,765 (9%)	242 (6%)	1, 827 (7%)	2,785 (10%)	5,448 (5%)	2,99 (8%)	216 (3%)	3,569 (7%)	768 (9%)	1, 869 (15%)	178 (4%)	985 (7%)	3,422 (6%)
No. of the subsequent tumours	2,042	5,169	266	2,009	3,090	5,774	2,337	227	3,862	844	2,074	198	1,092	3,708
Median follow-up duration (years)														
From the first diagnosis to January 1 2007	8	7	9	9	8	9	9	9	6	8	7	11	8	7
From the first diagnosis to the second one	3	2	4	4	3	4	3	4	2	3	1	6	4	3
Age on Jan 1 2007 (years, median)	68yrs	69 yrs	74 yrs	63 yrs	75 yrs	65 yrs	67 yrs	62 yrs	75 yrs	75 yrs	76 yrs	55 yrs	70 yrs	72 yrs
Distribution of subsequent tumors														
Mouth and pharynx	**24%**	2%	2%	2%	6%	2%	1%	1%	4%	2%	2%	4%	3%	4%
Upper GI[2]	3%	3%	4%	1%	2%	2%	1%	2%	3%	2%	2%	2%	3%	3%
Colorectal	8%	**21%**	12%	9%	11%	15%	12%	11%	20%	14%	9%	7%	13%	13%
Liver, gallbladder, biliary tract, pancreas, other	0%	1%	1%	1%	0%	1%	1%	1%	1%	2%	0%	1%	1%	1%
Lung, bronchus, and trachea, mesothelioma	15%	5%	8%	3%	4%	5%	4%	5%	8%	7%	7%	10%	6%	8%
Soft tissue	0%	1%	**2%**	1%	1%	1%	1%	1%	1%	0%	0%	6%	1%	1%
Skin, melanoma	2%	3%	8%	**14%**	8%	8%	4%	5%	5%	4%	2%	8%	5%	4%
Skin, squamous cell carcinoma	17%	14%	12%	**24%**	**27%**	15%	8%	13%	19%	8%	8%	14%	**27%**	**18%**
Breast	6%	12%	**14%**	18%	8%	**18%**	**34%**	n.a.	n.a.	11%	3%	**15%**	10%	12%
Female genital	1%	4%	3%	4%	2%	16%	**19%**	n.a.	n.a.	3%	1%	2%	3%	3%
Male genital[3]	1%	2%	0%	2%	2%	n.a.	n.a.	**3%**	3%	2%	1%	0%	0%	1%
Prostate	10%	15%	**14%**	10%	13%	n.a.	n,a.	**30%**	**1%**	**23%**	**30%**	6%	10%	13%
Kidney	0%	0%	2%	0%	0%	0%	0%	0%	1%	**0%**	9%	4%	3%	4%
Renal pelvis, urinary bladder, urethra	8%	12%	8%	6%	8%	6%	6%	15%	**27%**	11%	**23%**	5%	6%	7%
Endocrine glands	1%	0%	1%	1%	0%	1%	0%	2%	0%	1%	0%	3%	1%	1%
Hematolymphopoetic	2%	5%	6%	5%	5%	6%	4%	11%	8%	7%	3%	**16%**	**5%**	5%
Other[4]	1%	2%	5%	3%	2%	4%	5%	4%	2%	3%	1%	1%	3%	3%

Table 3 continued

[1] The percentage from the total first malignancies [2] Upper GI includes: esophagus, stomach, small intestine [3] Male genital: testis, penis and other male genital organs [4] Other: includes: carcinoid, appendix, eye & adnexa, thymoma, thymus, Central Nervous System (CNS) [5] Other includes: esophagus, stomach, small intestine, liver, gallbladder,biliary tract, pancreas, lung, bronchus, and trachea, mesothelioma, bone and joint, Kaposi sarcoma, skin other, brain & other CNS tumors, endocrine glands, other hematolymphopoetic malignancies, thymus, eye and adnexa, base of tongue Note: bold numbers are either the highest percentage among all subsequent tumours or share of subsequent tumours at the same site or tract as the first cancers

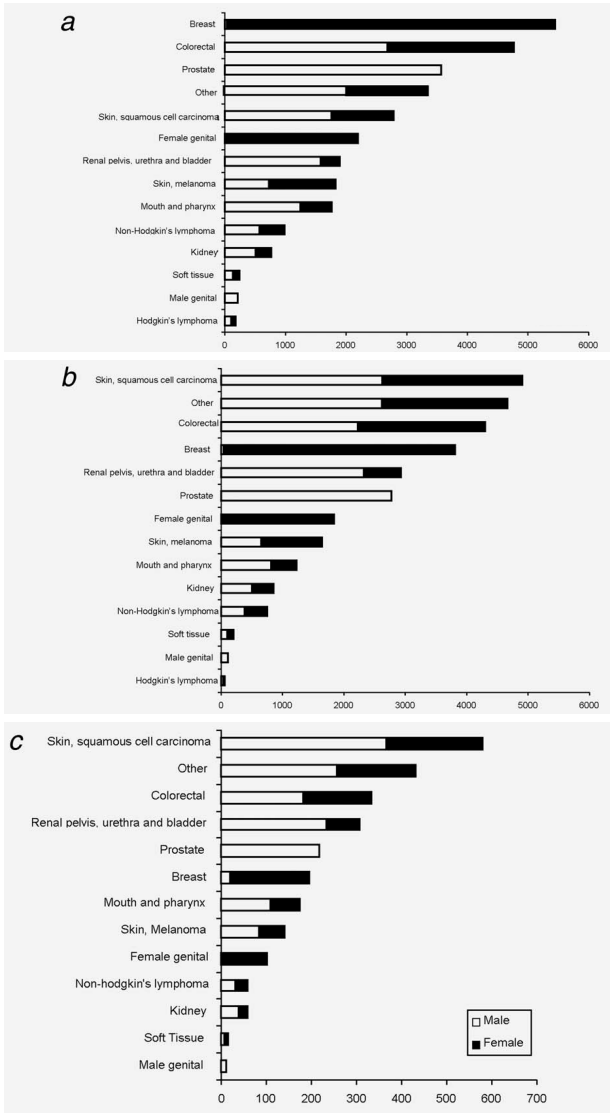

Figure 1. (*a*) Frequency rank of first cancers among patients with multiple malignancies, alive on January 1 2007, (*b*) Frequency rank of second cancers among patients with multiple malignancies, alive on January 1 2007 and (*c*) frequency rank of third and higher order cancers among patients with multiple malignancies, alive on January 1 2007.

Source: Netherlands Cancer Registry

between first and subsequent cancers were as follows 1) breast and female genital cancers (any order), 2) urinary tract and prostate cancers (any order), 3) Hodgkin's lymphoma and subsequent breast cancer, 4) non-Hodgkin's lymphoma and subsequent squamous cell skin cancer.

The frequency ranks of the first, second, third, fourth and higher-order cancers are shown in **Figures 1**A-C. The most commonly occurring second cancers were squamous cell cancer of the skin (n=5,468), colorectal cancers (n=4,634), and breast cancers (n=3,959). Higher order cancers (≥ 3) were most frequently found for cancers of the skin (squamous cell skin cancer, n=579), colon and rectum (n=333), and urinary tract (n=308).

DISCUSSION

This study assessed the burden of MMs in terms of prevalence within the Dutch population, of which the average incidence of cancer was 404 (per 100,000) from 1989-2006[23] and exhibited a 5-year crude survival of 60% in the period 2003-2007[27]. The prevalence of MMs included current survivors with at least one subsequent cancer diagnosis after a first invasive cancer within the observation period from 1989 to 2006. With a median follow-up time of 8 years, 30,064 patients were diagnosed with MMs, representing 7% of all cancer survivors on January 1 2007 in the Netherlands. A previous study in the USA reported 8% of cancer survivors had MMs in 2002[3].

The most common subsequent cancers were cancers of the skin (squamous cell skin cancer), colorectal cancer and female breast cancer. The prevalence of subsequent cancers is influenced by the age at first diagnosis, incidence and survival of the first and subsequent cancers, and the maximum and median length of follow-up time (e.g. history of cancer registry). The three most common subsequent cancers mentioned above are those with high incidence and a relatively good prognosis (5-year relative survival >50%) in the Netherlands[28]. Although lung cancer is one of the most common cancers and shares its main risk factor (smoking) with many other cancers, it contributes little to the prevalence of MMs because of its poor prognosis (5-year survival ~10%)[29].

The current population with MMs was composed mainly of elderly subjects (median age,74 years). The average age at diagnosis of first cancer was 65 years. The treatment of second or higher order cancers is complex due to old age and co-morbidity and might need to be tailored individually[30, 31]. The youngest patients with MMs had Hodgkin's lymphoma (55 years) and male genital cancer (62 years) as a first primary. Their young age at first cancer diagnosis (40-50 years) combined with the good prognosis (10-year relative survival is 75-95%) led to a long life expectancy after first diagnosis[28]. However, the risk of developing a subsequent cancer was 1.4 to 3.0 times higher compared to the general population[32-34]. It is plausible that prevention by means of lifestyle changes (such as quitting smoking) might decrease this group's risk of a second cancer and other chronic diseases[35]. However, the benefit and harm of intervention programs (for either primary or secondary prevention) remain to be investigated[17].

We observed four pairs of cancers that frequently occur together. It should be noted that this observed association on prevalence should not be simply interpreted as a result of shared risk factors, which is normally interpreted in the incidence data. Cancer prevalence is an interaction of various factors such as risk of getting cancer (incidence), risk of dying from cancer (mortality) and duration of time lived with cancer (survival) and many more. Therefore, the etiological link between the first and subsequent merits attention, but should be considered only one of the multitude of factors which determine the prevalence of MMs and, more particularly, the prevalence of specific combinations of multiple cancers. There are etiological theories concerning the development of subsequent cancers: 1) specific treatment effects[6, 9]; 2) shared risk factors between first and subsequent cancers (lifestyle or environmental factors[12, 36]); 3) shared genetic predisposition; and, 4) combinations of the above three[5, 10, 37]. Adverse effects of treatment (i.e. radiotherapy) may explain the high prevalence of breast cancer among Hodgkin's lymphoma survivors[38-40]. Although second lung cancer is also associated with radiotherapy[35] , the poor prognosis of lung cancer contributed to its low proportion of multiple cancers in this cancer type. Shared risk factors, e.g. hormonal risk factors such as nulliparity, obesity, and hormone-replacement therapy, probably relates breast cancer to female genital cancers[41, 42]. Moreover, carriers of BRCAI/II may contribute 2-5% in developing breast and ovarian cancers, especially among younger patients[43]. As to the last theory, the combination of the previous three factors, has hardly been studied and is difficult to explain with our data. In addition to the above general theories, disease or treatment-induced immunosuppression may explain the high frequency of squamous cell skin cancer after non-Hodgkin's lymphoma[44].

Finally and importantly, enhanced early detection programs (e.g. clinical follow-up and screening programs) may explain some of the high frequency cancer pairs, especially when the time interval between the first and the second cancer diagnosis is short; for instance, in case of prostate and urinary tract (usually bladder) cancer, the short interval between the first and the second cancer diagnosis (≈1 year) may reflect the common diagnostic process of these two cancers[45].

Recent Dutch studies of long-term survivors of breast, Hodgkin's and non-Hodgkin's lymphoma, prostate and endometrial cancer showed that disease progression (recurrence, metastasis and detection of other primary cancers) negatively affects health status and quality of life[20, 46]. Since data on quality of life among MMs patients is scarce, more studies are needed before designing interventions to improve the quality of life in this population.

To our knowledge, this is the first population-based, nation-wide report on the prevalence of MMs that includes all cancer types (excluding basal cell carcinomas of the skin). This ensures the representativeness and validity of the prevalence estimates.

Concerning the accuracy and completeness of cancer diagnoses in the NCR; most cases were histologically confirmed cancers retrieved from the nation-wide pathology network (PALGA) and therefore a high accuracy of cancer diagnosis may be expected. Furthermore, the National Registry of Hospital Discharge Diagnosis system collected data on patients who were only diagnosed clinically, which increases the completeness of the NCR data. Finally, the

application of IARC/IACR rules for multiple primary cancers[24] facilitates external comparison of the study results, as long as the same coding rules are applied.

The main limitation of the current prevalence data is the probable underestimation of MMs cases. First, 18 years of follow-up does not yield the lifetime prevalence but represents about 90% of the full estimate[47]. Second, 7% of ever diagnosed multiple cancer patients were lost to follow-up, which may have led to an underestimate of prevalence. Third, we were unable to include the most common cancer: basal cell carcinoma. Although this is the case in most registries, if this cancer had been taken into account, higher MMs prevalence values would have emerged. Finally, the coding rules that were used to record multiple primaries should be taken into consideration when making cross-countries comparisons. For example, in USA, the Surveillance, Epidemiology, and End Results (SEER) use different rules than those defined by IACR/IARC[48]. Differences between the coding guidelines include: the existence of two or more primary cancers do not depend on time in the IACR/IARC guidelines, however, only metachronous cancers (occurring 2 or more months after initial diagnosis) are recorded as separate primaries in the SEER guidelines; furthermore, regarding cancers originating from paired organs (e.g. ovary, Wilm's cancer, Retinoblasma), SEER guidelines treat them as independent, whereas, the IACR/IARC guidelines regard them as one single cancer unless a histological difference exists. In general, the IACR/IARC guidelines are more restrictive than those applied by SEER. Moreover, there are unresolved debates regarding coding of multiple primaries[49]. However, it is yet to be investigated how such coding differences affect differences in recorded prevalence.

In conclusion, in 2007, 30,064 patients were alive with multiple malignancies, representing 7% of all cancer survivors and 0.2% of the total Dutch population. The estimate is subject to a possible 10-15% of underestimation. As the number of cancer survivors continues to increase by 3-5% annually and prognosis improves with each year survived[50], MMs are becoming more important in the field of cancer surveillance.

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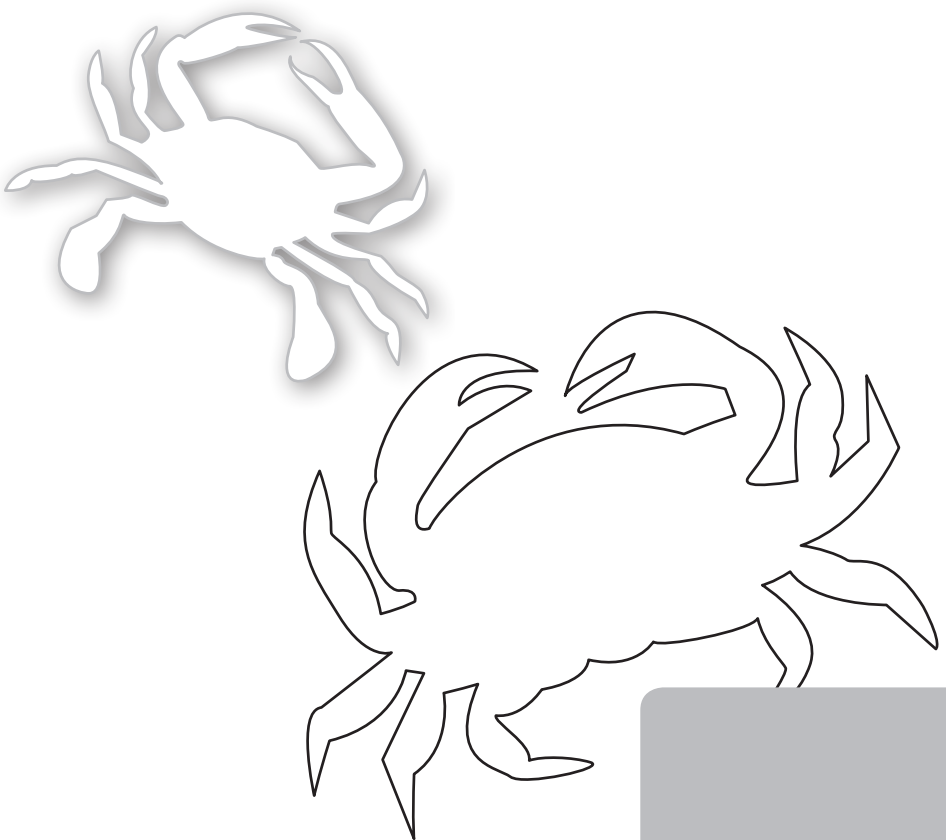
CHAPTER 2

Risk patterns of second primary cancers



CHAPTER 2.1

Second primary cancers in proximal-colon, distal-colon, and rectum among patients with a prior colorectal cancer

L. Liu, V.E. P. P. Lemmens, I. H.J. T. De Hingh, E. de Vries, J. A. Roukema, M. van Leerdam, J.W.W. Coebergh, I. Soerjomataram

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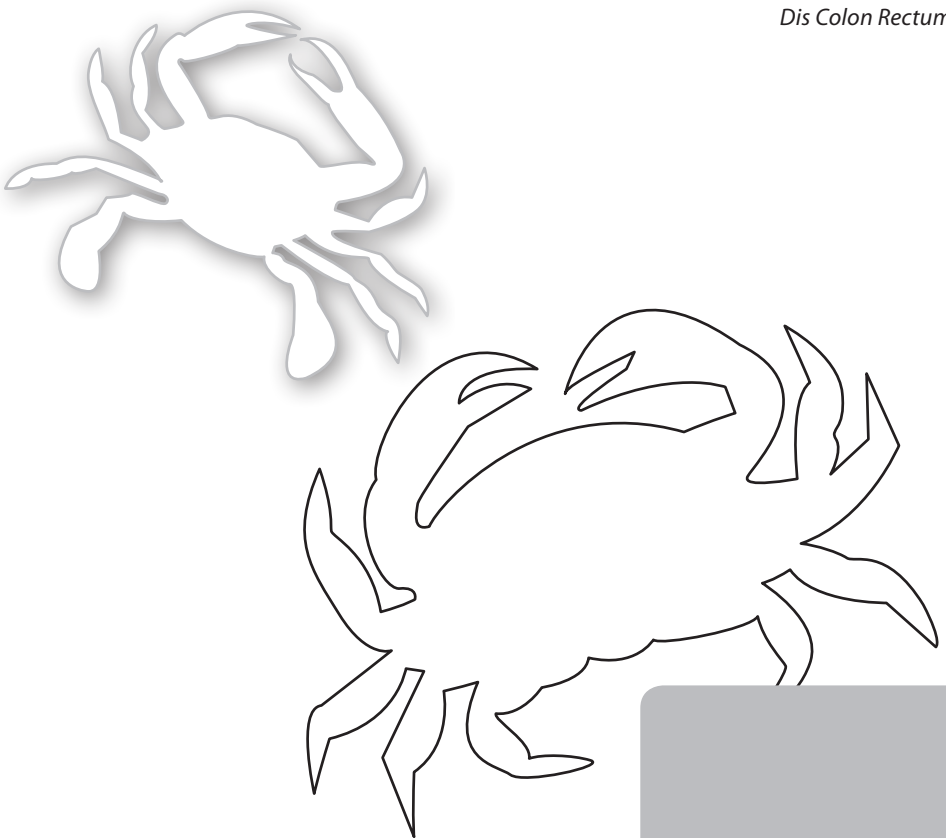


ABSTRACT

Background: Colorectal cancer patients are at higher risk for a second colorectal cancer. Yet detailed risk analysis by sub sites is scarce.

Objective: To describe the risk for second cancers by sub sites among colorectal cancer patients to underpin surveillance strategies.
DESIGN: prospective cohort from population-based cancer registry

Patients: Patients with a stage I-III colorectal cancer (N=123,347) from the Netherlands Cancer Registry were included.

Main outcome measures: Cumulative incidence, standardized incidence ratio, and absolute excess risk for second primary cancers in sub sites of colon and rectum at 2-5, 6-10, and >10 years after the index cancer were estimated.

Results: The 20 -year cumulative incidence for second cancers in proximal-colon, distal-colon, and rectum, was 3.5%, 1.2%, and 1.2 %, respectively. More than 60% of second cancers occurred within 5 years after the index cancer. Among patients older than 50 years the standardized incidence ratio was the highest in the proximal-colon (1.9 (95%CI: 1.8 -2.0)), followed by 1.0 (95%CI: 0.9-1.1) in the distal-colon, and 0.9 (95%CI: 0.8 -1.0) in rectum. The corresponding absolute excess risks were 9, 0.1, and -1 per 10,000 person years. After 5 years of follow-up, elevated risk was only observed in proximal-colon. Among patients younger than 50 years, similar risk pattern was observed. In addition, the absolute excess risk for a second cancer in proximal-colon increased over follow-up time. Stage distribution of the second proximal-colon cancers worsened with longer follow-up.

Limitations: lack of data on polypectomy rates and interval of surveillance colonoscopies.

Conclusions: Individuals with a prior colorectal cancer are at a higher risk for a second cancer in all sub sites of colon and rectum compared to general population. Among long-term survivors, risk remains elevated in proximal-colon. Further investigations are encouraged in finding a suiTable surveillance modality for these aged, high-risk long-term survivors.

Key words: Colon-ascending; Colorectal Neoplasms; Second Primary

INTRODUCTION

Colorectal cancer (CRC) is an important public health challenge because of its rising incidence, the plans for mass screening in Europe, and its increasing survival. In the western world, CRC is the second and third most common cancers among men and women, and the second leading cause of cancer death for both sexes[1]. The marked improving survival generates a higher chance of developing a second lesion among CRC survivors in the past decades[2-4]. In the Netherlands, CRC is one of the most prevalent second cancers among cancer survivors(~9% in 2007)[5].

Individuals with a prior CRC are at higher risk for a second cancer in colon and rectum compared to the general population[6-7]. Therefore post-resection surveillance is crucial to detect second lesions at an early stage. Studies showed that metachronous cancers that are detected during colonoscopic surveillance are diagnosed at earlier stages compared to index tumors, with high rates of potentially curative resection, and there is evidence that Intensive follow-up after curative intent surgery for CRC improves survival[8-10]. Dutch patients with CRC treated with curative intent are routinely followed until 5 years[11]. Yet the risk pattern of second CRC has rarely been studied by follow-up periods especially beyond this period and by sub sites.

This study analyzes risk for second primary cancers in proximal-colon, distal-colon, and rectum among individuals with a prior CRC diagnosis with a maximum follow-up of 20 years in order to underpin surveillance strategies.

MATERIAL AND METHODS

Data and patient selection

We used population-based data from the nationwide Netherlands Cancer Registry (NCR). Data registration started in 1989 and is maintained and hosted by the Comprehensive Cancer Centers[12]. The NCR is based on notification of all newly diagnosed malignancies in the Netherlands by the automated pathological archive (PALGA). An additional sources of patient identification is the national registry of hospital discharge diagnoses, which accounts for up to 8% of new cases[12]. Information on patient characteristics - such as gender and date of birth -as well as tumor characteristics - such as date of diagnosis, sub site (International Classification of Diseases for Oncology (ICD-O-3)[13]), histology, stage (Tumor Lymph Node Metastasis (TNM) classification[14]) and grade - are obtained routinely from the medical records at about 6-9 months after diagnosis. The quality of the data is high, due to thorough training of the registrars and computerized consistency checks at regional and national levels. Completeness is estimated to be at least 95%[15]. In addition to passive follow-up via hospitals, date of death is also retrieved from the Municipal Personal Records Database that contains all deaths

or emigrations in the Netherlands since October 1994. For patients diagnosed before October 1994, follow-up was completed through NCR by merging the database with municipality death records or with the Central Bureau for Genealogy, which registers all deaths in the Netherlands.

We included new stage I-III CRC case (N=123,347) diagnosed between1989-2008. Second CRCs diagnosed within 1st year after the initial cancer were excluded (N=1,441). Its frequency was presented as appendix.

Sub site of colon and rectum

Anatomical sites of CRC at diagnosis were registered according to the International Classification of Disease-Oncology (ICD-O). Sub sites of CRC is defined as proximal-colon, from caecum to splenic flexure (ICD-O C18.0 to C18.5); distal-colon, from descending colon to sigmoid colon plus other colon and NOS (ICD-O from C18.6-C18.8-9), and rectum,(including recto-sigmoid and rectum (ICD-O C19, C20).

Definition of second cancers in colon and rectum

A second primary cancer must be in a different segment than the primary cancer irrespective of time differences between the diagnoses of the two cancers. Cancers in the same segment of the colon and rectum are regarded as the same malignancy, and are counted as one primary cancer[13].

Statistical analysis

Due to possibly high rate of hereditary syndromes, patients younger than 50 years at initial cancer diagnosis were analyzed separately (N=8,886)[18].

We computed the cumulative incidence (CI) of second primary cancers in the proximal-colon, distal-colon, and rectum in the observing period of 20 years, treating other second cancers as competing risks[16].

The standardized incidence ratio (SIR) expresses the excess incidence of a second CRC among patients with a first CRC relative to the background incidence among the general population, that is the ratio between observed and expected number of patients with second primary CRC.

The absolute excess risk (AER) expresses additional incidence beyond the background incidence in the general population. The AER is defined as the difference between the observed and the expected number of patients with second primary CRC, divided by number of person years at risk, usually expressed per 10,000.

To compute the expected numbers, person years at risk for each of the sex-, age- (5-year band), and calendar year-specific (1-year band) strata were multiplied by the corresponding incidence rate in the general population and then summed across strata[17]. Person years at risk in each cohort was calculated by summing individual follow-up times at the date of first

cancer diagnosis until the occurrence of the second CRC, of other second cancer, end of study (December 31 2008), or death, whichever came first. In our study, the maximum individual follow-up time was therefore 20 years and the minimum follow-up time was one day.

SIR and AER of second primary cancers in proximal-colon, distal-colon, and rectum are presented according to follow-up periods (2-5, 6-10, and >10 years) as well as sub sites of first cancer (proximal-colon, distal-colon, and rectum).

We used Poisson regression to compute 95% confidence intervals (95%CI). All statistical analysis was performed in SAS system 9.1, SAS Institute, Cary, NC.

Sensitivity test

Almost every patient with stage I-III CRC will undergo resection[3]. Therefore, a certain length of the colon and rectum will be removed because of the treatment of the first cancer. It would not be surprising to detect less second primary cancers on a smaller compared to on a larger surface, resulting in an underestimation for SIR and AER. Therefore, we recalculated SIR and AER also by sub sites for remaining surface area after surgery. The surface area-adjusted SIR and AER are the excess risks to develop a second primary cancer on each 100 cm^2 of colon and rectum among individuals with a prior CRC compared to their general population controls.

Surface area-adjusted expected numbers according to sub sites are the original expected numbers divided by the surface area estimates for each site and expressed per 100 cm^2. We applied surface area estimates of 1,321 cm^2 (length=67cm), 735 cm^2 (length=63 cm), and 110 cm^2 (length=14cm) for proximal-colon, distal-colon, and rectum, respectively[19].

To calculate surface area-adjusted observed numbers, we assumed that on average 17cm (15-20cm) of colon (either proximal or distal) and 9 cm of rectum are excised through surgery. Hence, for patients with a first proximal-colon cancer, ((67-17cm)/67cm)*1,321cm^2=986 cm^2 of the proximal-colon is on average left after surgery where a second cancer can develop. Likewise for patients with a first distal-colon cancer, ((63-17cm)/63cm)*735cm^2=537 cm^2 of distal-colon is left, and for patients with a prior rectal cancer the post-surgery surface is ((14-9cm)/14cm)*110cm^2=39 cm^2. The average surface area among post-surgery CRC patients is expressed by following formula, taking first cancer was diagnosed in proximal-colon as an example: (986 cm^2 * number of patients with proximal-colon cancer+1,321 cm^2 * number of patients with CRC located in distal-colon or rectum)/total number of patients. Likewise, average surface area in distal-colon and rectum were produced. Finally we calculated the surface area-adjusted observed number divided by the average surface area calculated above and expressed per 100 cm^2.

RESULTS

Of the 123,347patients with a first invasive CRC, 1.5% (1,849) developed a second primary CRC one year after the initial cancer. Among them, 1,730 patients were over 50 years of age at first cancer diagnosis, whereas 119 patients were diagnosed before 50 years. Compared with the first CRC, second primary CRCs were more often located in the proximal-colon (55% vs. 34 %). On average patients developed a second CRC 3 years after the first cancer. There was higher proportion of stage I cancers among second cancers compared to those first lesions (28% vs. 24%). The median diagnosis interval between two CRCs was 44 months (IQR: 24-83 months) (**Table 1**&2).

Table 1 Characteristics of patients with a first and second colorectal cancer (CRC) in the Netherlands in 1989-2008

	First CRC (N=123,347)		Second CRC[1] (N=1,849)	
Sex	**Men**	**Women**	**Men**	**Women**
Total Number	62,746 (51%)	60,601 (49%)	920 (53%)	929 (47%)
Location				
Proximal -colon	18,830 (30%)	24,428 (40%)	489 (53%)	525 (57%)
Distal -colon	18,803 (30%)	17,240 (29%)	213 ,(23%)	215 (23%)
Rectum	25,113 (40%)	18,933 (31%)	218 (24%)	189 (20%)
Age at diagnosis (years)				
Median (years, IQR[2])	69 (61-76)	72 (63-79)	73 (66-80)	77 (69-82)
≤50 years	4,631 (7%)	4,255 (7%)	36 (4%)	28 (3%)
51-60 years	10,776 (17%)	8,536 (14%)	99 (11%)	65 (7%)
61-70 years	19,445 (31%)	14,729 (24%)	238 (26%)	178 (19%)
71-80 years	20,306 (32%)	20,196 (33%)	343 (37%)	357 (38%)
80+years	7,588 (12%)	12,885 (21%)	204 (22%)	301 (32%)
TNM Stage				
I	16,048 (26%)	14,147 (23%)	271 (29%)	247 (27%)
II	26,260 (42%)	26,082 (43%)	285 (31%)	315 (34%)
III	20,438 (32%)	20 ,372 (34%)	174 (19%)	185 (20%)
IV	n.a.	n.a.	124 (14%)	106 (11%)
Unknown	n.a.	n.a.	46 (7%)	76 (8%)
Follow up periods				
2-5 years	n.a.	n.a.	592 (64%)	560 (60%)
6-10 years	n.a.	n.a.	215 (23%)	259 (28%)
>10 years	n.a.	n.a.	113 (12%)	110 (12%)

Source: Netherlands Cancer Registry

[1] Total person years at risk: 582,648,

[2] IQR: interquartile range

n.a.: not applicable

Table 2 Diagnosis interval (median in months, (interquartile range)) between the first and the second primary colorectal cancer (CRC) (N=1,849)

	First CRC in					
	Proximal -colon		Distal -colon		Rectum	
Second CRC in	Men	Women	Men	Women	Men	Women
Proximal -colon	56 (29-99)	51 (29-89)	45 (22-86)	59 (29-102)	50 (27-94)	62 (30-110)
Distal -colon	37 (20-67)	33 (19-58)	42 (21-81)	40 (29-82)	41 (26-60)	32 (22-67)
Rectum	37 (22-72)	42 (24-73)	41 (21-59)	31 (19-72)	30 (20-44)	42 (19-62)

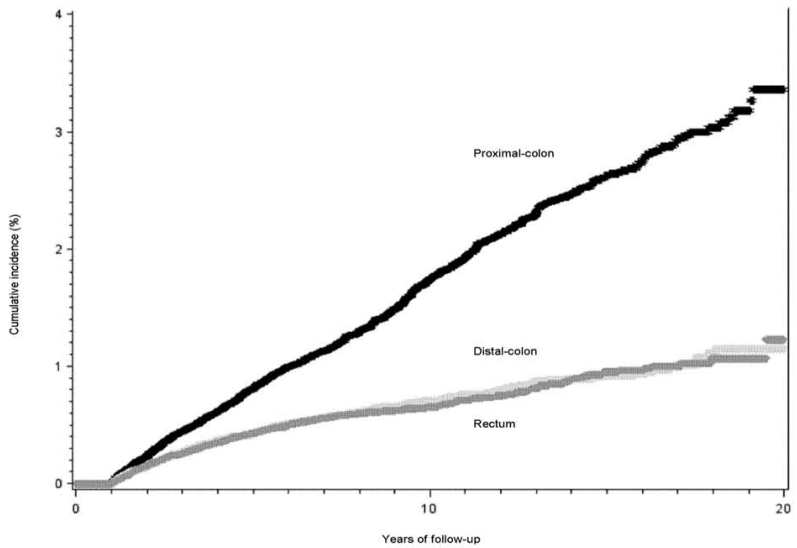
Source: Netherlands Cancer Registry

Patients older than 50 years

The 20 -year cumulative incidence for second cancers in proximal-colon, distal-colon, and rectum, was 3.4%, 1.2%, and 1.2 %, respectively (**Figure 1**.a).

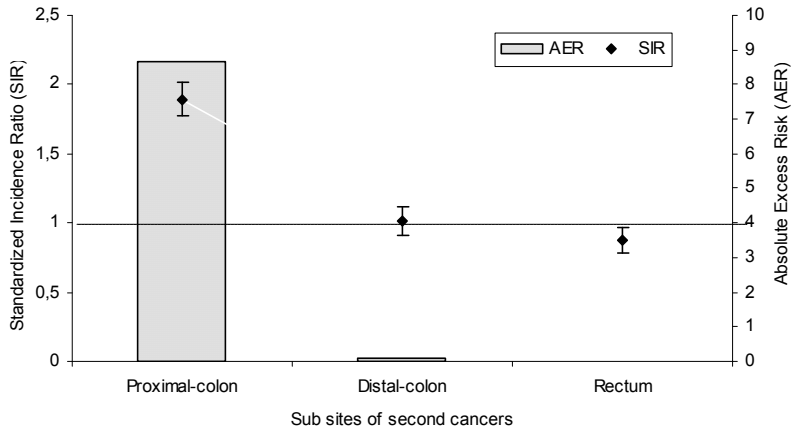
The standardized incidence ratio (SIR) was the highest with 1.9 (95%CI: 1.8 -2.0) in the proximal-colon, followed by 1.0 (95%CI: 0.9-1.1) in the distal-colon, and 0.9 (95%CI: 0.8 -1.0) in the rectum. The corresponding absolute excess risks (AER) were 9, 0.1, and -1 per 10,000 person years (**Figure 2.1**.a.).

The highest SIR and AER for a second cancer were observed in proximal-colon following a first cancer in distal-colon (SIR=2.6; 95%CI: 2.2 -2.8 AER=13.4 per 10,000 person years) (**Figure2.1**.b.).



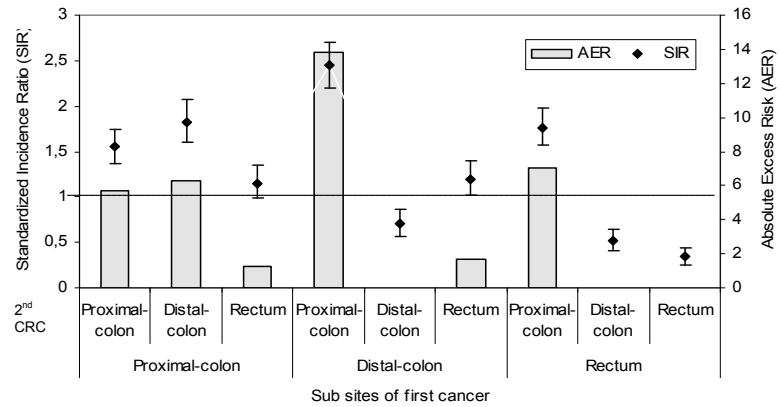
Source: Netherlands Cancer Registry

Figure1 a. Cumulative incidence (20-year) of second cancers in proximal-colon, distal–colon, and rectum among patients > 50 years of age (N=1,730)



Source: Netherlands Cancer Registry

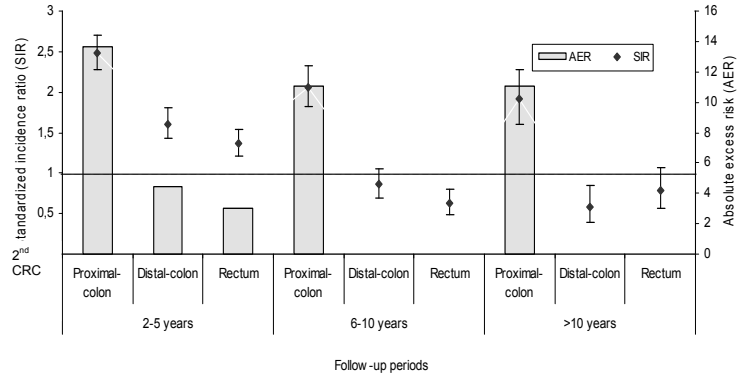
Figure 2.1 a. Standardized incidence ratio (SIR) and absolute excess risk (AER, per 10,000 person years) of second primary cancers in proximal- colon, distal–colon, and rectum among patients > 50 years of age (N=1,730)



Source: Netherlands Cancer Registry

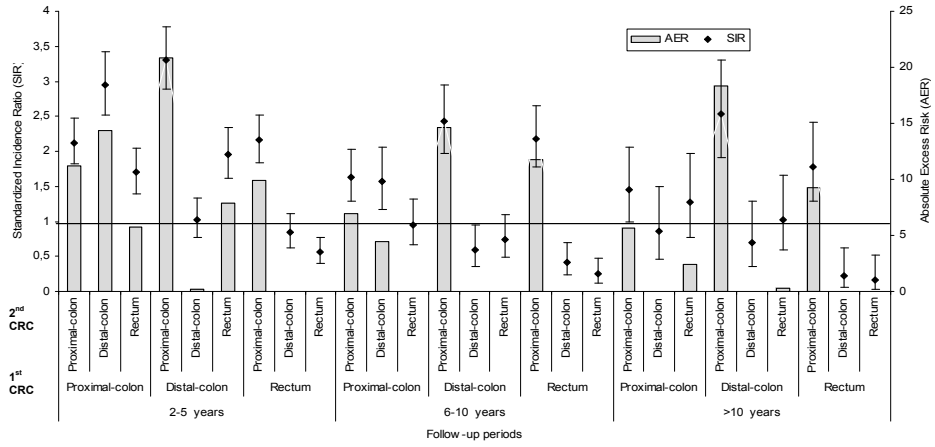
Figure 2.1 b Standardized incidence ratio (SIR) and absolute excess risk (AER, per 10,000 person years) of second primary cancers in proximal- colon, distal–colon, and rectum according to sub sites of first cancer among patients > 50 years of age (N=1,730)

Both SIR and AER were statistically significantly higher in proximal-colon compared to distal-colon and rectum in each of the respective follow-up period (2-5, 6-10, and > 10 years). Up to 5 years of follow-up, elevated excess risk (i.e. SIR >1 and AER>0) was observed in proximal-colon, distal-colon, and in rectum. After 5 years of follow-up, elevated SIR and AER were only observed in proximal-colon with a SIR of 1.6 (95%CI 1.5-1.7) and an AER of 15 per 10,000 person years, whereas the risk for second cancer in distal-colon and in rectum became lower compared to the general



Source: Netherlands Cancer Registry

Figure 3.1 a Standardized incidence ratio (SIR) and absolute excess risk (AER, per 10,000 person years) of second primary cancers in proximal-colon, distal-colon, and rectum by follow-up periods (2-5, 6-10, and >10 years among patients > 50 years of age (N=1,730)



Source: Netherlands Cancer Registry

Figure 3.1 b Standardized incidence ratio (SIR) and absolute excess risk (AER, per 10,000 person years) of second primary cancers in proximal-colon, distal-colon, and rectum by follow-up periods (2-5, 6-10, and >10 years) and by sub sites of first cancer among patients > 50 years of age (N=1,730)

population (i.e. SIR <1 and AER<0) (**Figure3.1**.a.). The long-lasting higher risk in proximal-colon was shown under each of the sub sites of first cancer (**Figure3.1**.b.)

Patients younger than 50 years

The 20 -year cumulative incidence for second cancers in proximal-colon, distal-colon, and rectum, was 2.0 %, 0.8 %, and 0.5 %, respectively (**Figure 1**.b).

The standardized incidence ratio (SIR) was the highest with 6.9 (95%CI: 5.2 -8.9) in the proximal-colon, followed by 4.0 (95%CI: 2.7-5.6) in the distal-colon, and by 2.3 (95%CI: 1.5 -3.4) in the rectum. The corresponding absolute excess risks (AER) were 7.9, 4.1, and 2.6 per 10,000

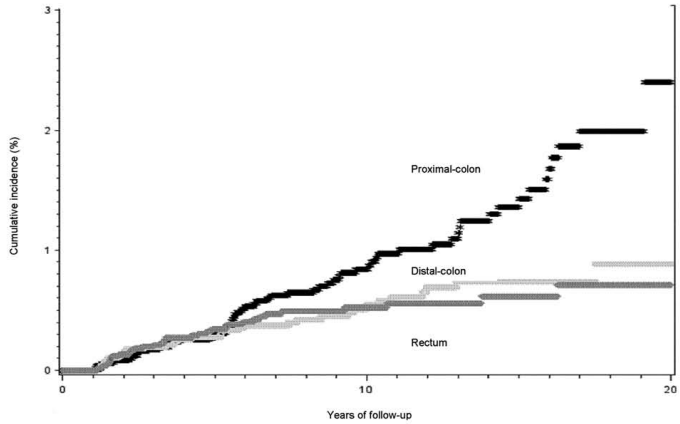


Figure 1. b. Cumulative incidence (20-year) of second cancers in proximal-colon, clistal-colon, and rectum amoung patients ≤ 50 years of age (N=119)

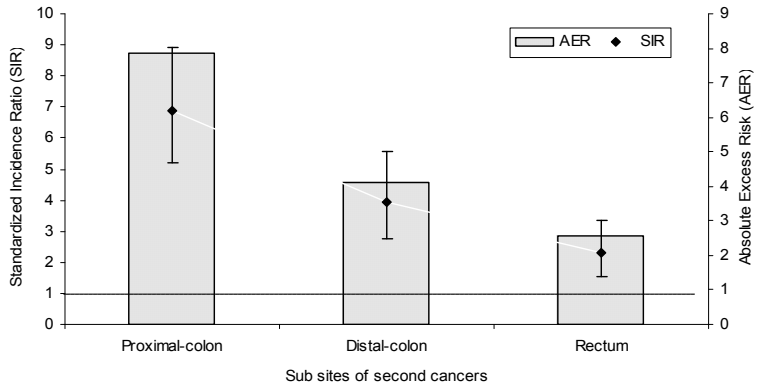


Figure 2.2 a Standardized incidence ratio (SIR) and absolute excess (AER, per 10,000 person years) of second primary cancers in proximal-colon, distal-colon, and rectrum among patients ≤50 years of age (N=119)

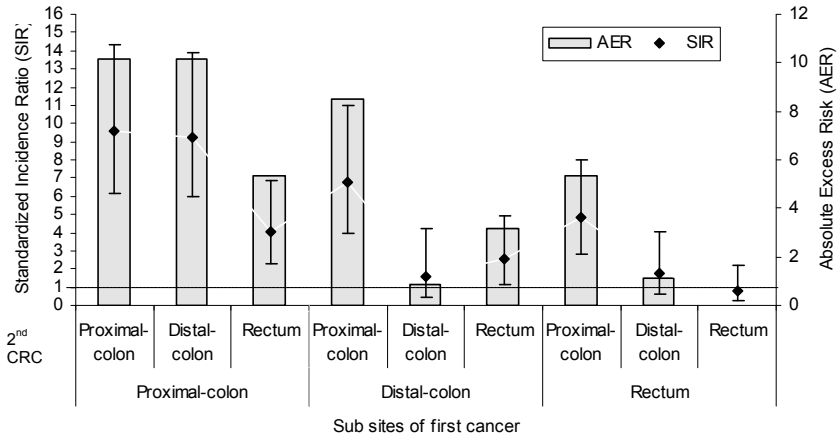
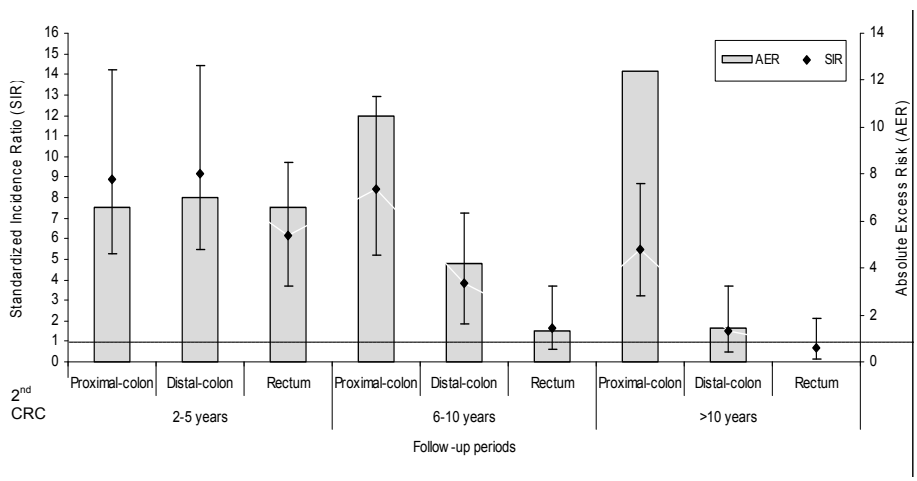


Figure 2.2 b Standardized incidence ratio (SIR) and absolute excess (AER, per 10,000 person years) of second primary cancers in proximal-colon, distal-colon, and rectrum according to sub sites of first cancer among patients ≤50 years of age (N=119)

person years (**Figure 2.2**.a.). The highest risk for a second cancer was observed in proximal-colon following a first proximal-colon cancer (SIR= 9.6 (95%CI: 2.2 -2.8); AER =10.2/10,000) (**Figure2.2**.b.).Up to 10 years of follow-up, elevated risk for a second cancer was observed in both proximal-colon and distal-colon. After 10 years, higher risk (i.e. SIR >1 and AER>0) for a second cancer only remained in proximal-colon with SIR was 5.5 (95%CI 3.2-8.7) and with AER was 12.4 per 10,000 person years. The absolute excess risk (AER) for a second cancer in proximal-colon increased from 6.6 to 12.4 per 10,000 person years along follow-up time, whereas AERs decreased in distal-colon as well as in rectum from 7 to 2 and from 6 to zero per 10,000 person years, respectively (**Figure3.2**.a.). When stratifying according to sub sites of first cancer, the increasing AER for a second cancer in proximal-colon was mainly pronounced in patients with a prior cancer in the rectum changing from 4 to 14 per 10,000 person years (**Figure3.2**.b.).

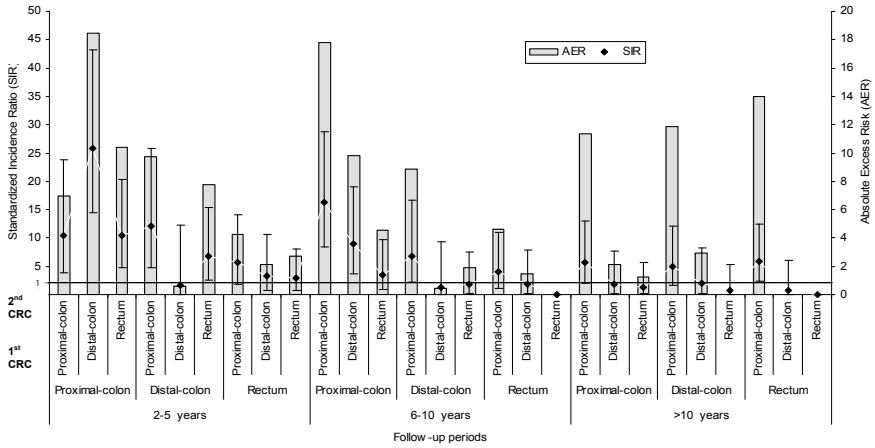
Stage of second cancer in proximal-colon worsened over follow-up time: the proportion of stage III and stage IV second cancers rose from 31% after the first year of follow-up to 38% after 10 years of follow-up (**Figure 4**).

In the sensitivity analysis, higher and persistently increased risk (i.e. SIR and AER) for second cancer in proximal-colon were still observed after adjusting for post-resection surface differences in proximal-colon, distal-colon, and the rectum. However, risks in distal-colon and in rectum were not any more significantly lower than the general population 5 years after first CRC diagnosis.



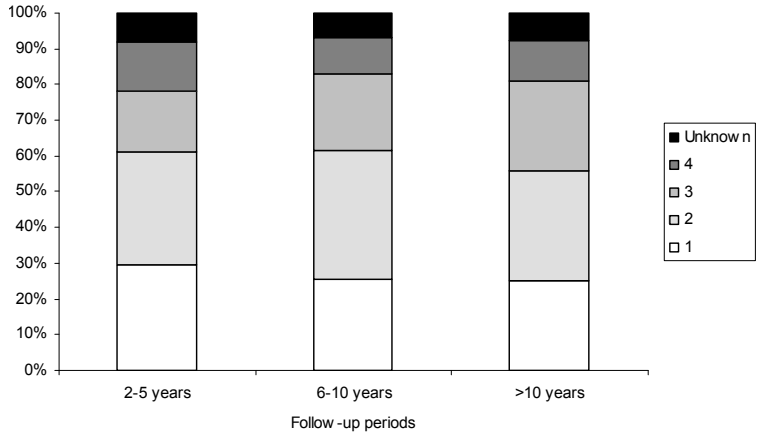
Source: Netherlands Cancer Registry

Figure 3.2.a Standardized incidence ratio (SIR) and absolute excess risk (AER, per 10,000 person years) of second primary cancers in proximal-colon, distal–colon, and rectum by follow-up periods (2-5, 6-10, and >10 years) among patients ≤50 years of age (n=119)



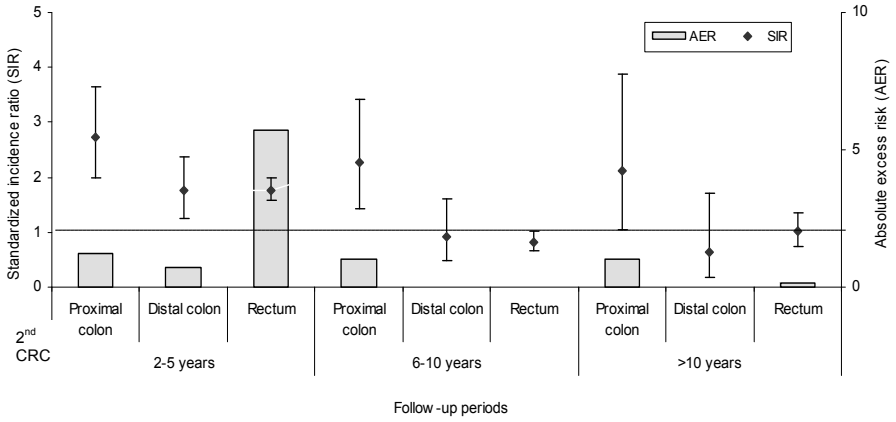
Source: Netherlands Cancer Registry

Figure 3.2.b Standardized incidence ratio (SIR) and absolute excess risk (AER, per 10,000 person years) of second primary cancers in proximal-colon, distal–colon, and rectum by follow-up periods (2-5, 6-10, and >10 years) and by sub sites of first cancer among patients ≤ 50 years of age (N=119)



Source: Netherlands Cancer Registry

Figure 4 Stage distribution of second primary cancer in proximal-colon by follow-up periods (2-5, 6-10, and >10 years) (N=1,849)



Source: Netherlands Cancer Registry

Sensitivity test: Surface adjusted standardized incidence ratio (SIR) and absolute excess risk (AER, per 10,000 person years) of second primary cancers in proximal-colon, distal–colon, and rectum by follow-up periods (2-5, 6-10, and >10 years) (N=1,849)

Note: surface estimate is 1,321 cm^2 (length=67cm), 735 cm^2 (length=63 cm) and 110 cm^2 (length=14cm) for proximal, distal colon and rectum respectively (Stang A, Kluttig A. Etiologic insights from surface adjustment of colorectal carcinoma incidences: an analysis of the U.S. SEER data 2000-2004. Am J Gastroenterol 2008;103:2853-2861). We assumed 17 cm of colon (either proximal or distal) and 9 cm of rectum were excised during surgical treatment of the first colorectal cancer.

DISCUSSION

Compared to general population, elevated risk for cancer was observed in all sub sites of colon and rectum among individuals with a prior colorectal cancer. More than 60% of second CRCs occurred within 5 years after the index cancer. Among long-term survivors (i.e. >5 years) elevated excess risk for a second cancer remained in proximal-colon and the stage of these proximal-located lesions worsened with increasing follow-up time. In patients younger than 50 years, similar risk pattern was observed however, interestingly, the absolute risk for a second cancer in the proximal-colon increases over follow-up time. We tried in the sensitivity test to minimize influence of post-resection surface differences in sub sites of colon and rectum on risk estimates, whereas finding on each 100 cm^2, risk pattern remains similar. These findings accord with two previous studies performing similar analyses[20-21].

Part of the excess risk for a second CRC can be explained by a surveillance effect during 2-5 years of follow-up. According to the Dutch clinical guidelines, patients with CRC (excluding those with stage IV CRC) are routinely followed up to 5 years[11]. Hence, during this period of time, asymptomatic lesions are more likely to be found in this patient group compared with the less often checked general population resulting in higher SIRs and AERs. As cancers in the proximal-colon remain often asymptomatic until causing anemia, their higher excess risk

is expected as compared to cancers in the distal-colon and in the rectum. Furthermore, we also observed that second CRCs diagnosed during this surveillance period underwent better staging compared with the first CRCs (results not shown), which might due to more frequent check-up hence lead to early detection of those second lesions (N=1,152).

Among long-term survivors (i.e.>5 years), proximal-colon is the only site with a higher risk for a second primary cancer compared to their general population controls (i.e. SIR=1.6 (95%CI 1.5-1.7) and an AER of 15 per 10,000 person years) (only refer to patients older than 50 years). Patient age increases from a median of 69 years at first diagnosis to a median age of 77 years at the second cancer (results not shown). This finding accords with the theory and observation that aging increases risk of lesions in proximal-colon[22-24]. In combination with the worsened stage over follow-up time in this site of the colon, our results may point to the need for an extended follow-up schedule beyond 5 years. However, at this point in time, patients are well over 75 years of age. Advanced age is an independent risk factor for adverse events (i.e. pulmonary complications and perforation) during colonoscopy[25]. Therefore, the benefits of colonoscopic surveillance of this extreme age group may no longer outweigh the possible risks related to screening. In UK, colonoscopic surveillance would cease when patient is around 75 years of age or when the patient is clearly unfit for further intervention[26]. In combination with the fact that co-existing conditions is often found in older patients (68% VS 42%; >65 years VS <65 years), which altered their treatment and prognostic feature as well as possible surveillance strategies[27]. Further investigations should be encouraged in finding a suiTable surveillance tool/modality in these elderly, high-risk long-term survivors[28-29].

Recognizing the higher risk of second cancers in the proximal-colon is of considerable clinical significance. First of all, due to the high miss rate of cancers/adenomas in the proximal-colon at colonoscopy, our results may prompt clinicians to pay extra attention to right colon at diagnosis and during post-resection surveillance[30]. Secondly, the long-lasting (i.e. >5 years) elevated relative and absolute risk in the proximal-colon suggests a possible benefit of long-term follow-up schedule. However, due to the advanced age of these patients (average: 77 years), special attentions should be paid on balancing the harm and benefits of early detection programs in this group.

Among patients younger than 50 years, though the high and long-lasting risk for a second cancer was still found in the proximal-colon, much higher relative risks (i.e. SIR> 5) were shown compared to that found in older patients. These high SIRs coinciding with moderately elevated absolute risks (AER) reflect the low CRC background incidence rate in this age group in general population as well as the small number of patients with a second CRC (N=119). Of importance, the rising trend of absolute risk for a second cancer in proximal-colon further emphasizes the need for a long-term follow-up schedule for this population in particular.

Limitation of the study is lack of data polypectomy rates and interval of surveillance colonoscopies, which may give further explanation for the observed risk estimates. However, The Netherlands Cancer Registry provided rich and accurate population-based data, supporting

the representativeness and validity of the results. Detailed subgroup analysis provided sound basis for group-specific follow-up guidelines. Adjustment for post-resection surface in sub sites of colon and rectum increased precision in SIR and AER estimates.

CONCLUSION

Individuals with a prior colorectal cancer are at higher risk for a second cancer in all sub sites of colon and rectum. Among long-term survivors, elevated risk was observed only in proximal-colon. However, due to the advanced age of this population, further studies on a suiTable surveillance modality should be encouraged.

ACKNOWLEDGMENTS

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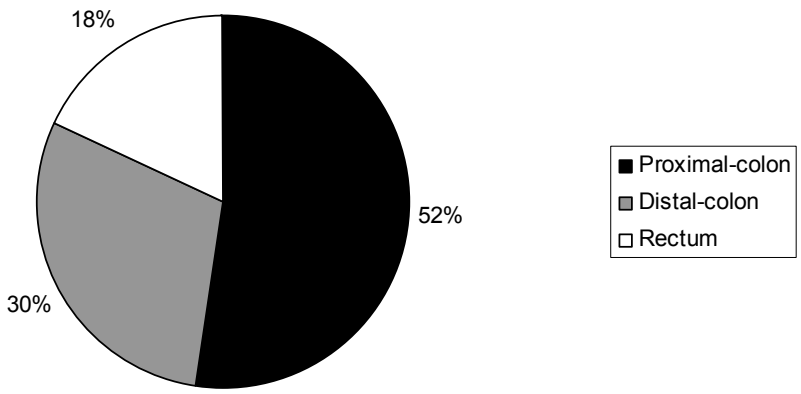
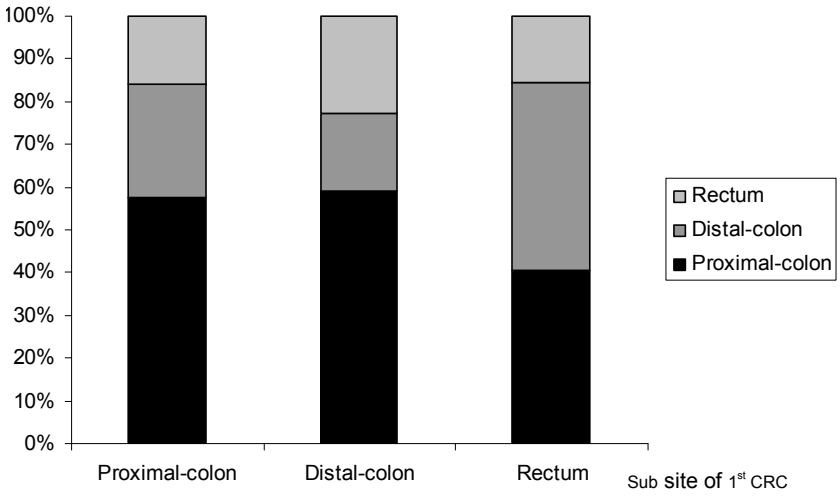
APPENDIX



Source: Netherlands Cancer Registry

Appendix 1. a. Sub site of 2nd cancers diagnosed in 0-1 year after first CRC (N=1,441)



Source: Netherlands Cancer Registry

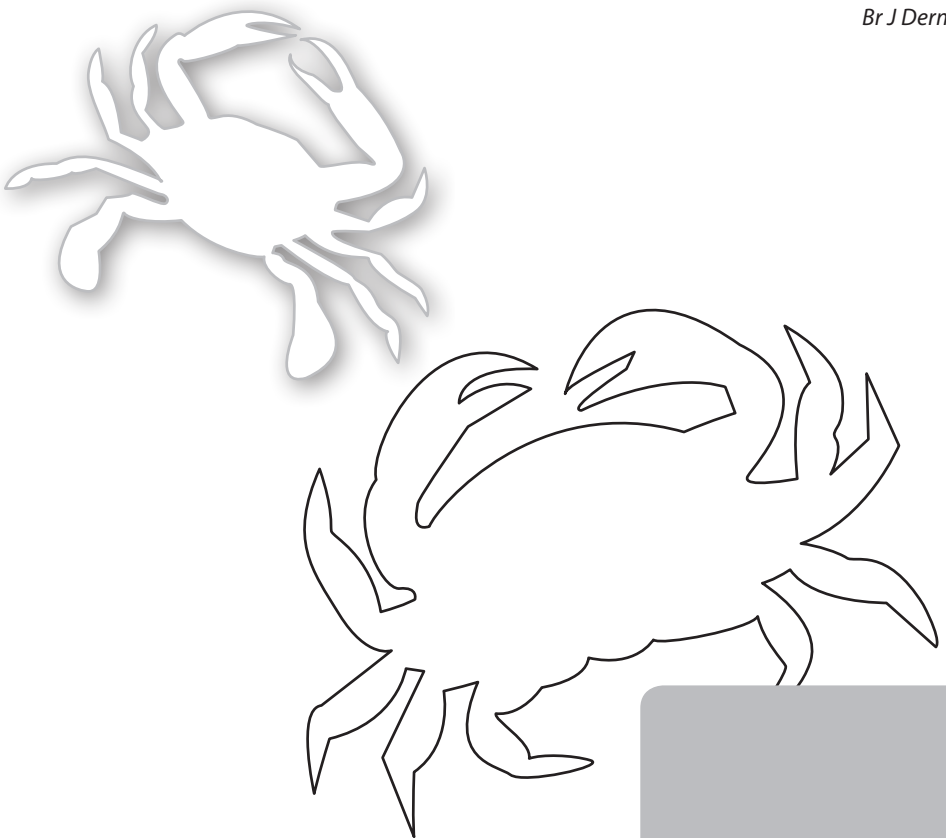
Appendix1.b. Sub site of 2nd cancers diagnosed in 0-1 year after first CRC according to site of first CRC (N=1,441)

CHAPTER 2.2

Risk of second primary in situ and invasive melanoma in a Dutch population-based cohort: 1989-2008

R.J.T. van der Leest, L. Liu, J.W.W. Coebergh, H.A.M. Neumann, W.J. Mooi, T. Nijsten, E. de Vries

Br J Dermat 2012, epub



ABSTRACT

Background: Melanoma patients are at increased risk of developing a subsequent melanoma.

Objectives: To estimate risks of developing a second primary *in situ* or invasive cutaneous melanoma after a first melanoma, between 1989 and 2008.

Methods: Patients were followed until diagnosis of a second melanoma, date of death or end of study. Cumulative risks, standardized incidence ratio (SIR, observed second melanomas divided by background age-, calendar- and sex-specific incidence rates of melanoma, as recorded in the Netherlands Cancer Registry) and absolute excess risk (AER, observed minus expected per 10,000 person-years) of second melanomas were calculated.

Results: In total, 10,765 *in situ* and 46,700 invasive melanoma patients were included. Cumulative risks of a second invasive melanoma after a first *in situ* or invasive melanoma at 20 years of follow-up were 6.2% and 5.0%, respectively. Relative risk of developing any melanoma (*in situ* or invasive) after any first melanoma (SIR) was 12.4 [invasive after invasive melanoma; 95% Confidence Interval(CI) = 11.6–13.2] to 26.4 [*in situ* after *in situ* melanoma; 95% CI = 22.6–30.7] fold increased compared to the general population. SIRs and AERs remained elevated up to 20 years after the first melanoma.

Conclusions: This study shows significantly increased long-term risks (both relative and absolute) of developing a second invasive melanoma after a first melanoma (invasive and *in situ*) which might serve as a basis for follow-up guidelines.

INTRODUCTION

The incidence rate of cutaneous melanoma (melanoma) in Europe has increased annually in the last 50 years[1]. In the Netherlands, the European standardized incidence rate has almost doubled between 1989 and 2008 from 11 per 100,000 person-years to 22 with an Estimated Annual Percentage Change of 4.1% (95% Confidence Interval: 3.6 – 4.5)[2]. This rising trend has been reported previously in several studies[1,3-5], and is usually attributed to increased sun exposure in the general population, especially at young ages. The majority of melanomas are detected in early stages[2], when simple excision often results in cure. Consequentially, survival rates are relatively high (in the time period 2004-2008 the 10-year relative survival of melanoma in the Netherlands was 77% and 88% for males and females, respectively)[2]. Thirty percent of melanoma patients report symptoms of psychological distress[6]. Second melanomas detected among melanoma patients who were not under active follow-up had a higher Breslow thickness compared to those in follow-up[7], suggesting a beneficial effect, although methodological difficulties in that study preclude an unequivocal conclusion.

The melanoma guideline in the Netherlands advises different follow-up schemes for cutaneous melanoma patients depending on Breslow thickness: patients with melanomas with a Breslow thickness of less than 1 millimeter (mm) require a single control visit, one month after treatment; 1 to 2 mm are advised a follow-up time of 5 years and more than 2 mm are advised to be in follow-up for 10 years (www.cbo.nl, accessed 1 February 2012; Guideline Melanoma of the skin, 2005). Internationally, follow-up guidelines vary considerably, from one control visit one month after treatment in the Netherlands, to lifelong annual follow-up visits for all stage I melanomas in Australia / New Zealand[8], which suggests a perception of the underlying risk. Follow-up schemes for *in situ* melanoma patients have not been formulated in the Dutch guideline.

In this study we investigated the risk pattern of second primary cutaneous melanomas among patients with melanoma (both invasive and *in situ*) in the Netherlands, by duration of follow-up, in order to provide information for optimal follow-up guidelines.

MATERIALS AND METHODS

Data

The population-based Netherlands Cancer Registry (NCR) provided incidence data of all patients diagnosed with *in situ* (International Classification of Diseases (ICD)-10 D.03) and invasive (ICD-10 C.43) cutaneous melanoma between 1989 and 2008. Information on vital status was obtained by linkage with the Dutch Municipality Register. Recurrence data were not collected. Detailed description of data has been described elsewhere[2]. Locations of the *in*

situ and invasive melanomas were subdivided in the categories head and neck, trunk, arms, legs, other (including genital region) and unknown. The most common histopathological subtypes of melanoma were categorized (superficial spreading melanoma, nodular melanoma, acrolentiginous melanoma, lentigo maligna melanoma, lentigo maligna, melanoma *in situ* and other). Breslow thickness was categorized into 5 categories: lower than or equal to 1 mm, 1.01 – 2.0 mm, 2.01 – 4.0 mm, higher than 4 mm and unknown. Tumour stage was not used as the criteria have changed repeatedly in the past.

Patient selection

Patients diagnosed with an either *in situ* or invasive cutaneous melanoma between 1989 and 2008 were included. Person-years at risk were calculated as time from first cancer diagnosis until the diagnosis of a second primary melanoma (for invasive and *in situ*, separately), date of death or end of follow-up (December 31 2008), whichever comes first. Of note, all the second melanomas were included. For instance, after a first melanoma diagnosis, if the second cancer is non-melanoma cancer and the third is melanoma, this melanoma is included, and so forth for other rank cancers. Patients were excluded if other invasive cancers were diagnosed before the first primary melanoma.

Statistical analysis

To analyze heterogeneity in characteristics (sex, tumour location, Breslow thickness and histopathological subtype) between first primary invasive melanomas and second primary melanomas the Chi-square test was used. Cumulative risk of second melanoma up to 20 years after diagnosis of the first melanoma was calculated taking the competing risks invasive cancers (other than melanoma) and death into account[9]. The standardized incidence ratio (SIR) is the ratio between the observed number of second melanomas and the expected number from the general population. It is a useful multiplicative measure for determining excess risk of second melanoma relative to the background risk in the general population. To derive the expected numbers, person-years under age-specific (5-year band), calendar-specific (1-year band) and sex-specific stratum were multiplied with the corresponding background incidence rate from the general Dutch population. SIR > 1 indicates the risk of developing a second melanoma is higher among melanoma patients than the general population. Absolute excess risk (AER), is an additive measure for determining additional incidence beyond background incidence due to occurrence of second melanoma. It is expressed as the difference between the observed number and the expected number per 10,000 person-years (i.e. (O-E) / person-years at risk x 10,000). Both SIR and AER were illustrated under follow-up periods of 0-1 year, 2-5 years, 6-10 years, 10-15 years and 16-20 years after the first melanoma diagnosis. The 95% CI was under Poisson distribution and the statistical significance level was estimated at two-sided at 0.05.

RESULTS

Cohort characteristics

Of the 57,465 patients with a first primary melanoma (10,765 *in situ* and 46,700 invasive conditions), 3.2 % (n=1,840) developed a second primary melanoma between 1989 and 2008. The majority of second melanomas (71%) were invasive (n=1,301). Median follow-up time for *in situ* melanoma patients was 5.4 years (Interquartile range (IQR) = 2.3-9.9 years; male) and 6.1 years (IQR = 2.7-10.7 years; female) and for invasive melanoma patients 4.2 years (IQR = 1.7-8.9 years; male) and 5.6 years (IQR = 2.3-10.8 years; female).

Table 1 shows the characteristics of the first and second melanomas among the *in situ* and invasive melanoma patients with second primary melanomas. Median age of the first *in situ* melanoma was 64 years (Interquartile range (IQR) = 52–74 years) and of the first invasive melanoma 52 years (IQR = 40–64 years) of age, respectively. First *in situ* melanomas were most frequently (61%) located in the head / neck area, whereas first invasive melanomas were most frequently located on the trunk (36%). Frequently occurring / common histopathological subtypes of the first and second invasive melanomas were superficial spreading melanoma (SSM, 57% and 67% respectively) and nodular melanoma (NM, 13% and 9% respectively). First and second *in situ* melanomas were predominantly lentigo maligna (62% and 76%, respectively). On average, second melanomas were thinner than the first invasive melanomas. In the majority of the cases second melanomas occurred in the first 5 years after the first melanoma diagnosis. Gender differences of patients with a second primary melanoma are shown in Supplementary (Table S1).

Table 1 Characteristics of patients with second melanomas after a first in situ or invasive melanoma, 1989-2008

		1st *in situ* melanoma[a]			1st invasive melanoma[b]		
		n	%	Median age (yr) (IQR)	n	%	Median age (yr) (IQR)
Number patients with 2nd melanoma	Total	471	4.4	64 (52 - 74)	1,369	2.9	52 (40 - 64)
	Second *in situ*	173	36.7	70 (60 - 79)	366	26.7	60 (46 - 72)
	Second invasive	298	63.3	69 (55 - 78)	1,003	73.3	55 (43 - 66)
Site of 1st melanoma	Head	287	60.9	68 (61 - 77)	208	15.2	64 (50 - 75)
	Trunk	74	15.7	52 (42 - 63)	498	36.4	49 (39 - 60)
	Arms	56	11.9	53 (38 - 64)	285	20.8	54 (42 - 65)
	Legs	50	10.6	50 (35 - 67)	359	26.2	48 (36 - 60)
	unknown / other	4	0.8	67 (65 - 75)	19	1.4	55 (41 - 64)
Site of 2nd *in situ* melanoma	Head	118	68.2	73 (64 - 81)	104	28.4	72 (62 - 80)
	Trunk	11	6.4	60 (44 - 63)	98	26.8	54 (42 - 63)
	Arms	17	9.8	61 (52 - 71)	85	23.2	62 (49 - 73)
	Legs	25	14.5	55 (45 - 72)	78	21.3	50 (38 - 62)
	unknown / other	2	1.2	76 (75 - 77)	1	0.3	63 (63 - 63)
Site of 2nd invasive melanoma	Head	144	48.3	75 (67 - 82)	167	16.7	64 (48 - 77)
	Trunk	60	20.1	57 (45 - 68)	361	36.0	54 (43 - 63)
	Arms	41	13.8	67 (57 - 76)	216	21.5	56 (44 - 69)
	Legs	47	15.8	59 (43 - 71)	254	25.3	52 (41 - 63)
	unknown / other	6	2.0	51 (38 - 68)	5	0.5	65 (54 - 75)
Histopathological subtype 1st melanoma	NM[c]	1	0.2	73 (73 - 73)	NM	181	13.2	56 (41 - 66)
	SSM[c]	47	10.0	50 (36 - 63)	SSM	776	56.7	49 (38 - 60)
	LM	291	61.8	68 (61 - 77)	LMM	52	3.8	70 (62 - 78)
	MEL IN SITU	113	24.0	49 (40 - 63)	MM NOS	304	22.2	51 (41 - 65)
	ALM[c]	1	0.2	54 (54 - 54)	ALM	8	0.6	67 (59 - 78)
	other	18	3.8	70 (62 - 73)	other	48	3.5	60 (52 - 69)
Histopathological subtype 2nd *in situ* melanoma	SSM[c]	11	6.4	65 (54 - 77)	SSM[c]	29	7.9	56 (46 - 65)
	LM	131	75.7	73 (63 – 80)	LM	147	40.2	71 (59 - 78)
	MEL IN SITU	29	16.8	56 (44 - 68)	MEL IN SITU	185	50.5	51 (41 - 63)
	ALM[c]	1	0.6	67 (67 - 67)	ALM[c]	1	0.3	32 (32 - 32)
	other	1	0.6	52 (52 - 52)	other	4	1.1	70 (62 - 80)
Histopathological subtype 2nd invasive melanoma	NM	29	9.7	72 (62 - 81)	NM	91	9.1	54 (40 - 69)
	SSM	134	45.0	62 (46 - 72)	SSM	667	66.5	54 (42 - 64)
	LMM	59	19.8	75 (64 - 80)	LMM	42	4.2	69 (62 - 79)
	MM NOS	59	19.8	68 (52 - 81)	MM NOS	164	16.4	54 (43 - 70)
	ALM	0	0.0	NA	ALM	4	0.4	59 (52 - 71)
	other	17	5.7	71 (69 - 78)	other	35	3.5	62 (55 - 74)
Breslow thickness 1st invasive melanoma[d]					≤ 1 mm	586	55.5	49 (39 - 61)
					1.01 - 2.0 mm	230	21.8	54 (46 - 66)
					2.01 - 4.0 mm	142	13.5	59 (46 - 70)
					> 4 mm	62	5.9	65 (56 - 72)
					Unknown	35	3.3	54 (40 - 73)

Breslow thickness 2nd invasive melanoma[d]	≤ 1mm	176	61.8	64 (49 - 75)	≤ 1mm	660	70.3	54 (43 - 65)
	1.01 - 2.0 mm	42	14.7	73 (59 - 82)	1.01 - 2.0 mm	160	17.0	56 (44 - 67)
	2.01 - 4.0 mm	34	11.9	77 (69 - 81)	2.01 - 4.0 mm	55	5.9	64 (51 - 77)
	> 4 mm	14	4.9	79 (67 - 93)	> 4 mm	34	3.6	72 (57 - 82)
	Unknown	19	6.7	71 (63 - 80)	Unknown	30	3.2	57 (46 - 71)
Time to 2nd *in situ* melanoma	0 – 1 year	40	23.1	NA		134	36.6	NA
	2 – 5 years	75	43.4	NA		134	36.6	NA
	6 – 10 years	43	24.9	NA		61	16.7	NA
	11 – 14 years	12	6.9	NA		28	7.7	NA
	15 – 20 years	3	1.7	NA		9	2.5	NA
Time to 2nd invasive melanoma	0 – 1 year	53	17.8	NA		312	31.1	NA
	2 – 5 years	125	41.9	NA		347	34.6	NA
	6 – 10 years	74	24.8	NA		221	22.0	NA
	11 – 14 years	36	12.1	NA		94	9.4	NA
	15 – 20 years	10	3.4	NA		29	2.9	NA

Source: Netherlands Cancer Registry

[a] Total cohort of 10 765 in situ melanoma patients at risk; Person-years at risk 73 743; Median follow-up time males 5.4 years [IQR 2.3-9.9] and females 6.1 years [2.7-10.7]. [b] Total cohort of 46 700 invasive melanoma patients at risk; Person-years at risk 301 758; Median follow-up time males 4.2 years [IQR 1.7 - 8.9] and females 5.6 years [2.3 – 10.8]. [c] In situ melanoma with (erroneous) invasive morphology code. [d] Only Breslow thickness available in time period 1993 – 2008. Abbreviations: 'IQR'= Interquartile range, 'NM'= Nodular melanoma, 'SSM'= Superficial spreading melanoma, 'LM'= Lentigo Maligna, 'LMM'= Lentigo Maligna Melanoma, 'MEL IN SITU'= Melanoma in situ, 'MM NOS'= Malignant melanoma not otherwise specified, 'ALM'= Acrolentiginous melanoma, 'mm'= millimeter, 'NA'= not applicable.

In **Table 2** the characteristics of the first and second invasive melanomas are compared. Patients' sex distributions of the first and the second primary melanomas were comparable. The localisation distribution differed significantly; second melanomas were more likely to occur in the head region than the first melanomas (24% vs. 13%, p<0.0001 with 4 degrees of freedom) as is confirmed by the significantly higher proportion of lentigo maligna melanoma (LMM) among the second melanomas (8% versus 3%). Second primary melanoma showed a higher frequency of superficial spreading melanoma (SSM) compared to the first melanoma (62% and 55% respectively, p<0.0001 with 5 degrees of freedom). The Breslow thickness of second melanomas was less than or equal to 2 mm in 85% of the cases compared to 75% in the first melanoma group. Thick melanomas (>4 mm) were more common in the first invasive melanoma group (8% vs. 4%, p<0.0001 with 4 degrees of freedom).

Table 2 Comparison of tumour characteristics of the first invasive melanoma and a second primary invasive melanoma

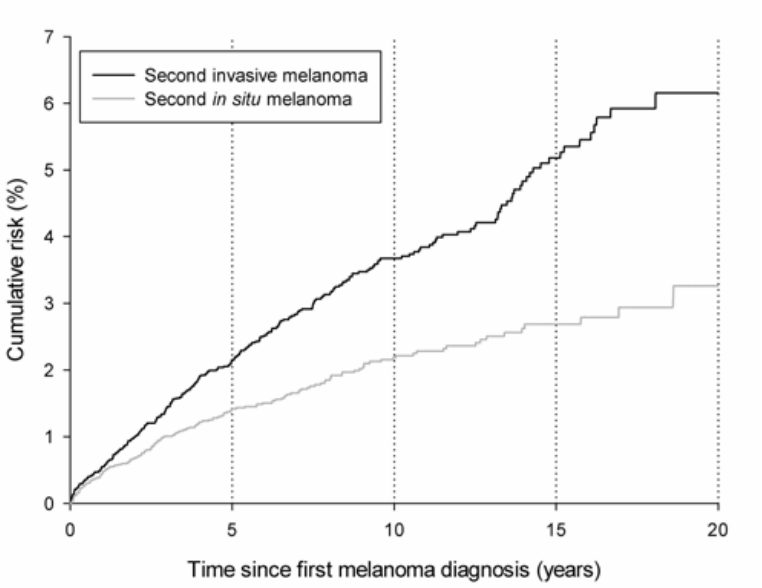
	1st melanoma (n)[a]	%	2nd melanoma (n)	%	p-value[b] (degrees of freedom)
Sex					
Male	19,664	42.1	569	43.7	0.2407 (1)
Female	27,036	57.9	732	56.3	
Site of melanoma					
Head	5,866	12.6	311	23.9	<0.0001 (4)
Trunk	16,156	34.6	421	32.4	
Arms	8,865	19.0	257	19.8	
Legs	13,864	29.7	301	23.1	
unknown / other	1,949	4.2	11	0.9	
Histopathological subtype					
NM	6,546	14.0	120	9.2	<0.0001 (5)
SSM	25,576	54.8	801	61.6	
LMM	1,332	2.9	101	7.8	
MM NOS	10,999	23.6	223	17.1	
ALM	382	0.8	4	0.3	
other	1,865	4.0	52	4.0	
Breslow thickness					
≤ 1 mm	21,276	54.9	836	68.3	<0.0001 (4)
1.01 - 2.0 mm	7,952	20.5	202	16.5	
2.01 - 4.0 mm	5,061	13.0	89	7.3	
> 4 mm	3,111	8.0	48	3.9	
Unknown	1,384	3.6	49	4.0	

Source: Netherlands Cancer Registry

[a]All first invasive melanomas in the database, regardless of occurrence of a second melanoma in the same patient. [b]Chi-square test. Abbreviations: 'SSM'= Superficial spreading melanoma, 'NM'= Nodular melanoma, 'LMM'= Lentigo Maligna Melanoma, 'ALM'= Acrolentiginous melanoma, 'mm'= millimeter.

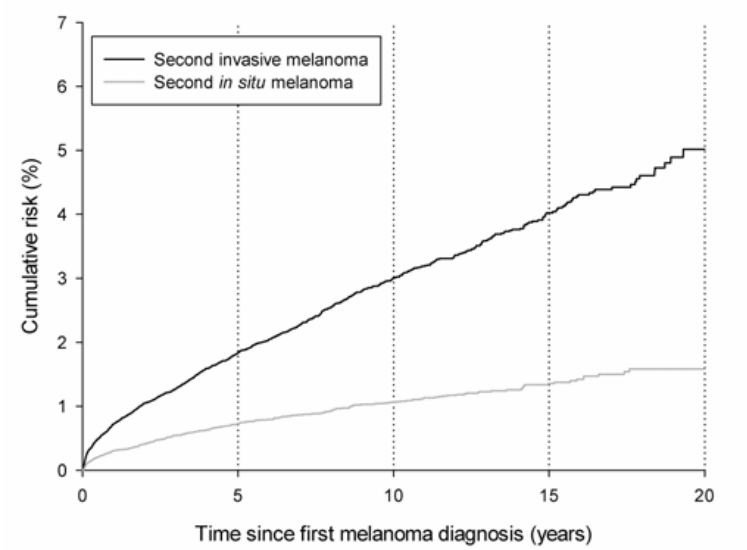
Cumulative risk

The 5-year cumulative risk of getting a second invasive melanoma after a first *in situ* or first invasive melanoma was 2.1% and 1.8%, respectively, 10-year cumulative risk was 3.7% and 3.0%, 15-year cumulative risk was 5.2% and 4.0% and 20-year cumulative risk was 6.2% and 5.0%. The cumulative risk of developing a second primary *in situ* or invasive melanoma increased constantly with follow-up time (follow-up time 0–20 years) (**Figure 1**). Cumulative risk of an invasive melanoma after a first invasive melanoma was consistently higher for females than for males (**Figure 2**).



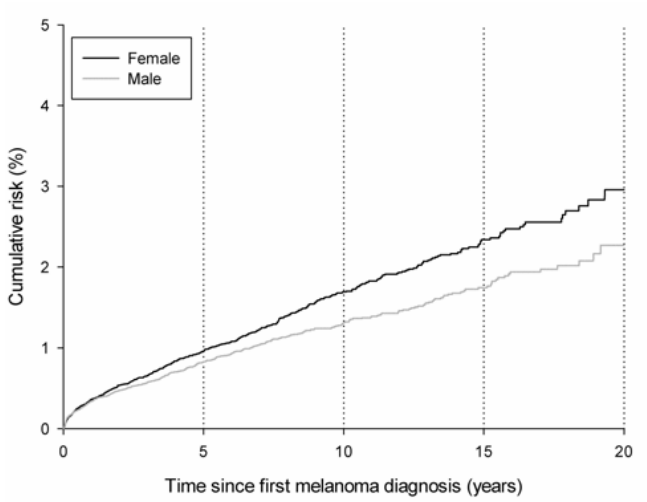
Source: Netherlands Cancer Registry

Figure 1 (a) Cumuative risk of second melanomas after a first *in situ* melanoma



Source: Netherlands Cancer Registry

Figure 1 (b) Cumulative risk of second melanomas after a first inasive melanoma



Source: Netherlands Cancer Registry

Figure 2 Cumulative risk of second invasive melanomas in male and female patients with invasive melanomas

Standardized incidence ratio (SIR) and Absolute excess risk (AER)

SIRs of developing a second primary melanoma after a first melanoma were highest in the first year after the first melanoma diagnosis for all groups (SIRs 16.5 [95% CI = 11.0 – 24.0] – 53.7 [95% CI = 40.2 – 70.4]) but remained elevated up to 20 years after the first melanoma diagnosis (**Table 3**). Patients with an *in situ* melanoma were at increased risk of developing a second *in situ* melanoma (SIR 26.4 [95% CI = 22.6 – 30.7]) or second invasive melanoma compared to the general population (SIR 15.4 [13.7 – 17.3]). SIR of an invasive melanoma after an invasive melanoma was 12.4 [11.6 – 13.2] and SIRs of this group were consistently higher for male patients compared to female patients, regardless of time since diagnosis. AERs were highest in the first year after the first melanoma and decreased over follow-up time. The AERs of an invasive melanoma after a first invasive melanoma were 36.4 / 10,000 (males) and 27.0 / 10,000 (females) person-years, and after a first *in situ* melanoma 44.0 / 10,000 (males) and 34.4 / 10,000 (females) person-years (**Table 3**).

DISCUSSION

This large population based study investigating risks of developing second melanomas in cohorts of both *in situ* and invasive melanoma patients showed markedly increased total relative (12 to 26 fold) and absolute risks (11 to 38 per 10,000 person-years). These risks remained increased for more than 15 years after the first melanoma diagnosis.

Table 3 Standardized Incidence Ratio (SIR and 95% confidence intervals) and Absolute Excess Risk (AER, per 10,000 person-years) of second primary melanomas after melanomas in different follow-up periods

Second *in situ* melanoma after first *in situ* melanoma								**Second *in situ* melanoma after first invasive melanoma**							
	Follow-up period	O	E	SIR	95% CI	PY at risk	AER		Follow-up period	O	E	SIR	95% CI	PY at risk	AER
Male	0 - 1 year	13	0.3	45.5	24.2 - 78.9	3,744.9	11.5	**Male**	0 - 1 year	53	1.0	53.7	40.2 - 70.4	18,018.7	28.9
	2 - 5 years	20	0.9	23.2	14.1 - 36.1	11,068.6	25.7		2 - 5 years	45	2.8	16.1	11.7 - 21.6	48,736.2	8.7
	6 - 10 years	14	0.6	21.7	11.9 - 37.0	7,451.0	49.9		6 - 10 years	20	2.0	10.1	6.2 - 15.7	30,947.5	5.8
	11 - 14 years	2	0.3	7.8	0.9 - 32.7	2,678.3	16.7		11 - 14 years	11	0.9	12.6	6.3 - 22.9	11,920.6	8.5
	15 - 20 years	0	0.1	0.0	NA	1,045.1	-1.1		15 - 20 years	2	0.5	4.3	0.5 - 17.8	5,228.9	2.9
	Total	49	2.2	22.7	16.8 - 30.1	25,988.0	18.0		Total	131	7.1	18.4	15.4 - 21.9	114,851.7	10.8
Female	0 - 1 year	27	0.5	50.3	33.1 - 73.6	6,338.9	41.7	**Female**	0 - 1 year	81	1.7	47.9	38.0 - 59.6	25,288.7	31.4
	2 - 5 years	55	1.7	32.3	24.4 - 42.2	19,675.2	27.1		2 - 5 years	89	5.3	16.8	13.5 - 20.6	75,120.0	11.1
	6 - 10 years	29	1.3	21.8	14.6 - 31.5	14,022.7	19.7		6 - 10 years	41	4.3	9.6	6.9 - 13.0	53,792.5	6.8
	11 - 14 years	10	0.6	17.9	8.5 - 33.6	5,417.0	17.4		11 - 14 years	17	2.0	8.4	4.9 - 13.5	22,216.8	6.7
	15 - 20 years	3	0.3	11.5	2.3 - 36.7	2,301.2	11.9		15 - 20 years	7	1.1	6.3	2.5 - 13.5	10,488.0	5.6
	Total	124	4.4	28.3	23.5 - 33.7	47,755.0	25.0		Total	235	14.4	16.3	14.3 - 18.5	186,906.0	11.8
Total		173	6.5	26.4	22.6 - 30.7	73,743.0	22.6	**Total**		366	21.5	17.0	15.3 - 18.8	301,757.7	11.4

Table 3 (continued)

	Second invasive melanoma after first *in situ* melanoma								Second invasive melanoma after first invasive melanoma						
	Follow-up period	O	E	SIR	95% CI	PY at risk	AER		Follow-up period	O	E	SIR	95% CI	PY at risk	AER
Male	0 - 1 year	25	1.0	25.2	16.3 - 37.4	3,744.9	64.1	**Male**	0 - 1 year	151	4.2	36.0	30.5 - 42.3	18,018.7	81.5
	2 - 5 years	49	3.0	16.1	11.9 - 21.3	11,068.6	41.5		2 - 5 years	155	11.7	13.2	11.2 - 15.5	48,736.2	29.4
	6 - 10 years	26	2.2	11.6	7.6 - 17.1	7,451.0	31.9		6 - 10 years	89	8.2	10.9	8.7 - 13.4	30,947.5	26.1
	11 - 14 years	19	0.9	21.5	12.9 - 33.8	2,678.3	67.6		11 - 14 years	38	3.6	10.7	7.5 - 14.7	11,920.6	28.9
	15 - 20 years	3	0.4	8.0	1.6 - 25.7	1,045.1	25.1		15 - 20 years	14	1.8	7.8	4.3 - 13.3	5,228.9	23.4
	Total	122	7.5	16.2	13.4 - 19.3	25,988.0	44.0		Total	447	29.4	15.2	13.8 - 16.7	11,4851.7	36.4
Female	0 - 1 year	28	1.7	16.5	11.0 - 24.0	6,338.9	41.5	**Female**	0 - 1 year	161	6.3	25.4	21.7 - 29.7	25,288.7	61.2
	2 - 5 years	76	3.4	22.4	17.6 - 28.0	19,675.2	36.9		2 - 5 years	192	19.4	9.9	8.6 - 11.4	75,120.0	23.0
	6 - 10 years	48	4.1	11.6	8.6 - 15.4	14,022.7	31.3		6 - 10 years	132	15.2	8.7	7.3 - 10.3	53,792.5	21.7
	11 - 14 years	17	1.7	9.8	5.7 - 15.8	5,417.0	28.2		11 - 14 years	56	6.9	8.1	6.1 - 10.5	22,216.8	22.1
	15 - 20 years	7	0.8	8.6	3.5 - 18.4	2,301.2	26.9		15 - 20 years	15	3.6	4.1	2.3 - 6.9	10,488.0	10.8
	Total	176	11.8	14.9	12.8 - 17.3	47,755.0	34.4		Total	556	51.4	10.8	9.9 - 11.7	186,906.0	27.0
Total		298	19.3	15.4	13.7 - 17.3	73,743.0	37.8	**Total**		1,003	80.9	12.4	11.6 - 13.2	301,757.7	30.6

Source: Netherlands Cancer Registry

Abbreviations: 'O'= Observed number of cases, 'E'= Expected number of cases, 'SIR'=Standardized Incidence Ratio, '95% CI'=95% Confidence Intervals, 'PY'= Person-years, 'AER'= Absolute Excess Risk per 10,000 person-years, 'NA'= Not applicable.

Table 4 Recent studies reporting risks (proportion, cumulative risk and Standardized Incidence Ratio (SIR)) of developing a second primary melanoma after a first melanoma

Reference	Time- period	1st melanoma (n)	2nd melanoma (n)	Cumulative risk	Person-years at risk	Age 1st melanoma (years)	Follow-Up (years)	Total SIR (95%CI)[b]	Follow-up SIR (years)[b]				
Balamurugan	**1992 - 2006**	***In situ***	**Invasive**				**mean**	[a]	**0-0.1**[a]	**0.1-1**[a]	**1-5**[a]	**5-10**[a]	**>10**[a]
2011	**Male**	22,013	812 (3.7 %)					8.4*	36.3*	9.9*	7.4*	7.3*	7.5*
United States	**Female**	18,868	438 (2.3 %)					12.3*	77.2*	16.2*	10.0*	9.9*	7.2*
	Total	40,881	1,250 (3.1 %)				5.6						
		Invasive	**Invasive**				**mean**		**0-0.1**	**0.1-1**	**1-5**	**5-10**	**>10**
	Male	41,715	1,850 (4.4 %)					12.5*	102.1*	16.8*	9.9*	8.5*	6.2*
	Female	34,326	957 (2.8 %)					15.7*	127.6*	22.1*	13.0*	9.9*	9.2*
	Total	76,041	2,807 (3.7 %)				5.6						
Karahalios	**1982 - 2005**	**Invasive**	**Invasive**	**23 years**		**mean**	**mean**		**0-1**	**1-5**	**5-10**	**10-15**	**15-23**
2009	**Male**	14,241		8.1 %	100,188	57	7.0	7.3 (6.7 - 7.8)	10.7*	8.1*	6.2*	5.7*	5.0*
Australia	**Female**	14,011		6.2 %	116,375	55	8.3	7.2 (6.6 - 7.9)	9.6*	8.5*	5.9*	6.4*	5.9*
	Total	28,252											
Cantwell	**1993 - 2002**	**Invasive**	**Invasive**			**mean**							
2009	**Male**					57							
Northern Ireland	**Female**					55							
	Total	1,839						4.8 (1.2 - 8.3)					
Levi	**1974 - 2003**	**Invasive**	**Invasive**	**20 years**		**median**							
2005	**Male**	1,571	15 (1.0 %)					3.4 (1.9 - 5.6)					
Switzerland	**Female**	1,868	28 (1.5 %)					5.7 (3.8 - 8.3)					
	Total	3,439	43 (1.3 %)	5.0 %	24,930	57		4.6 (3.4 - 6.2)					
Schmid-Wendtner	**1977 - 1992**	**Invasive**	**Invasive**				**median**	**SIR within 10 years**[c]					
2001	**Male**	2,083						38.5 (30.4 – 48.1)					

Table 4 (continued)

Reference	Time- period	1st melanoma (n)	2nd melanoma (n)	Cumulative risk	Person-years at risk	Age 1st melanoma (years)	Follow-Up (years)	Total SIR (95%CI)[b]	Follow-up SIR (years)[b]				
Germany	Female	2,514						29.0 (22.0 – 37.5)					
	Total	4,597	152 (3.3 %)				7.2	33.8 (28.3 – 39.9)					
Dong	1958 - 1996	Invasive	Invasive			median	median		0-1	0-9	1-9	10-38	
2001	Male	10,704	195 (1.8 %)		81,758	55	5.0			9.5*		5.7*	
Sweden	Female	11,460	170 (1.5 %)		107,767	50	7.0			7.9*		6.5*	
	Total	22,164	365 (1.6 %)						16.0*		8.0*	6.1*	
Wassberg	1958 - 1992	*In situ*	Invasive			mean	mean	[a]	0-1[a]	1-4[a]	5-9[a]	10-14[a]	>15[a]
1999	Male	1,542	51 (3.3 %)					23.8 (17.7 – 31.3)					
Sweden	Female	2,224	57 (2.6 %)					20.9 (15.8 – 27.1)					
	Total	3,766	108 (2.9 %)		20,038	56	5.3	22.2 (18.2 – 26.8)	28.2*	22.5*	19.4*	25.0*	7.4
Burden	1979 - 1991	Invasive	Invasive										
1994	Male												
Scotland	Female												
	Total	3,818	45 (1.2 %)										
Current study	1989 - 2008	*In situ*	Invasive	20 years		median	median	[a]	0-1[a]	2-5[a]	6-10[a]	11-14[a]	15-20[a]
2011	Male	4,005	122 (3.0 %)			64	5.4	16.2 (13.4 – 19.3)	25.2*	16.1*	11.6*	21.5*	8.0*
The Netherlands	Female	6,760	176 (2.6 %)			64	6.1	14.9 (12.8 – 17.3)	16.5*	22.4*	11.6*	9.8*	8.6*
Source: NCR	Total	10,765	298 (2.8 %)	6.2 %	73,743	64		15.4 (13.7 – 17.3)					
		Invasive	Invasive			median	median		0-1	2-5	6-10	11-14	15-20
	Male	19,664	447 (2.3 %)			55	4.2	15.2 (13.8 – 16.7)	36.0*	13.2*	10.9*	10.7*	7.8*
	Female	27,036	556 (2.1 %)			49	5.6	10.8 (9.9 – 11.7)	25.4*	9.9*	8.7*	8.1*	4.1*
	Total	46,700	1003 (2.1 %)	5.0 %	301,758	52		12.4 (11.6 – 13.2)					

[a]SIR invasive melanoma after first *in situ* melanoma. [b]All SIRs reported were statistically significant increased. [c]*in situ* melanomas included in analysis. *SIR differs significantly from 1 ($p < 0.05$). Abbreviations: 'NCR'= Netherlands Cancer Registry, 'CI'= Confidence Intervals, 'SIR'= Standardized Incidence Ratio.

In our data, 2.1% of patients developed a second primary invasive melanoma after a first invasive melanoma and the average 20-year cumulative risk was 5.6%. Internationally, considerable variations in incidence Figures of a second melanoma after a first melanoma (range proportions: 1.0% - 4.4% and cumulative risks: 5.0% - 8.1%) have been reported (**Table 4**)[10-16]. The SIRs in the Netherlands were high compared to relative risks reported in other countries which varied from 3.4 [95% CI = 1.9 – 5.6] to 38.5 [95% CI = 30.4 – 48.1] (**Table 4**)[10-15,17]. Explanations should be sought in underlying incidence rates (shared risk factors or detection), chance of survival after the first cancer[18] or diagnostic bias / misclassification. Besides, as the SIR is a ratio of incidence rates in the cohort under study and the background population, the level of SIR will be strongly influenced by background incidence rates, the high background incidence rates in Australia may explain the lower SIR from Victoria, Australia[11]. A German study showed a high SIR of up to 38.5[13], probably caused by high numbers of second melanomas detected in a selected hospital-based study population which were divided by cancer registry background incidence rates. Finally, estimates will be influenced by the length of follow-up and degree of completeness of the cancer registry[19]. The Netherlands Cancer Registry is assumed to be 98.3% complete[20]. At this moment only two studies have calculated SIRs after a first *in situ* melanoma in which increased risks for more than 10 years after the first *in situ* melanoma were reported as well[10,15]. However, the Swedish data were relatively old and sample size was low. AER was calculated in two previous studies, our findings accords with the previous studies[10,21].

High incidence of melanoma in a group of melanoma patients might be related to high risk factor exposure, but also to increased patients' and doctors' awareness, diagnostic bias or registry artefacts. Slowly growing tumours are more likely to be discovered through this mechanism, illustrating length-time bias[19,22]. Previous studies observed high relative risks of developing a second melanoma related to fair skin type, presence of many or atypical moles and family history / genetic susceptibility of the melanoma patients, and modestly increased risks for patients whose first melanoma was an *in situ* / lentigo maligna or invasive melanoma[23-25] suggesting biologically increased risks. The NCR does not have information on risk factors like phototype or sun exposure and therefore we performed univariate analysis for age, sex, histopathological subtype, Breslow thickness and tumour location to predict occurrence of second melanomas, however, none of the above-listed factors yielded statistical significance (data not shown).

The histological interpretation of very small and difficult to interpret melanocytic lesions from patients with a history of melanoma is likely to result in some melanoma overdiagnosis, and in enrichment of the total group of second primary melanomas with exceedingly small and thin lesions that have been inappropriately labelled as melanoma. Benign lesions that are misclassified as melanoma could be a cause of, or contribute to, the melanoma 'epidemic'[26-28]. A recent paper stated that follow-up visits are an effective method to increase early detection of melanoma[7]. However, the second melanomas in the follow-up group of this study were extremely thin (mean Breslow thickness: 0.36 mm) or melanomas *in situ,* and could indeed have included overdiagnosed small melanoma simulators. So, intensive follow-up visits

might increase the risk of an inappropriate additional diagnosis of melanoma. Indications for this phenomenon to occur is also present in our data (**Table 1**); we found that the majority of the second melanomas were found in the first 5 years after the first melanoma diagnosis when the most follow-up visits are scheduled. However, whether or not patients follow the Dutch guideline follow-up visit scheme in our study is unknown.

Females could be at increased risk (**Figure 2**) of developing second melanomas compared to males because of higher awareness. This increased risk could also correspond to the higher incidence in females of primary melanoma in most European countries[5], the better survival of female melanoma patients[29-30] allowing females more time to develop a subsequent melanoma.

The increased risk of developing a second primary melanoma up to 20 years after the first melanoma diagnosis might be an indication for more extensive follow-up programs, although the effectiveness of follow-up programs in improving prognosis is controversial[8,31-32]. Analyses on potential differences in survival of the group of multiple melanoma patients versus the group with only one melanoma could give further information on the prognostic importance of the diagnosis of a second melanoma. This data may shed light on importance of increased surveillance of patients with a first primary melanoma.

Currently, there is not enough available evidence to prove efficacy of skin cancer screening[33-35]. Selecting and examining high-risk populations (for melanoma e.g., genodermatosis including Familial Atypical Mole - Malignant Melanoma (FAMMM) syndrome) and performing full body skin examination of people visiting physicians (i.e., 'case finding' by clinicians) might be the best strategy to decrease the burden of skin cancer[34]. Education of nurses or physiotherapists could also be an important method to improve early detection[36], but large studies are lacking.

In addition to disease progression and psychological support, follow-up visits suggested by malignant melanoma guidelines should include total body skin examinations to exclude second primary melanoma, because this patient group is at a highly increased risk. A SIR greater than 10.0 with an AER of more than 5.0 per 10,000 person-years is, in our opinion, large enough to conclude that a history of either an *in situ* or invasive melanoma is a strong risk indicator for detection of subsequent invasive melanomas and that both *in situ* and invasive melanoma patients must be considered to be at high risk and patient education and full body skin examinations should be performed during follow-up visits. Since the excess risk is persistent in time (up to 20 years), the duration of current follow-up recommendations for this indication remains debaTable. A melanoma follow-up study found a relatively low delay in diagnosis when a follow-up schedule with lower frequency than current guidelines was used[37]. However, large randomized controlled trials investigating duration and frequency of follow-up visits and follow-up procedures are suggested.

In conclusion, the risk of developing a second primary melanoma is elevated for at least 20 years after the first melanoma diagnosis. The explanation of this increased risk is multifacto-

rial and includes genetic predisposition, shared environmental risk factors and overdiagnosis. Nevertheless, patients and physicians need to be aware of the high and persistent risk of developing second primary melanomas.

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Table S1 Supplementary: Characteristics of male and female patients with second melanomas after a first in situ or invasive melanoma, 1989-2008

		1st *in situ* melanoma[a]					1st invasive melanoma[b]			
		Male (n)	%	Female (n)	%		Male (n)	%	Female (n)	%
Number patients with 2nd melanoma	Total	171	36.3	300	63.7		578	42.2	791	57.8
	Second *in situ*	49	28.3	124	71.7		131	35.8	235	64.2
	Second invasive	122	40.9	176	59.1		447	44.6	556	55.4
Site of 1st melanoma	Head	112	65.5	175	58.3		107	18.5	101	12.8
	Trunk	34	19.9	40	13.3		276	47.8	222	28.1
	Arms	15	8.8	41	13.7		98	17.0	187	23.6
	Legs	9	5.3	41	13.7		84	14.5	275	34.8
	unknown / other	1	0.6	3	1.0		13	2.2	6	0.8
Site of 2nd *in situ* melanoma	Head	32	65.3	86	69.4		46	35.1	58	24.7
	Trunk	7	14.3	4	3.2		41	31.3	57	24.3
	Arms	4	8.2	13	10.5		26	19.8	59	25.1
	Legs	5	10.2	20	16.1		17	13.0	61	26.0
	unknown / other	1	2.0	1	0.8		1	0.8	0	0.0
Site of 2nd invasive melanoma	Head	63	51.6	81	46.0		93	20.8	74	13.3
	Trunk	33	27.0	27	15.3		195	43.6	166	29.9
	Arms	14	11.5	27	15.3		83	18.6	133	23.9
	Legs	10	8.2	37	21.0		73	16.3	181	32.6
	unknown / other	2	1.6	4	2.3		3	0.7	2	0.4
Histopathological subtype 1st melanoma	NM[c]	1	0.6	0	0.0	NM	98	17.0	83	10.5
	SSM[c]	11	6.4	36	12.0	SSM	304	52.6	472	59.7
	LM	112	65.5	179	59.7	LMM	18	3.1	34	4.3
	MEL IN SITU	40	23.4	73	24.3	MM NOS	127	22.0	177	22.4
	ALM[c]	1	0.6	0	0.0	ALM	4	0.7	4	0.5
	other	6	3.5	12	4.0	other	27	4.7	21	2.7
Histopathological subtype 2nd *in situ* melanoma	SSM[c]	4	8.2	7	5.6	SSM[c]	11	8.4	18	7.7
	LM	34	69.4	97	78.2	LM	54	41.2	93	39.6
	MEL IN SITU	10	20.4	19	15.3	MEL IN SITU	64	48.9	121	51.5
	ALM[c]	1	2.0	0	0.0	ALM[c]	0	0.0	1	0.4
	other	0	0.0	1	0.8	other	2	1.5	2	0.9
Histopathological subtype 2nd invasive melanoma	NM	11	9.0	18	10.2	NM	55	12.3	36	6.5
	SSM	49	40.2	85	48.3	SSM	269	60.2	398	71.6
	LMM	24	19.7	35	19.9	LMM	18	4.0	24	4.3
	MM NOS	27	22.1	32	18.2	MM NOS	81	18.1	83	14.9
	ALM	0	0.0	0	0.0	ALM	3	0.7	1	0.2
	other	11	9.0	6	3.4	other	21	4.7	14	2.5

Table S1 Supplementary (continued)

		1st *in situ* melanoma[a]					1st invasive melanoma[b]			
		Male (n)	%	Female (n)	%		Male (n)	%	Female (n)	%
Breslow thickness 1st invasive melanoma[d]						≤ 1 mm	228	49.5	358	60.3
						1.01 - 2.0 mm	108	23.4	122	20.5
						2.01 - 4.0 mm	76	16.5	66	11.1
						> 4 mm	39	8.5	23	3.9
						Unknown	10	2.2	25	4.2
Breslow thickness 2nd invasive melanoma[d]	≤ 1mm	65	56.0	111	65.7	≤ 1mm	285	67.2	375	72.8
	1.01 - 2.0 mm	20	17.2	22	13.0	1.01 - 2.0 mm	76	17.9	84	16.3
	2.01 - 4.0 mm	17	14.7	17	10.1	2.01 - 4.0 mm	29	6.8	26	5.0
	> 4 mm	5	4.3	9	5.3	> 4 mm	19	4.5	15	2.9
	Unknown	9	7.8	10	5.9	Unknown	15	3.5	15	2.9
Time to 2nd *in situ* melanoma	0 – 1 year	13	26.5	27	21.8		53	40.5	81	34.5
	2 – 5 years	20	40.8	55	44.4		45	34.4	89	37.9
	6 – 10 years	14	28.6	29	23.4		20	15.3	41	17.4
	11 – 14 years	2	4.1	10	8.1		11	8.4	17	7.2
	15 – 20 years	0	0.0	3	2.4		2	1.5	7	3.0
Time to 2nd invasive melanoma	0 – 1 year	25	20.5	28	15.9		151	33.8	161	29.0
	2 – 5 years	49	40.2	76	43.2		155	34.7	192	34.5
	6 – 10 years	26	21.3	48	27.3		89	19.9	132	23.7
	11 – 14 years	19	15.6	17	9.7		38	8.5	56	10.1
	15 – 20 years	3	2.5	7	4.0		14	3.1	15	2.7

Source: Netherlands Cancer Registry

[a] Total cohort of 10 765 in situ melanoma patients at risk. [b] Total cohort of 46 700 invasive melanoma patients at risk. [c] In situ melanoma with (erroneous) invasive morphology code. [d] Only Breslow thickness available in time period 1993 – 2008. Abbreviations: 'IQR'= Interquartile range, 'NM'= Nodular melanoma, 'SSM'= Superficial spreading melanoma, 'LM'= Lentigo Maligna, 'LMM'= Lentigo Maligna Melanoma, 'MEL IN SITU'= Melanoma in situ, 'MM NOS'= Malignant melanoma not otherwise specified, 'ALM'= Acrolentiginous melanoma, 'mm'= millimeter, 'NA'= not applicable.

CHAPTER 2.3

Increased risks of third primary cancers of non-breast origin among women with bilateral breast cancer

A.B.G. Kwast, L. Liu, J.A. Roukema, A.C. Voogd, J.J. Jobsen, J.W.W. Coebergh, I. Soerjomataram, S. Siesling

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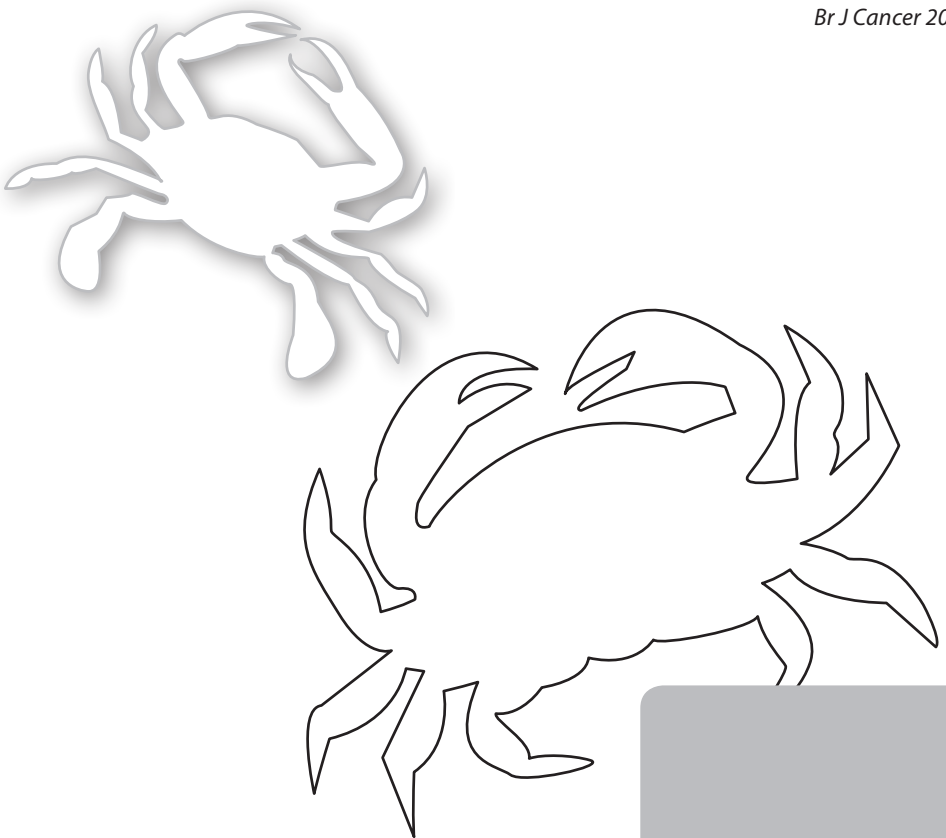


ABSTRACT

Background: This study examined the risk of third cancer of non-breast origin (TNBC) among women with bilateral breast cancer (BBC; either synchronous or metachronous), focussing on the relation with breast cancer treatment.

Methods: Risk was assessed, among 8,752 Dutch women diagnosed with BBC between 1989-2008, using standardised incidence ratios (SIR) and Cox regression analyses to estimate the Hazard Ratio (HR) of TNBC for different treatment modalities.

Results: Significant increased SIRs were observed for all TNBCs combined, haematological malignancies, stomach, colorectal, non-melanoma skin, lung, head and neck, endometrial and ovarian cancer. A tenfold increased risk was found for ovarian cancer among women younger <50 years (SIR=10.0, 95%CI=5.3-17.4). Radiotherapy was associated with increased risks of all TNBCs combined (HR=1.3; 95%CI=1.1-1.6, respectively). Endocrine therapy was associated with increased risks of all TNBCs combined (HR=1.2; 95%CI=1.0-1.5), haematological malignancies (HR=2.0; 95%CI=1.1-3.9) and head and neck cancer (HR=3.3; 95%CI=1.1-10.4). After chemotherapy decreased risks were found for all TNBCs combined (HR=0.63; 95%CI=0.5-0.87).

Conclusion: Increased risk of TNBC could be influenced by genetic factors (ovarian cancer) or an effect of treatment (radiotherapy and endocrine therapy). More insight in the TNBC risk should further optimise and individualise treatment and surveillance protocols in (young) women with BBC.

Keywords: bilateral breast cancer, third primary cancer, risk, radiotherapy, chemotherapy, endocrine therapy

INTRODUCTION

Breast cancer is by far the most frequent cancer in European and North American women[1]. Due to earlier diagnosis and improved treatment, breast cancer survival has increased, increasing the risk of metachronous breast cancer, among the survivors[2]. Women with a history of breast cancer have a 2-3 fold higher risk of developing a contralateral breast cancer as compared with the general female population[3-6]. In a Dutch population based study 18% of breast cancer patients were diagnosed with a second breast cancer in the period 1989-2006[7]. Similar results were observed among women at high risk, who either had an unilateral breast cancer or a twin sister with breast cancer, 9% to 18% experienced a breast cancer event after 20 years of follow-up[8]. However, incidence declined since 1980 due to the increasing use of adjuvant therapy[9].

Besides an elevated risk of contralateral breast cancer, several studies revealed that women with a primary breast cancer have an increased risk of developing a subsequent non-breast cancer. Increased risks were most consistently found for tumours of the ovary, endometrium, soft tissue and for leukaemia[3-6, 10-15]. Excess risks of melanoma of the skin and cancer of the bone, oesophagus, kidney and lung have also been reported, though less consistently[3,5-6,10-12, 14-15]. Risks of subsequent non-breast cancer appears to be associated with genetic and other risk factors that are common for both, breast cancer patients with primary breast cancer experienced an increased risk of lung cancer and soft tissue sarcomas that could be attributed to radiation. Increased risks of melanoma of the skin, uterine cancer and leukaemia were found to be associated with the use of chemotherapy for patients older than 50 years while the increased risk of endometrial cancer was related to endocrine therapy. At the same time chemotherapy was associated with a reduced risk of colon and lung cancer for women younger than 50 years[6].

However, information about the risk of third cancer of non-breast origin (third non-breast cancer; TNBC) after synchronous or metachronous invasive bilateral breast cancer (BBC) is lacking. Patients with BBC may have been exposed to more carcinogenic or carcinoprotective cancer treatment. Moreover a higher risk could be expected for genetic, reproductive, or lifestyle-related cancers. More insight in these risks may further optimise and individualise surveillance protocols in women with BBC. Therefore we assessed in this study, the risks of TNBC after BBC in a nationwide study based on the Netherlands Cancer Registry (NCR). In addition we studied the associations of TNBC risk with breast cancer treatment.

Materials and Methods

The cohort: Bilateral breast cancer patients

Patients were selected from the population-based nationwide NCR that reached complete coverage of cancer incidence in The Netherlands since 1989[16]. Patient registration is based on notification on a weekly basis of all newly diagnosed malignancies by the automated national

pathology archive and a yearly link with the national registry of hospital discharge diagnoses. In case of multiple primaries, the definition of a new primary tumour is a primary cancer that is not an extension, a recurrence, or a metastasis of a known tumour, located at another anatomic site, or when arising in the same anatomic site, belonging to a different histological subgroup or to a different behaviour subgroup (in situ vs invasive growth). Subsequently, information on patient and tumour characteristics and primary treatment, are retrieved directly from the medical records by specially trained registrars. Staging is coded according to the tumour, node and metastasis system (TNM) classification[17], topography and histology are coded according to the International Classification of Diseases for Oncology (ICD-O)[18]. Basic treatment information was available: whether patients were surgical treated, received radiotherapy, chemotherapy or endocrine therapy. Data on vital status and migration are annually updated through linkage with the national population demographics registry of the municipal administrations (Gemeentelijke basisadministratie). Data quality is high[19] and data completeness is estimated to be at least 95%[20].

All women diagnosed with BBC, defined as invasive first breast cancer and a synchronous or metachronous invasive second contralateral primary breast cancer (without cancer before the first breast cancer or between the first and second breast cancer), diagnosed between 1989 and 2008 in the Netherlands were selected (n=9,718). BBC patients were excluded with a metastasis at time of diagnosis of the first or second breast cancer (stage IV, n=909), with a sarcoma of the breast either for the first or second breast cancer (morphology code 8830-9990, n=17), as well as patients who developed a third primary breast cancer after BBC (n=40). In total 8,752 women with BBC were included in our study.

Statistical analysis

The patient and tumour characteristics are reported as frequencies and compared using χ^2 test. To estimate the risks of TNBC after BBC Standardised Incidence Ratios (SIR) were calculated. The SIR is the ratio of the observed to the expected numbers of TNBC cases. Observed numbers are the TNBC cases diagnosed during follow-up period. Patients with zero follow-up time between second breast cancer and the TNBC or the end of study period, were excluded for the SIR calculation (n=6). To determine the expected numbers, person years at risk by 5-year age categories and 1-year calendar period categories were multiplied with the corresponding background cancer incidence in the general Dutch female population and then summed up. Person years at risk started at the second breast cancer diagnosis and ended at the date of TNBC diagnosis, date of death, or the end of the study period (e.g. 31 December 2008), whichever came first. A SIR value higher than 1 implies an increased risk, while values lower than 1 suggest a decreased risk. Ninety-five percent confidence intervals (95%CI) were estimated assuming Poisson distribution of the TNBC occurrence. SIRs were computed for three age categories based on age at time of the second breast cancer diagnosis (<50, 50-64 and 65+ years) and for four follow-up intervals since the second breast cancer diagnosis (<1 year, 1-5 years, 6-10 years and ≥11 years)

and were plotted on a log scale. These subgroup analysis makes comparison with other studies possible and could give additional information in order to discuss and explain other outcomes. Tests for linear trend in relation to period of diagnosis were performed by incorporating a parameter in the relevant Poisson regression model with consecutive nonnegative integer values corresponding to increasing or decreasing levels of the factor and comparing the deviance statistic with that of a model without the relevant parameter.

Multivariable Cox proportional hazard analysis was used to examine the effect of breast cancer treatment on the different TNBC risks. The follow-up time was defined as the time between the date of first breast cancer diagnosis and the date of TNBC diagnosis. Patients were censored at the date of death, migration or the end of the study period (e.g. 31 December 2008). Proportional hazards were tested for all entered variables using graphical (Kaplan Meier plots) and statistical methods. The interval between first and second breast cancer (BCFI) appeared to be a non proportional factor and therefore analyses were stratified by BCFI categories (<1 year, 1-5 years, 6-10 years and >10 years) using the strata option in STATA. Factors included in the model were treatment of first breast cancer (radiotherapy (no, yes), chemotherapy (no, yes), endocrine therapy (no, yes)), age at first breast cancer (<50, 50-64, ≥65), year of first breast cancer incidence (continue variable). Second breast cancer treatment variables (radiotherapy (no, yes), chemotherapy (no, yes), endocrine therapy (no, yes)) were entered to the model as time dependent covariates, allocating patients to no second breast cancer treatment until second breast cancer occurrence.

Statistical significance was defined as a 2-sided P value of less than 0.05. Statistical analyses were performed in SAS version 9.2.

Results

In the Netherlands eligible 8,752 patients were diagnosed with invasive BBC between 1989 and 2008, with a median time of 2.4 years between the first and second breast cancer (**Table 1**). The patients accumulated 44,399 person years of follow-up since second breast cancer. Overall 586 patients developed a TNBC with a median follow-up time between the second breast cancer and TNBC of 3.9 years. Compared to patients without a TNBC, patients with a TNBC were significantly (P<0.001) more likely to be older than 65 years at first and second breast cancer diagnosis (respectively, 40% vs 47% and 59% vs 49%), had more often a stage I second breast cancer (61% vs 53%), were more often surgical treated for first and second breast cancer (respectively, 98% vs 95% and 96% vs 92%) and received less often chemotherapy for first and second breast cancer (respectively, 9% vs 19% and 9% vs 19%).

Risk of TNBC compared with the general female population

Table 2 shows the observed and expected numbers of TNBC and SIRs for TNBC by cancer site. The risk of all TNBCs combined after BBC was 1.6 (95%CI=1.5-1.7). Elevated risks were seen for

Table 1 Patient and tumour characteristics of patients with bilateral breast cancer

	Total N (%)	**With a TNBC**[a] N (%)	**Without a TNBC** N (%)	**P**[b]
Total	8,752	586	8,166	
Age at 1st breast cancer				**<0.001**
<50 years	2,245 (26)	106 (18)	2,139 (26)	
50-64 years	2,993 (34)	206 (35)	2,787 (34)	
≥65 years	3,514 (40)	274 (47)	3,240 (40)	
Age at 2nd breast cancer				**<0.001**
<50 years	1,470 (17)	65 (11)	1,405 (17)	
50-64 years	2,922 (33)	175 (30)	2,747 (34)	
≥65 years	4,360 (50)	346 (59)	4,014 (49)	
Time between first and second breast cancer				0.552
Median (25-75% range)	2.4 (0.04–6.1)	2.2 (0.03-5.6)	2.4 (0.04-6.2)	
<1 year	3,243 (37)	225 (38)	3,018 (37)	
>1-5 years	2,687 (31)	186 (32)	2,501 (31)	
>5-10 years	1,882 (22)	121 (21)	1,761(22)	
>10 years	940 (11)	54 (9)	886 (11)	
Time between second breast cancer and TNBC				
Median (25-75% range)	NA[c]	3.9 (1.5-7.2)	NA	
<1 year	NA	102 (17)	NA	
>1-5 years	NA	255 (44)	NA	
>5-10 years	NA	166 (28)	NA	
>10 years	NA	63 (11)	NA	
Stage of first breast cancer				**0.024**
I	3,712 (42)	249 (43)	3,463 (42)	
II	3,402 (39)	253 (43)	3,149 (39)	
III	682 (8)	34 (6)	648 (8)	
unknown	956 (11)	50 (9)	906 (11)	
Stage of second breast cancer				**<0.001**
I	4,664 (53)	359 (61)	4,305 (53)	
II	2,832 (32)	170 (29)	2,662 (33)	
III	618 (7)	25 (4)	593 (7)	
unknown	638 (7)	32 (5)	606 (7)	
Treatment				
Surgery				
First breast cancer	8,303 (95)	573 (98)	7,730 (95)	**0.001**
Second breast cancer	8,063 (92)	565 (96)	7,498 (92)	**<0.001**
Radiotherapy				
First breast cancer	4,698 (54)	325 (55)	4,373 (54)	0.371
Second breast cancer	3,620 (41)	249 (42)	3,371 (41)	0.565
Chemotherapy				
First breast cancer	1,640 (19)	50 (9)	1,590 (19)	**<0.001**
Second breast cancer	1,628 (19)	55 (9)	1,573 (19)	**<0.001**

Table 1 (continued)

	Total N (%)	**With a TNBC**[a] N (%)	**Without a TNBC** N (%)	**P**[b]
Endocrine therapy				
First breast cancer	2,638 (30)	171 (29)	2,467 (30)	0.600
Second breast cancer	3,417 (39)	209 (36)	3,208 (39)	0.083

[a]TNBC, third non-breast cancer; [b]P value χ^2 test indicating differences between patients with and without a TNBC; [c]NA, not applicable Bold denotes statistical significance

Table 2 Observed and expected numbers and standardised incidence ratios with 95% confidence intervals for third non- breast cancers after bilateral breast cancer

Site of TNBC[a]	**Observed numbers**	**Expected numbers**	**SIR**[b]	**95% CI**[c]		
Head and neck	18	9	**2.0**	1.2	-	3.2
Thyroid	3	2	1.4	0.29	-	4.6
Oesophagus	5	6	0.84	0.27	-	2.1
Stomach	25	12	**2.1**	1.4	-	3.2
Pancreas	15	12	1.2	0.67	-	2.0
Liver, intrahepatic bile ducts and biliary tract	7	5	1.5	0.60	-	3.2
Colorectal	91	74	1.2	0.99	-	1.5
Digestive organs, other	5	3	1.6	0.52	-	3.9
Lung	77	35	**2.2**	1.7	-	2.8
Soft tissue	8	2	**3.6**	1.5	-	7.3
Melanoma of skin	25	18	1.4	0.89	-	2.1
Non-melanoma skin	80	50	**1.6**	1.3	-	2.0
Ovarian	33	14	**2.3**	1.6	-	3.4
Endometrial	58	22	**2.6**	2.0	-	3.4
Cervix uteri	5	5	0.97	0.31	-	2.4
Vulva	5	4	1.1	0.36	-	2.8
Female genitalorgans, other[d]	6	1	**4.6**	1.7	-	10.4
Urinary bladder	19	15	1.3	0.78	-	2.0
Kidney	20	8	**2.4**	1.5	-	3.8
Brain	2	4	0.50	0.06	-	2.1
Haematological	48	33	**1.5**	1.1	-	1.9
All TNBCs[e]	582	363	1.6	1.5	-	1.7

[a]TNBC, third non breast cancer; [b]SIR, standardised incidence ratio; [c]CI, confidence interval; [d] Included, not otherwise specified and vagina; [e] Included others than the specific sites denoted: renal pelvis (2 observed cases), thymus (1 observed case), eye (3 observed cases), other or unspecified sites (4 observed cases), primary sites unknown (10 observed cases) and benign brain tumour (7 observed cases); Bold denotes statistical significance

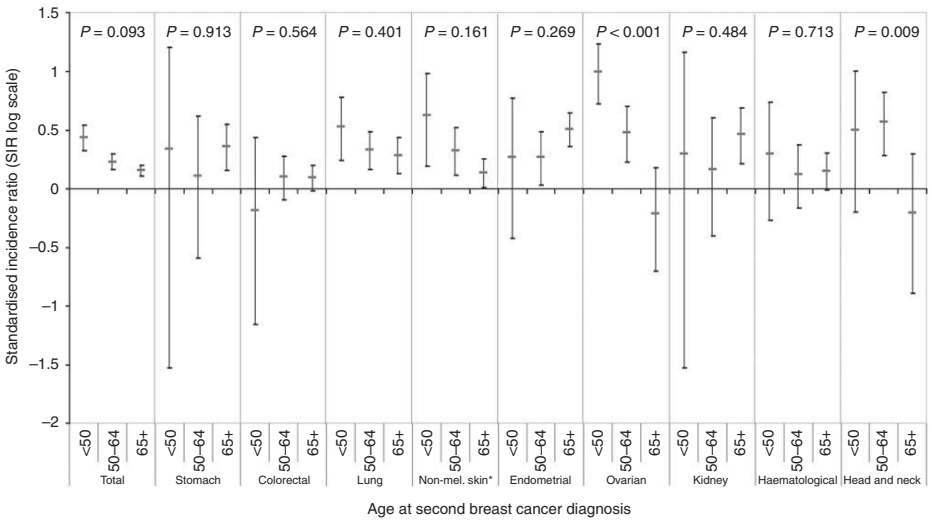
head and neck, stomach, lung, soft tissue, non-melanoma skin, ovarian, endometrial , other female genital organs and kidney cancer and haematological malignancies.

The risk of TNBCs overall was highest among women younger than 50 years at diagnosis of second breast cancer (SIR=2.8, 95%CI=2.1-3.5) (**Figure 1**). Differences between age

groups were especially large for ovarian cancer, with a relative risk of 10 (95%CI=5.3-17.4) in women younger than 50 at second breast cancer diagnosis. Relative risks for endometrial, stomach and kidney cancer were highest for patients older than 65 years (respective SIR=3.4; 95%CI=2.3-4.5, SIR=; 95%CI= and SIR=2.9; 95%CI=1.6-4.9). Overall, the risk of TNBCs tended to slightly increase with longer follow-up time since second breast cancer diagnosis (**Figure 2**). Increasing SIRs over time were seen for lung and ovarian cancer and haematological malignancies. For kidney and head and neck cancer the SIRs tended to decrease with time. No significant trends with follow-up time were found.

Risk of TNBC compared within the cohort

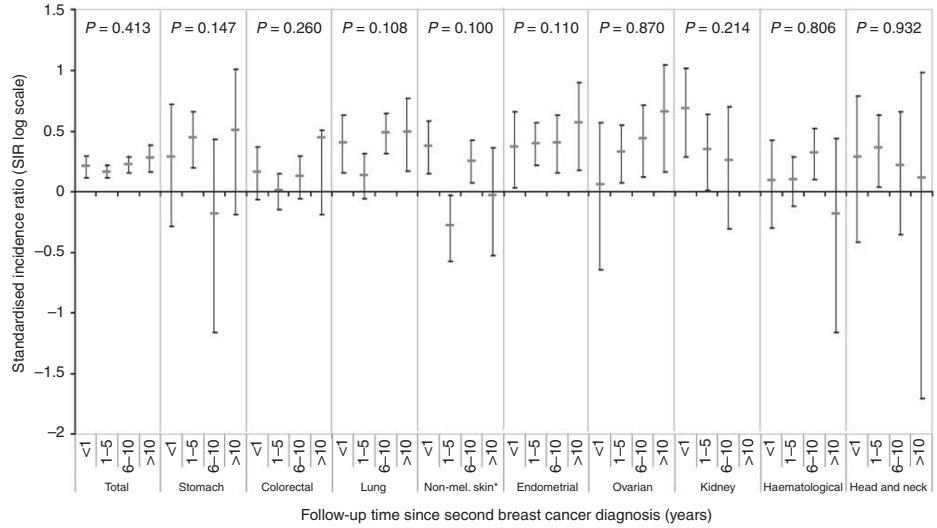
Table 3 shows the independent effects of cancer treatment on the risk of developing TNBC. Except for lung, ovarian and head and neck cancer the risk of a TNBC was highest in the older age patients. For lung, ovarian and head and neck cancer a decreased risk was seen for patients older than 65 years of age (respective hazard ratio (HR)=0.47; 95%CI=0.23-0.95, HR=0.13; 95%CI=0.03-0.49 and HR=0.07; 95%CI=0.11-0.39). Chemotherapy for the first breast cancer was associated with a decreased risk of all TNBCs combined (HR=0.63; 95%CI=0.45-0.87). After radiotherapy for the second breast cancer increased risks were found for all TNBCs combined (HR=1.3; 95%CI=1.1-1.6). After endocrine therapy for the second breast cancer, risks increased for all TNBCs combined (HR=1.2; 95%CI=1.0-1.5), haematological (HR=2.0; 95%CI=1.1-3.9) and head and neck cancer (HR=3.3; 95%CI=1.1-10.4).



Source: Netherlands Cancer Registry

Figure 1 Standardised incidence ratios, 95% confidence intervals and P values for trend analyses for selected third non-breast cancers (>10 cases, increased SIRa overall) according to age at second breast cancer diagnosis

[a] SIR: Standardised incidence ratio, *Non-mel. skin: Non-melanoma skin



Source: Netherlands Cancer Registry

Figure 2 Standardised incidence ratios, 95% confidence intervals and P values for trend analyses for selected third non-breast cancers (>10 cases, increased SIRa overall) according to follow-up time since second breast cancer diagnosis (years)

[a] SIR: Standardised incidence ratio, *Non-mel. skin: Non-melanoma skin

Table 3 Multivariate Cox regression analyses for the association of risk of selected third non-breast cancer (>10 cases, increased SIR[a] overall) with breast cancer treatment.

	All TNBCs[b]	**Stomach**	**Colorectal**	**Lung**	**Non-melanoma skin**	**Endometrial**	**Ovarian**	**Kidney**	**Haematological**	**Head and Neck**
	HR[c] (95% CI[d])	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
No. of patients	583	25	91	77	80	58	33	20	49	18
Age at 1st BC (years)										
<50	1	1	1	1	1	1	1	1	1	1
50-64	**1.3 (1.0-1.7)**	2.5 (0.45-13.5)	**3.5 (1.3-9.2)**	1.0 (0.58-1.8)	1.9 (0.82-4.2)	2.1 (0.82-5.1)	0.63 (0.29-1.4)	1.2 (0.32-4.8)	1.6 (0.66-3.9)	0.45 (0.14-1.4)
65+	**1.8 (1.4-2.3)**	**8.1 (1.5-43.8)**	**6.4 (2.4-17.1)**	**0.47 (0.23-0.95)**	**4.6 (2.0-10.6)**	**3.2 (1.2-8.3)**	**0.13 (0.03-0.49)**	1.9 (0.46-8.1)	2.2 (0.87-5.6)	**0.07 (0.11-0.39)**
Incidence year first BC	**1.1 (1.0-1.1)**	1.0 (0.91-1.1)	**1.1 (1.0-1.2)**	**1.1 (1.0-1.2)**	**1.1 (1.1-1.2)**	1.0 (0.93-1.1)	0.93 (0.84-1.0)	1.0 (0.88-1.1)	**1.1 (1.01-1.2)**	1.0 (0.91-1.2)
First BC										
Radiotherapy	1.1 (0.87-1.3)	1.8 (0.71-5.0)	0.69 (0.42-1.2)	0.93 (0.56-1.6)	1.5 (0.88-2.5)	0.69 (0.37-1.3)	1.4 (0.60-3.1)	1.6 (0.58-4.3)	1.6 (0.82-3.1)	2.9 (0.87-9.9)
Chemotherapy	**0.63 (0.45-0.87)**	0.32 (0.03-3.2)	0.40 (0.11-1.5)	0.49 (0.21-1.2)	1.4 (0.61-3.3)	1.1 (0.41-3.2)	0.24 (0.05-1.1)	0.28 (0.03-2.4)	0.82 (0.29-2.3)	0.13 (0.01-1.2)
Endocrine therapy	1.0 (0.82-1.3)	1.2 (0.43-3.5)	0.63 (0.34-1.2)	1.2 (0.66-2.3)	0.69 (0.37-1.3)	1.4 (0.70-2.7)	1.2 (0.38-3.5)	1.7 (0.60-5.0)	0.62 (0.27-1.4)	2.0 (0.54-7.3)
Second BC										
Radiotherapy	**1.3 (1.1-1.6)**	1.6 (0.63-4.2)	1.4 (0.8-2.4)	1.5 (0.89-2.5)	1.1 (0.68-1.9)	1.3 (0.69-2.4)	1.8 (0.82-4.0)	0.90 (0.33-2.5)	1.1 (0.56-2.1)	0.74 (0.26-2.1)
Chemotherapy	0.93 (0.67-1.3)	2.3 (0.38-14.0)	0.80 (0.25-2.6)	0.58 (0.25-1.4)	0.55 (0.19-1.6)	0.95 (0.31-2.9)	0.95 (0.33-2.7)	2.1 (0.48-8.8)	0.70 (0.22-2.2)	0.54 (0.10-2.8)
Endocrine therapy	**1.2 (1.0-1.5)**	0.66 (0.22-2.0)	1.5 (0.87-2.5)	1.08 (0.61-1.9)	1.6 (0.94-2.7)	1.5 (0.81-2.9)	0.57 (0.20-1.7)	2.3 (0.86-6.1)	**2.0 (1.1-3.9)**	**3.3 (1.1-10.4)**

[a]SIR Standardised Incidence Ratio; [b]TNBC: third non-breast cancer; [c]HR: Hazard Ratio; [d]CI: confidence interval; [e] BC: breast cancer; Bold denotes statistical significance

DISCUSSION

This is the first population-based study reporting the risks for TNBC in patients with BBC. Results showed an elevated risk for all TNBCs combined and a more than twofold increased risk of head and neck, stomach, lung, soft tissue, ovarian, endometrial, other female genital organs and kidney cancer was found for women with BBC compared with women without cancer. The risk was highest for women with BBC younger than 50 years at time of their second breast cancer. Especially marked was the ten-fold increased risk of ovarian cancer among young BBC patients. Interestingly, chemotherapy was associated with a reduced risk of all TNBC combined.

Studies among patients with primary breast cancer reported a 23%-40% increased risk of subsequent cancer[5,10,14]. Our results showed an elevated risk of all TNBC combined after BBC (SIR=1.6; 95%CI=1.5-1.7), and even higher risks (SIR=2.8) were found in women younger than 50 years at second breast diagnosis . Other studies support higher risks for subsequent breast cancer after primary breast cancer in young women with SIRs varying from 1.3 until 5.5[3,5,12,21-22]. The high risk of TNBC in young women overall is influenced by the marked ten-fold increased risk of ovarian cancer among women younger than 50 years (SIR=10). This is likely related to BRCA mutations. Women with BRCA1 or BRCA2 are prone to early age breast cancer, multiple breast cancers and have a higher risk of developing an ovarian cancer[23].

Radiotherapy is widely used for treatment of breast cancer. Over time modern radiation techniques reduce the exposure of normal tissue around the breast. Increased risks after radiation exposure of subsequent cancers of the oesophagus, lung, thyroid gland, soft tissue and leukaemia have been earlier reported[4,6,10,13,15,22,24-25]. Our study showed excess risk of all TNBC after BBC for patients treated with radiotherapy for the second breast cancer. Although increased risk of lung cancer was expected among women with previous radiotherapy[15,24-25], we observed no significant relation between radiation and lung cancer. We found elevated risks for lung cancer after a longer follow-up period (SIR=3.1 after 5 years of follow-up). From literature it is known that there is at least a 5 year lag period between radiation exposure and cancer induction. Furthermore, Kaufman[26] found no elevated risks for lung cancer among non smoking breast cancer patients after radiotherapy. However among ever-smokers without radiotherapy and ever-smokers treated with radiotherapy the risk of lung cancer was significantly increased (odds ratio (OR)=5.9 and OR = 18.9 respectively). Unfortunately no information about smoking was available in this study, hence it remains important to study the effect of radiotherapy on lung cancer taking smoking in to account.

Due to its radio sensitivity, also ovaries though further located from the breast are prone to biological changes related to radiation[27]. Two large studies found a relation between radiation of the breast and higher risk of subsequent ovarian cancer[13,15]. Although other studies found no relation[10,22] or even an adverse effect for women older than 50 years treated with radiotherapy[6]. We found a non significant increased risk of ovarian cancer after radiotherapy for the second breast cancer.

Our results showed a decreased risk after chemotherapy for the first breast cancer for all TNBC combined and it may have a protective effect for colorectal, lung, ovarian and head and neck cancer. In addition, younger BBC patients had a higher risk of lung, ovarian and head and neck cancer than those older than 65 years of age. Schaapveld et al[6] showed a protective effect of chemotherapy only among women younger than 50 for all second non breast cancers combined, colon and lung cancer. The study of Andersson et al[22] found in univariable analyses a protective effect of chemotherapy for bladder cancer. Rubino et al[10] found no risk differences of TNBC after primary breast cancer treated with or without chemotherapy, however information on chemotherapy was lacking in this study. An explanation for the protective effect might be that TNBCs undergo a growth delay from the use of chemotherapy. Especially for colon cancer fluorouracil containing chemotherapy could be effective.

Acute myeloid leukaemia (AML) is considered as a (anthracycline containing) chemotherapy-induced cancer, which can present within a few years after breast cancer diagnosis[29]. We observed no association between chemotherapy and increased risks for haematological malignancies. Probably because this group not only contains AML but also (non) Hodgkin's lymphoma and other types of leukaemia. Surprisingly, we found a significant higher risk of haematological malignancies for patients treated with endocrine therapy. As far as we now this association was not earlier reported and we could not found a clear explanation for this association.

Since 1975 tamoxifen is used for the treatment of postmenopausal breast cancer in patients with positive oestrogen receptor. Tamoxifen is linked to a 1.3–7.5-fold increased risk of endometrial cancer[30]. Although no significant relation was found between endocrine treatment and the risk of endometrial cancer within the group of BBC patients, we found a twofold elevated risk for endometrial cancer after BBC compared to the general female population, particularly for women older than 65 years at second breast cancer diagnosis and women treated with endocrine therapy (results not shown). However, in line with other studies, the SIR for endometrial cancer was also increased for women who received no endocrine therapy (results not shown)[6]. Therefore, other shared risk factors like family history, reproductive factors (e.g. parity, hormone replacement treatment) or high body mass index probably contribute to the increased risk of endometrial cancer[34-37].

Some strengths and limitations of our study should be considered. The strengths of this study include the large population based cohort with nearly complete follow-up data for vital status and TNBC, which enables us to provide reliable estimates of TNBC risk after BBC and effects of treatment. However, information of other risk factors such as lifestyle factors, including smoking, alcohol consumption and body mass index were not available as well as genetic information.

Treatment information was restricted. No information was available about the specific type of radiotherapy and the doses. We found no significant differences in TNBC risks between patients treated with radiation for the first or the second breast cancer. Because we included BBC patients, radiotherapy was given on different sites of the body so a cumulative effect

could be expected for ovary and endometrial cancer and leukaemia, because of the equal distant to both sites and the radio sensitivity. Furthermore information of specific endocrine therapy was not available in our database. Apart from tamoxifen also aromatase inhibitors or luteinising hormone-releasing hormone (LHRH) agonists have been administered. Therefore the effect of endocrine therapy could be slightly underestimated.

Risks were estimated for the first and second breast cancer treatment. Patients with synchronous breast cancer could have received chemotherapy or endocrine therapy for both breasts, however in fact they received only one dosage. Although the cox regression model was corrected for BCFI and variables for second breast cancer treatment were incorporated as time dependent covariates, outcomes need to be interpreted with caution.

CONCLUSION

Women with BBC had a 1.5 times higher risk of all TNBC combined. Young women had a 2.8 times higher risk of all TNBC combined and a ten-fold higher risk of ovarian cancer, compared to the general population, which is probably related to genetic factors. Chemotherapy was associated with a decreased risk of all TNBC combined, while radiotherapy and endocrine therapy were associated with a increased risk. Next to the relations between treatment and the risk of TNBC and the possible role of genetics, shared environmental factors are likely to be involved for most elevated risks. Therefore follow-up care should also be focussed on improving healthy lifestyle. This study gave more insight in the risks of TNBC and results could further optimise and individualise treatment and surveillance protocols in (young) women with BBC.

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CHAPTER 2.4

Risk of prostate cancer among cancer survivors in the Netherlands

D.E.G. Kok, S.A.M. van de Schans, L. Liu, E. Kampman, J.W.W. Coebergh, L.A.L.M. Kiemeney, I.Soerjomataram, K.K.H. Aben

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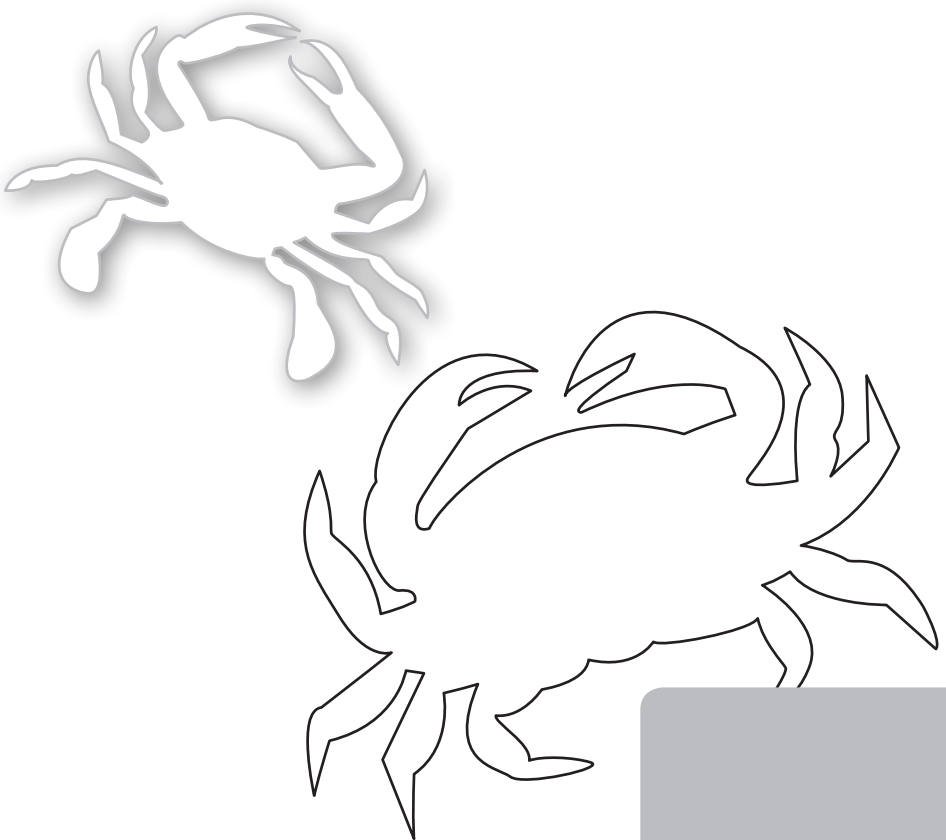


ABSTRACT

In parallel with increasing numbers of cancer patients and improving cancer survival, the occurrence of second primary cancers becomes a relevant issue. The aim of our study was to evaluate risk of prostate cancer as second primary cancer in a population-based setting. Data from the Netherlands Cancer Registry were used to estimate standardized incidence ratios (SIRs) and 95% confidence interval (CI) for prostate cancer as second primary cancer. The effect of time since first cancer diagnosis, specific first cancer sites, age, and pelvic radiotherapy was taken into account. Out of 551,553 male patients diagnosed with a first primary cancer between 1989-2008, 9,243 patients were subsequently diagnosed with prostate cancer. Overall, cancer survivors showed an increased risk (SIR 1.3, 95% CI 1.2-1.3) of prostate cancer. The increased prostate cancer risk was limited to the first year of follow-up for the majority of the specific first cancer sites. More than ten years after the first cancer diagnosis, only melanoma patients were at increased risk (SIR 1.5, 95% CI 1.2-1.9), while patients with head or neck cancers were at decreased risk (SIR 0.7, 95% CI 0.5-0.9) of being diagnosed with prostate cancer. Patients who underwent primary pelvic radiotherapy for their first cancer had a decreased risk of prostate cancer in the long term (SIR 0.5, 95% CI 0.4-0.6). In conclusion, our data showed that cancer survivors have an increased prostate cancer risk in the first year after a first cancer diagnosis, which is most likely the result of active screening or incidental detection.

INTRODUCTION

The number of patients newly diagnosed with cancer increased substantially during the past decades and this trend is expected to continue during coming years[1, 2]. At the same time, survival for most cancer sites improved by early detection and more effective treatment strategies[3, 4]. As a growing number of patients survive their first cancer, the development of second primary cancers becomes a relevant issue[5]. Prostate cancer is the most common cancer among elderly men in Western countries[2, 6]. The incidence of prostate cancer as second primary cancer is likely to increase as a consequence of demographic aging and increased diagnostic activities, combined with the improved cancer survival[7]. Risk of prostate cancer among cancer survivors might also depend on various clinical as well as biological factors. It has been suggested that initial cancer treatment might influence subsequent cancer risk. As such, pelvic radiotherapy for a first cancer has been associated with a reduced prostate cancer risk as compared to non-irradiated patients or the general population[8-11]. Furthermore, incidental detection in surgical specimens or during follow-up, or intensive screening after a previous cancer diagnosis might also influence prostate cancer risk. Likewise, the detection of prostate tumours in cystoprostatectomy specimens[12] is therefore a plausible explanation for the reported co-occurrence of bladder cancer and prostate cancer[13, 14]. Finally, common aetiological factors, such as genetic susceptibility or shared environmental factors, might explain an association between prostate cancer and other malignancies.

Insight into the occurrence of prostate cancer as second primary cancer may yield important implications for aetiological research. Several studies have addressed the relevance of prostate cancer as a second cancer. Most of these studies, however, were limited to specific first cancer sites[13, 15-17] or focussed on treatment effects[8, 9, 11] or family history of the first cancer[18] in particular. A comprehensive overview of prostate cancer risk among cancer survivors, however, is lacking. The aim of the present study was to evaluate the risk of prostate cancer as second primary cancer in a population-based setting and taking into account the first cancer sites and time since first cancer diagnosis. This approach allowed us to compare prostate cancer risks among different first cancer sites, and to evaluate the possible effect of detection and treatment, occurring during follow-up.

PATIENTS AND METHODS

Male patients diagnosed with a first primary cancer between 1989 and 2008 were identified through the nationwide, population-based Netherlands Cancer Registry[19].The analyses were restricted to primary cancers as defined by the International Agency for Research on Cancer (IARC)[20]. Non-invasive cancers, except from bladder cancer because of its common non-invasive character, were excluded from all analyses. Patients with a first and second primary cancer diagnosed on the same day, and patients diagnosed with cancer found during

autopsy were not included in the analyses. Furthermore, patients with a first primary prostate cancer were excluded, resulting in a study population of 551,553 male cancer patients.

Follow-up duration was defined as the time between date of first primary cancer diagnosis until date of death, emigration, diagnosis of prostate cancer as second primary cancer, diagnosis of any (other than prostate cancer) second primary cancer, or end of follow-up (1st of January 2009), whichever came first. Information on death and emigration were obtained from the municipal registries and since 1995 from the Dutch Municipal Personal Records Database, which keeps information about vital status of all inhabitants in the Netherlands. Information on primary cancer treatment was recorded from the medical charts. Clinical tumour stages were categorized into groups (0, I, II, III, IV, and other/unknown) according to the fourth (tumours diagnosed before 1999), fifth (tumours diagnosed between 1999 and 2002) or sixth (tumours diagnosed after 2002) edition of the American Joint Committee on Cancer guidelines (AJCC). The categories represent anatomical groups based on the tumour (T), regional lymph nodes (N) and metastases (M) stages and did not take into account histological grades or PSA levels.

Standardized incidence ratios (SIRs) were estimated to compare incidence rates of prostate cancer as second cancer in the study population versus incidence rates of prostate cancer in the general Dutch population. The SIR was calculated as the number of observed patients with prostate cancer as second cancer divided by the number of expected patients. The number of expected patients with prostate cancer was estimated by multiplying age- and calendar period-specific incidence rates (5-year age and 1-calendar year groups, respectively) in the general Dutch population by the number of person-years at risk. The 95% confidence intervals (CIs) were calculated assuming a Poisson distribution for the observed number of prostate cancers. Absolute excess risks (AERs) were calculated to estimate the excess burden of the prostate cancers occurring as second cancer. The AER (expressed per 10,000 person-years) was calculated as the number of expected patients subtracted from the number of observed patients in the study population and subsequently divided by the person-years at risk. Analyses were presented according to the time since first cancer diagnosis, the first cancer site or age of the patients at first cancer diagnosis. Besides provided estimates for all cancer sites together, data on all sites excluding invasive and non-invasive bladder cancer were presented in order to take into account possible distorting effects of early and incidental detection of prostate tumours in cystoprostatectomy specimens.

In order to assess the effects of radiotherapy on the subsequent prostate cancer risk, we computed SIRs for patients treated with or without pelvic radiotherapy. Pelvic radiotherapy was defined as primary radiotherapy for one of the following first primary cancers: sigmoid colon, rectum, anus and anal canal, penis, testis, other male genital organs, renal pelvis, ureter, and other urinary tract. Patients with (invasive and non-invasive) bladder cancer were not included in these analyses, because most patients not treated with pelvic radiotherapy were likely to undergo radical cystoprostatectomy and were not at risk of developing prostate cancer in the long term. Subgroup analyses for patients treated without pelvic radiotherapy

comprised all patients diagnosed with the aforementioned pelvic tumours (again without invasive and non-invasive bladder cancer), who were not treated with primary radiotherapy.

SAS software (version 9.3, SAS Institute, Cary, North Carolina) was used for all analyses.

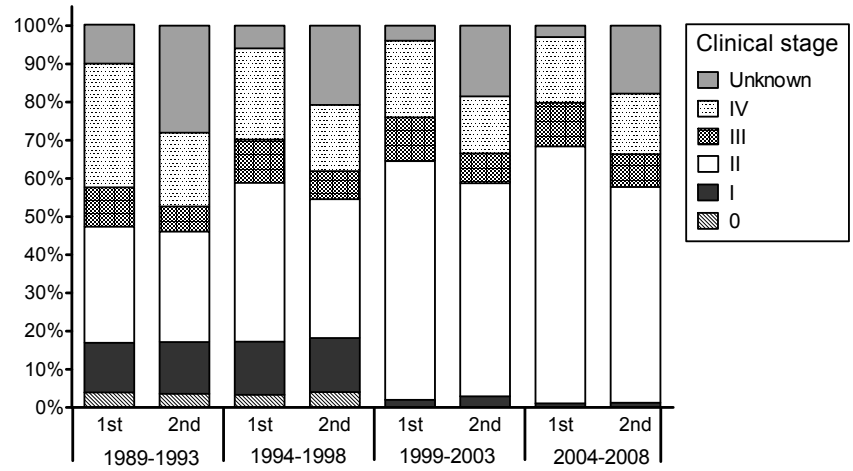
RESULTS

The study population includes 551,553 male cancer patients diagnosed with a first primary cancer between 1989 and 2008. Of these, 9,243 patients subsequently developed prostate cancer after a median follow-up of 2.3 years (range: 1 day to 19 years). The median age (interquartile range (IQR)) of these patients was 70 years (64-76) at time of first cancer diag-

Table 1 Characteristics of patients diagnosed with or without prostate cancer as second primary cancer after a first primary cancer diagnosis between 1989 and 2008 in the Netherlands

	Without prostate cancer as second primary cancer (n=542,310)	With prostate cancer as second primary cancer (n=9,243)
Age at first cancer diagnosis (years)		
Median (interquartile range)	68 (58-75)	70 (64-76)
< 50	71,116 (13%)	167 (2%)
50-74	327,929 (60%)	6,338 (69%)
75+	143,265 (26%)	2,738 (30%)
Period of first cancer diagnosis		
1989-1993	124,057 (23%)	2,717 (29%)
1994-1998	128,434 (24%)	2,694 (29%)
1999-2003	135,556 (25%)	2,316 (25%)
2004-2008	154,263 (28%)	1,516 (16%)
Time at risk (years)		
Median (interquartile range)	1.3 (0.3-4.5)	2.3 (0.3-5.9)
< 1	241,149 (44%)	3,386 (37%)
1-10	248,943 (46%)	4,946 (54%)
10+	52,218 (10%)	911 (10%)
Treatment for first cancer		
Surgery		
Yes	377,008 (70%)	7,994 (86%)
No	132,211 (24%)	1,007 (11%)
Radiotherapy		
Yes	110,105 (20%)	1,206 (13%)
No	399,114 (74%)	7,795 (84%)
Chemotherapy		
Yes	119,690 (22%)	1,301 (14%)
No	389,529 (72%)	7,700 (83%)
Other	27,062 (5%)	192 (2%)
Unknown	6,029 (1%)	50 (1%)

Source: Netherlands Cancer Registry



Source: Netherlands Cancer Registry

Figure 1 Clinical stage distribution of prostate cancer diagnosed as a first primary cancer (from the general population) and as a second primary cancer (among previously diagnosed cancer patients) in the Netherlands between 1989 and 2008 according to period of prostate cancer diagnosis

nosis (**Table 1**). Clinical tumour stages of the prostate cancers occurring as second cancer were compared to clinical stages of first prostate cancers diagnosed in the general Dutch population in the same period (**Figure 1**). Overall, stage III and IV tumours were somewhat less common in subsequent prostate cancers (especially during early follow-up) as compared to first prostate cancers, while the opposite was observed for unknown tumour stages. Also for subsequent prostate cancers diagnosed more recently (2004+), a larger percentage of unknown tumour stages was found, while especially stage II tumours tended to be less common in comparison to first prostate cancers.

Risks of prostate cancer as second primary cancer according to first cancer site and years since first cancer diagnosis are presented in **Table 2.** Overall, cancer survivors showed an increased risk (SIR 1.3, 95% CI 1.2-1.3) of being diagnosed with prostate cancer as compared to the general Dutch population. This effect was mainly observed shortly (0-1 year) after the first cancer diagnosis (SIR 2.1, 95% CI 2.0-2.2). The increased prostate cancer risk in the first year following the first cancer diagnosis was also shown for several specific cancer sites. The corresponding SIRs ranged from 1.3 (95% CI 1.1-1.5) for cancers in the digestive tract (without colorectal cancer) up to 9.2 (95% CI 8.7-9.8) for invasive bladder cancer. These effects disappeared after one year of follow-up for most of the specific cancer sites. Contrary, for patients with skin cancer as first primary cancer, an increased prostate cancer risk was mainly observed after one year since first cancer diagnosis. These effects were most pronounced for melanoma skin cancer. Prostate cancer risk was reduced in patients diagnosed with head or

Table 2 Risk of prostate cancer as a second primary cancer according to first cancer site and time since first cancer diagnosis

	Time since first cancer diagnosis (years)											
	0-1				1-10				10+			
First cancer site	**PY at risk**	**Obs.**	**SIR (95% CI)**	**AER**	**PY at risk**	**Obs.**	**SIR (95% CI)**	**AER**	**PY at risk**	**Obs.**	**SIR (95% CI)**	**AER**
All sites[a]	392,642	3,388	**2.1 (2.0-2.2)**	45	1,200,526	4945	1.0 (0.98-1.0)	0.2	2,033,19	910	1.1 (0.99-1.1)	2
All sites without bladder cancer[b]												
Invasive bladder	23,166	1,090	**9.2 (8.7-9.8)**	419	76,628	361	**0.9 (0.8-0.98)**	-6	12,156	64	0.9 (0.7-1.1)	-6
Non-invasive bladder	27,078	295	**2.4 (2.1-2.6)**	63	125,226	712	**1.2 (1.1-1.2)**	8	22,084	133	1.1 (0.9-1.3)	6
Renal pelvis and ureter	1,921	16	**1.8 (1.0-2.9)**	36	4,785	28	1.2 (0.8-1.7)	9	727	5	1.3 (0.4-2.9)	14
Other urinary tract	207	8	**7.3 (3.1-14)**	333	536	2	0.7 (0.08-2.5)	-16	106	0	0 (0-5.8)	-60
Penis, testis and other male genital organs	10,872	11	1.2 (0.6-2.1)	1	59,997	51	1.1 (0.8-1.4)	1	16,640	18	1.1 (0.7-1.8)	1
Kidney	11,904	124	**3.0 (2.5-3.5)**	69	41,997	232	**1.4 (1.3-1.6)**	17	7,555	39	1.1 (0.8-1.5)	6
Colorectal	66,093	521	**1.7 (1.6-1.8)**	32	221,187	1053	0.9 (0.9-1.01)	-3	33,453	196	1.1 (0.9-1.2)	3
Digestive tract without colorectal	34,328	195	**1.3 (1.1-1.5)**	13	50,522	203	0.9 (0.8-1.05)	-4	6,969	40	1.1 (0.8-1.5)	6
Male Breast	1,021	11	**2.6 (1.3-4.6)**	66	4,113	17	0.9 (0.5-1.5)	-4	606	3	1.0 (0.2-2.8)	-2
Skin (non-melanoma)[c]	33,254	175	0.9 (0.8-1.1)	-3	132,240	792	**1.1 (1.003-1.2)**	4	19,510	126	1.2 (0.97-1.4)	9
Melanoma	18,160	49	1.2 (0.9-1.6)	5	78,968	256	**1.4 (1.3-1.6)**	10	16,455	69	**1.5 (1.2-1.9)**	14
Lung, bronchus and trachea	71,739	458	**1.4 (1.3-1.5)**	18	96,178	390	**0.8 (0.8-0.9)**	-8	11,289	70	1.1 (0.8-1.4)	5
Head or neck	25,069	73	0.9 (0.7-1.1)	-5	93,491	332	0.9 (0.8-1.001)	-4	16,062	53	**0.7 (0.5-0.9)**	-17
Eye and adnexa	1,450	8	1.9 (0.8-3.8)	26	6,194	19	1.1 (0.6-1.7)	2	1,397	5	1.2 (0.4-2.7)	5
Haematolymphopoetic	43,146	229	**1.6 (1.4-1.8)**	20	149,260	399	0.9 (0.8-1.004)	-3	25,296	62	1.0 (0.8-1.3)	-0.3
Bone, joint and soft tissue	6,637	18	1.5 (0.9-2.3)	9	25,862	55	1.1 (0.9-1.5)	3	6,365	14	1.1 (0.6-1.8)	1
Central nervous system	6,772	13	1.2 (0.6-2.1)	3	15,532	10	0.9 (0.4-1.6)	-1	3,139	1	0.3 (0.004-1.7)	-7
Endocrine glands	2,096	6	1.7 (0.6-3.7)	11	9,954	11	0.7 (0.3-1.2)	-5	2,611	8	1.6 (0.7-3.2)	12
Primary site unknown	7,247	88	**2.8 (2.3-3.5)**	78	6,426	17	0.7 (0.4-1.1)	-12	659	3	1.0 (0.2-3.0)	1
Other (e.g. thymus)	472	0	0 (0-2.5)	-31	1,396	5	1.3 (0.4-3.1)	9	224	1	1.3 (0.02-7.0)	9

Source: Netherlands Cancer Registry

Abbreviations: AER = absolute excess risk per 10,000 person-years, CI = confidence intervals, Obs. = number of observed cases, PY = person-years, SIR = standardized incidence ratio. [a] All invasive primary cancer sites, excluding prostate cancer and including non-invasive bladder cancer. [b] All primary cancer sites, excluding prostate cancer, invasive bladder cancer and non-invasive bladder cancer. [c] Basal cell carcinomas were not included.

Table 3 Risk of prostate cancer as a second primary cancer according to age at first cancer diagnosis, treatment and time since first cancer diagnosis

	Time since first cancer diagnosis (years)											
	0-1				1-10				10+			
	PY at risk	Obs.	SIR (95% CI)	AER	PY at risk	Obs.	SIR (95% CI)	AER	PY at risk	Obs.	SIR (95% CI)	AER
Age at first cancer diagnosis (years)												
< 50	61,121	27	**12 (8.0-17)**	4	280,993	54	1.2 (0.9-1.6)	0.4	79,658	86	1.2 (0.9-1.5)	2
50-74	241,611	1,989	**2.2 (2.1-2.3)**	45	732,833	3,584	1.0 (0.998-1.07)	1	115,057	765	1.0 (0.96-1.1)	2
75+	89,910	1,372	**1.9 (1.8-2.0)**	73	186,701	1,307	**0.9 (0.9-0.98)**	-5	8,604	59	1.3 (0.97-1.6)	15
Pelvic radiotherapy for first primary cancer[a]												
Yes	16,294	104	**1.9 (1.6-2.3)**	31	56,558	82	**0.5 (0.4-0.6)**	-17	9,381	16	**0.6 (0.3-0.98)**	-11
No	41,460	305	**1.8 (1.6-2.0)**	33	159,662	653	1.0 (0.9-1.1)	0	30,045	138	1.2 (0.97-1.4)	6

Source: Netherlands Cancer Registry

Abbreviations: AER = absolute excess risk per 10,000 person-years, CI = confidence intervals, Obs. = number of observed cases, PY = person-years, SIR = standardized incidence ratio.

[a] Restricted to first primary cancers of the: sigmoid colon, rectum, anus and anal canal, penis, testis, other male genital organs, renal pelvis, ureter, and other urinary tract.

neck cancer. This effect was observed ten years since first cancer diagnosis in particular (SIR 0.7, 95% CI 0.5-0.9).

The analyses stratified by age at first cancer diagnosis further confirmed that cancer survivors had an increased prostate cancer risk mainly during the first year following first cancer diagnosis (**Table 3**). This finding applies to all age groups, although a more pronounced effect was found for patients who were diagnosed with a first cancer at a relatively young (<50 years) age (SIR 12, 95% CI 8.0-17).

As shown in **Table 3**, both patients treated with or without pelvic radiotherapy for their first primary cancer had an increased risk of prostate cancer during the first year following first cancer diagnosis. Patients who underwent pelvic radiotherapy, however, showed a decreased prostate cancer risk in the long term (SIR 0.5, 95% CI 0.4-0.6 and SIR 0.6, 95% CI 0.3-0.98, for 1-10 and 10+ years after first cancer diagnosis, respectively).

DISCUSSION

Overall, our study showed a 30% increased risk of prostate cancer among Dutch cancer survivors in the first year of follow-up, whereas in the long term prostate cancer risk did not differ from risk in the general Dutch population. An increased prostate cancer risk shortly after a first cancer diagnosis strongly suggests an effect of active screening or incidental detection, resulting from either an increased awareness or anxiety of the patient, or active medical surveillance indicated by the supervising specialist.

It has been shown that incidental prostate cancers are frequently detected in cystoprostatectomy specimens[12, 21]. Furthermore, urological patients might request their urologists for PSA testing as a consequence of anxiety or persisting urological complaints. In these situations, the stage of disease would presumably be lower in comparison to prostate cancer detected among the general Dutch population. Our data tended to show that unfavourable tumour stages (III and IV) were less common in patients with prostate cancer diagnosed as a second rather than a first primary cancer. The larger percentage of prostate cancers with an unknown tumour stage might indicate that staging is less accurate or considered less important in patients with prostate cancer diagnosed as a second cancer. As expected, the risk of prostate cancer was reduced 1-10 years after an invasive bladder cancer diagnosis, probably because the patients who underwent a cystoprostatectomy were no longer at risk of developing prostate cancer. Notably, this finding was not applicable to non-invasive bladder cancer, wherefore the increased prostate cancer risk persisted up to ten years following diagnosis. This contrary finding may be due to more expectant treatment strategies for non-invasive bladder cancer, which have resulted in prolonged detection effects.

For patients with a previous diagnosis of melanoma as well as non-melanoma skin cancer, an increased prostate cancer risk was mainly found during later years of follow-up. Contrary to our findings, a previous study with data from one of the regional cancer registries in the Netherlands showed that patients with (non-melanoma) skin cancer had a reduced risk of prostate cancer[22]. It was hypothesized that patients with skin cancer might have had relatively high levels of vitamin D as a consequence of sun exposure in the past, which may protect them against the development of prostate cancer[22]. Several other studies, however, did not confirm these findings[23], or showed an increased prostate cancer risk following a skin cancer diagnosis[17, 24]. Focusing on melanoma, data from the Surveillance, Epidemiology, and End Results (SEER) program showed an increased prostate cancer risk up to ten years following melanoma diagnosis[25, 26], which is consistent with our findings. Possible explanations for the increased prostate cancer risk in melanoma patients might refer to shared environmental or genetic aspects. A recent study demonstrated that at least two prostate cancer risk alleles (*rs1512268*, odds ratio (OR) 3.9, 95% CI 1.4-10.9 and *rs5759167* OR 2.6, 95% CI 1.2-5.6) were associated with an increased risk of melanoma in prostate cancer patients[27]. We cannot fully exclude the possibility that increased awareness and screening also contributed to the

excess of prostate cancer in melanoma patients, although the lack of an effect during the first year of follow-up argues against this.

We observed a reduced risk of prostate cancer, especially after a follow-up period of more than ten years, among patients who were diagnosed with a head or neck cancer. The possible mechanisms for the reduced prostate cancer risk in these patients are unclear. So far, there is no indication that the main established risk factors for head and neck cancers, such as smoking, alcohol intake, and infections with the human papillomavirus[28] are likely to protect against the development of prostate cancer. Future studies should focus on the possible associations between prostate cancer and different specific tumours in the head and neck region as well as the possible underlying mechanisms.

Consistent with previous literature[8-11], we showed an overall reduced prostate cancer risk following primary pelvic radiotherapy. Nevertheless, for the first year of follow-up, the subsequent prostate cancer risk was increased among patients who received pelvic radiotherapy. Similar findings were observed for patients who did not receive pelvic radiotherapy suggesting once more the effects of detection. A possible explanation for the consistently reported reduced prostate cancer risk following pelvic radiotherapy, which is confirmed by our study, would be that early and indolent prostate tumours are suppressed by the irradiation exposure. Another hypothesis[9, 10] refers to the possibility that radiotherapy initially increases, but in the long term lowers PSA production[29, 30]. In theory, the incidence of screening-detected prostate cancers would then, due to masked PSA levels, be lower as compared to non-irradiated patients. As a consequence, the prostate tumours in irradiated patients are detected later, and hence are more advanced or high-grade as compared to tumours in non-irradiated patients[9]. Others, however, did not find an effect of previous pelvic radiotherapy on prostate cancer stage or grade[10], neither on the decline in PSA levels after irradiation of the non-malignant prostate[31]. We did not compare clinical tumour stages for patients treated with or without pelvic radiotherapy, because we cannot exclude the possibility that period-specific changes in treatment regimens during our extensive follow-up period (1989-2008) will account for possible differences between these two groups.

Strengths of our study include the comprehensive approach which allows a simultaneous evaluation of all specific first cancers sites in relation to subsequent prostate cancer risk during an extensive follow-up period. Furthermore, we used population-based data of a high-quality cancer registry with a large number of first and second cancer patients. Possible limitations of our study are the relatively small number of patients in some of the subgroup analyses and the limited data on secondary cancer treatment. As a consequence, patients who were classified as 'not having pelvic radiotherapy' in the subgroup analyses, might still have undergone pelvic radiotherapy as secondary therapy. Although this limitation might have influenced the risk estimates for this subgroup, it is not likely to bias the findings for the subgroup of patients who were classified as 'having pelvic radiotherapy'[32].

In conclusion, our data showed that cancer survivors have an increased risk of being diagnosed with prostate cancer as a second primary cancer. The effects were mostly restricted to the first year following the first cancer diagnosis, which might implicate an effect of active screening or incidental detection.

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Conflicts of interest

None declared.

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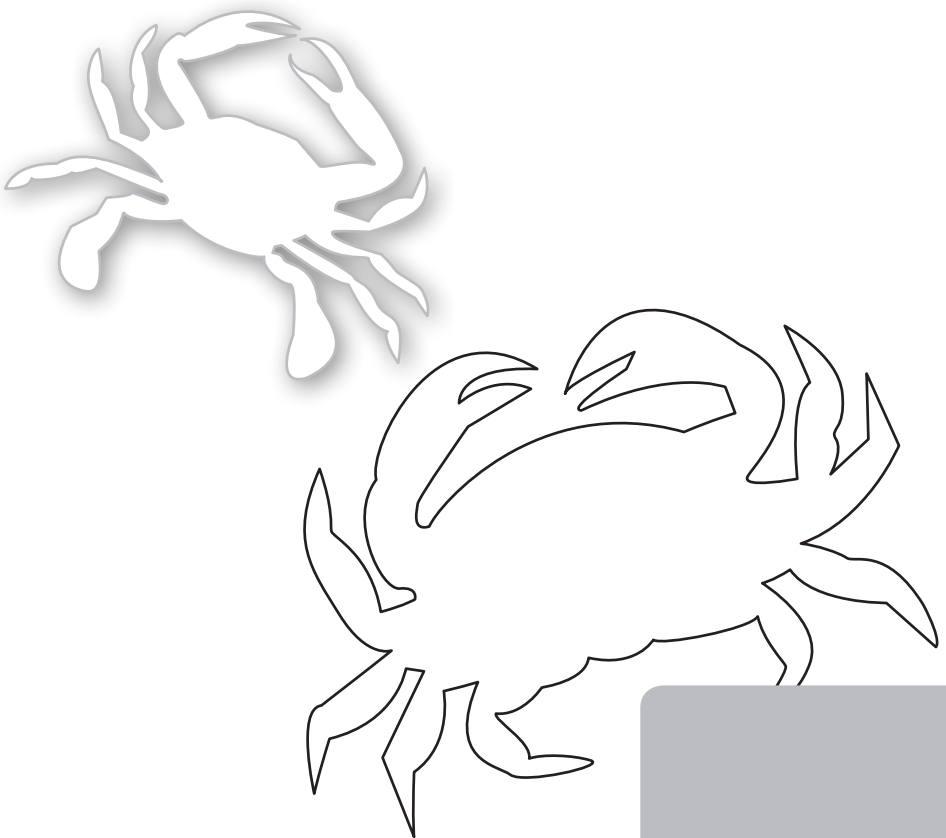
CHAPTER 2.5

Minimal increased risk of Chronic Lymphocytic Leukaemia among cancer survivors in the Netherlands

E.C. van den Broek, L. Liu, E.F.M. Posthuma, M.L.G. Janssen-Heijnen, J.W.W. Coebergh, I. Soerjomataram

Submitted



ABSTRACT

We assessed the risk of Chronic Lymphocytic Leukaemia (CLL) following a first primary malignancy (FPM). We utilised the national cancer registry data of 1,270,595 Dutch cancer survivors who were at risk to be subsequently diagnosed with CLL between 1998-2008.

Cancer survivors were categorized based on time since diagnosis of FPM, age and gender, and therapy for FPM. CLL was regarded synchronous when diagnosed within three months after diagnosis of FPM.

Overall, we found that cancer survivors had a 50% higher risk than the general population to be diagnosed with CLL. Excess risk of second CLL was observed 10 years after diagnosis of the FPM (Standardised Incidence Ratio (SIR): 1.3; 95% Confidence Interval (CI): 1.1-1.6). In the first year after diagnosis we found a threefold increased risk of CLL (SIR: 3.0; 95% CI: 2.7-3.3), however no increased risk was observed after excluding synchronous cases.

An increased risk for metachronous CLL was found in males younger than 65 years at time of diagnosis of FPM (SIR: 1.2; 95% CI: 1.1-1.5). A slightly decreased risk of CLL was found among cancer survivors who underwent chemotherapy (SIR: 0.8; 95% CI 0.6-1.1), radiotherapy (SIR: 0.9; 95% CI 0.7-1.0) or both (SIR: 0.5; 95% CI 0.2-0.9).

Increased detection due to intensive clinical check-ups after diagnosis of the FPM is the most likely explanation for the increased risk of CLL among cancer survivors.

INTRODUCTION

Although overall incidence rates of Chronic Lymphocytic Leukaemia (CLL) have been stable over the last decades, an increasing incidence in younger patients has recently been reported[1,2]. This increase might be associated with the increasing number of cancer survivors[3], due to several possible mechanisms, such as shared risk factors or carcinogenity of the treatment for the first malignancy.

The etiology of CLL is unknown, and the only established risk factors are genetic predisposition [4] and occupational exposure to benzene [5] and several other chemicals[6].

In general, CLL is not regarded as a radiation-induced cancer, though, in spite of elaborate research, controversies on this issue persist[7,8]. The relation between chemotherapy and subsequent development of CLL has been less intensively studied. Most studies of leukaemia after chemotherapy for a previous malignancy have excluded CLL[9,10].

Increased detection rates among the growing number of cancer survivors is a third potential cause of increased CLL incidence, as cancer patients undergo many extensive checkups, which increase the chance of CLL being detected coincidentally. Increased detection rates can lead to overdiagnosis, with all its negative physical, psychological and economic effects.

Albeit the fact that studying the incidence of CLL as a Second Primary Malignancy (SPM) might lead to important insights into the aforementioned causal factors, literature on this topic is scarce. Two articles describe an increased incidence of CLL among skin cancer survivors[11,12].

Although the influence of second CLL on the survival of cancer survivors is not established yet[13], it is known that multiple cancer diagnoses have been related to worse survival[14]. Because of this possible impact on prognosis, it is important to determine which group of the survivors has an increased risk of CLL, so an adequate follow-up strategy and tailored care can be offered to these patients.

In this paper we describe the incidence of CLL as a second malignancy and the effect of potential risk factors such as therapy for the first malignancy, using a nation-wide cancer registry database. This study can provide insights into the characteristics of survivor groups with increased risk of CLL.

PATIENTS AND METHODS

As part of a broad study of the burden of second malignancies, thereby exploring determinants of risk and prognosis of all patients with cancer diagnosed in the Netherlands between 1989 and 2008 [15] a study of CLL was performed upon an earlier analysis of trends in incidence and survival [2] and as background information for another study of the penetration of targeted drugs among patients with CLL in recent years.

We retrieved all cancer cases diagnosed in the Netherlands between 1989 and 2008 from the Netherlands Cancer Registry (NCR) database which was fed by regional cancer registries

of eight comprehensive cancer centres. We included patients diagnosed with a first primary invasive cancer (N=1,270,595) and followed these patients until the occurrence of CLL, other SPM, death or end of follow-up (December 31, 2008), which ever came first. The history of malignancies was retrieved from the medical records and used to determine the order of the cancer diagnosis, according to the International Rules for Multiple Primary Cancers[16].

CLL was defined as ICD-O-2 codes 9592 and 9803 and ICD-O-2 / ICD-O-3 codes 9670, 9800, 9820, and 9823 (in accordance to ICD-O-3, Small Lymphocytic Lymphoma was also regarded as CLL)[17]. We found 967 patients diagnosed with CLL as a SPM.

Median interval between diagnosis of FPM and CLL was calculated by age and gender.

Excess risk (standardised incidence ratio; SIR) was calculated as the ratio of the observed cases to the expected cases. The number of expected cases in the cohort was calculated based on the age-, gender- and calendar year-specific incidence rates for CLL in the general Dutch population, multiplied by the person-years at risk. 95% Confidence Intervals (95% CI) were calculated based on a Poisson distribution.

SIRs were calculated according to gender, age at diagnosis of FPM, diagnosis interval between FPM and CLL (0-12 months, 13-60 months, 61-120 months and ≥120 months) and treatment of FPM. As different trends in CLL incidence rates were observed among persons aged 0-64 years, 65-74 years and ≥75 years and these differences might be associated with differences in the incidence of CLL as a SPM[2], we chose to categorize age at diagnosis into these three categories. Treatment of FPM was categorized into five categories: surgery (without chemotherapy, radiotherapy or any other (neo) adjuvant therapy), chemotherapy (with or without surgery), radiotherapy (with or without surgery), chemo- and radiotherapy (with or without surgery) and other.

As CLL is easily detected in routine blood tests that are frequently performed immediately after cancer diagnosis, patients diagnosed within three months after diagnosis of FPM (N=281; 29% of total second CLL) were regarded as synchronous. (The group of patients with a diagnostic interval of more than three months was indicated as metachronous).To assess the role of increased detection, all SIRs were calculated before and after exclusion of the synchronous cases. (SAS software (SAS system 9.2, SAS Institute, Cary, NC) was used to perform the statistical analyses.

RESULTS

In the past 20 years, 967 patients were recorded in the NCR with a diagnosis of CLL following a prior malignancy. This is 7% of all patients with CLL. Almost half of the patients were older than 75 at the time of the CLL diagnosis. Breast and prostate cancers were the most frequent sites of FPM, contributing to 41% and 31% of all FPMs among women and men with CLL. (**Table 1**) Eleven percent of the male patients had lung cancer as FPM. After excluding synchronous cases, only 5.5 % of the male second CLL patients had earlier been diagnosed with lung cancer. (Results not shown) The median interval between diagnosis of FPM and CLL

Table 1 Characteristics of cancer survivors who developed a second Chronic Lymphocytic Leukaemia (CLL) in the Netherlands in 1989-2008

	Male	Female
Nr of patients	621	346
Age at diagnosis FPM		
0-64 years	182 (29%)	117 (34%)
65-74 years	235 (38%)	123 (36%)
75-95 years	204 (33%)	106 (31%)
Age at diagnosis of CLL as SPM		
30-64 years	114 (18%)	78 (23%)
65-74 years	227 (37%)	107 (31%)
75-95 years	280 (45%)	161 (47%)
Ranking of FPM by site		
1	Prostate (31%)	Breast (41%)
2	Skin, other[2] (14%)	Colon and Rectum (14%)
3	Colon and Rectum (13%)	Skin, other[2] (10%)
4	Lung, Bronchus and Trachea (11%)	Corpus Uteri (7%)
5	Haematolymphopoetic (6%)	Skin, Melanoma (6%)
Median diagnosis interval in months (IQR)[1] by age at FPM diagnosis		
0-64 years	45 (3-96)	59 (4-111)
65-74 years	22 (3-58)	30 (1-82)
75-95 years	13 (1-46)	13 (1-46)

Source: Netherlands Cancer Registry

[1] Interquartile range

[2] non-melanoma skin cancers excluding basal cell carcinoma

was two years. Diagnostic intervals were shorter among those diagnosed with a FPM at older age: 13 months for those aged 75+, 22 and 30 months for patients between 65 and 74 years (males and females respectively) and 45 and 59 months (males and females respectively) for those younger than 65 years.

Overall, cancer survivors had a 50% higher risk to be diagnosed with CLL than the general population (SIR 1.5; 95% CI: 1.4-1.6). **Table 2** shows that this increased risk of CLL was observed among all cancer survivors regardless of gender and age at diagnosis of FPM. The excess risk compared to the general population ranged between 30% and 80%. The group with the highest risk consisted of oldest male survivors with an 80% higher risk than the population (95% CI: 1.5-2.0). After exclusion of synchronous CLL, increased risk was no longer observed in any of the subgroups, except for males who were younger than 65 at diagnosis of FPM (SIR 1.2; 95% CI: 1.1-1.5).

The risk for CLL was highest in the first year after FPM diagnosis (SIR: 3.0; 95% CI: 2.7-3.3). After excluding synchronous CLL, SIRs were no longer elevated during the first ten years after FPM diagnosis (**Table 3**). After ten years of follow-up an increased risk of 30% was observed.

Table 2 Standardized Incidence Ratio (SIR) according to age at diagnosis of First Primary Malignancy for all second Chronic Lymphocytic Leukaemia (CLL) cases and for Metachronous CLL cases only

Age (years)	Synchronous and metachronous CLL cases						Metachronous CLL cases only					
	Males			Females			Males			Females		
	N	SIR	95% CI	N	SIR	95% CI	N	SIR	95% CI	N	SIR	95% CI
0-64	182	1.6*	1.4-1.9	117	1.4*	1.1-1.6	136	1.2*	1.1-1.5	90	1.0*	0.8-1.3
65-74	235	1.3*	1.2-1.5	123	1.4*	1.2-1.7	169	1.0*	0.8-1.1	87	1.0*	0.8-1.2
75+	204	1.8*	1.5-2.0	106	1.4*	1.2 -1.7	135	1.2*	1.0-1.4	69	0.9*	0.7-1.2

Source: Netherlands Cancer Registry

*) p< 0.05 N: Numbers, 95% CI: 95% Confidence Interval

We additionally analysed the distribution of treatment and sites of FPM for patients who were diagnosed with a CLL more than ten years following the FPM diagnosis. We found no difference in the pattern to that observed for the general patients included in this study. **Table 4** illustrates the SIRs for CLL by treatment of the FPM. An increased risk of CLL was found for patients in all treatment categories except for those who received both chemo- and radiotherapy as treatment of FPM. If synchronous CLL cases were excluded from the analysis, only patients who had surgical treatment (without radiation or chemotherapy) remained at increased risk of CLL (SIR 1.2; 95% CI 1.1-1.4). Patients who received both chemo- and radiotherapy had a reduced risk of CLL (SIR 0.5; 95% CI 0.2-0.9).

DISCUSSION

We found 967 patients with CLL following a prior malignancy over the past 20 years, which forms 7% of all newly diagnosed CLL cases. Overall, cancer survivors in the Netherlands had a 50% higher risk

Table 3 Standardized Incidence Ratio (SIR) for second Chronic Lymphocytic Leukaemia CLL according to number of months since diagnosis of First Primary Malignancy (FPM)

Months after diagnosis FPM	All			Males			Females		
	N	SIR	95% CI	N	SIR	95% CI	N	SIR	95% CI
0-121	**401**	**3.0***	**2.7-3.3**	**261**	**2.9***	**2.6-3.3**	**140**	**3.3***	**2.7-3.9**
4-12[2]	120	0.9*	0.8-1.1	80	0.9*	0.7-1.1	40	0.9*	0.7-1.3
13-60	290	1.0*	0.9-1.1	203	1.1*	1.0-1.3	87	0.8*	0.7-1.0
61-120	181	1.1*	1.0-1.3	106	1.1*	0.9-1.4	75	1.1*	0.9-1.4
>120	95	1.3*	1.1-1.6	51	1.4*	1.0-1.8	44	1.2*	0.9-1.6

Source: Netherlands Cancer Registry

[1]. Synchronous cases included

[2]. Synchronous cases excluded

*) p< 0.05

N: Numbers, 95% CI: 95% Confidence Interval

Table 4 Standardized Incidence Ratio (SIR) according to treatment received for First Primary Malignancy (FPM) for all second Chronic Lymphocytic Leukaemia CLL cases and for Metachronous CLL cases only

Treatment of FPM	Syn- and metachronous CLL cases			Metachronous CLL cases only		
	N	SIR	95% CI	N	SIR	95% CI
Chemotherapy	72	1.4*	1.1-1.8	41	0.8**	0.6-1.1
Radiotherapy	206	1.3*	1.1-1.4	145	0.9**	0.7-1.0
Chemo- and Radiotherapy	19	1.1*	0.7-1.7	8	0.5**	0.2-0.9
Surgery only	492	1.6*	1.5-1.7	380	1.2**	1.1-1.4
Other	178	1.6*	1.4-1.8	112	1.0**	0.8-1.2

Source: Netherlands Cancer Registry

*) $p < 0.05$

N: Numbers, 95% CI: 95% Confidence Interval

to be diagnosed with CLL than the general population. This risk was highest for males older than 75 years. However, after excluding synchronous cases, an increased risk for CLL was only observed in males younger than 65 years at the time of diagnosis of FPM. Furthermore, no excess risk of second CLL was observed within ten years after diagnosis of the FPM. Neither did we find an increased risk of CLL among cancer survivors who underwent chemo- and / or radiotherapy, rather being reversed.

The median interval between a FPM and CLL (two years) was shorter than the median interval between a FPM and a general second malignancy (all types of second cancer; three years)[15]. The short time to detection could be the result of increased surveillance in cancer survivors. CLL is often typically diagnosed coincidentally, when lymphocytosis is noticed during routine blood tests. At the time of cancer diagnosis, intensive clinical check-ups might thus incidentally detect subclinical CLL that otherwise would remained undetected for a long time if not for ever. We also hypothesize that this explains the presence of lung cancer as one of the most frequent sites of FPM to precede CLL. In general lung cancer should contribute little to the incidence of SPMs, because of its poor prognosis[15]. However, intensified check-ups start soon after the diagnosis, neutralising the effect of survival time on the incidence of SPMs, hence the emergence of lung cancer patient as one of the most common FPMs before CLL diagnosis.

After exclusion of synchronous cases, male cancer survivors who were younger than 65 at the time of diagnosis of FPM remained the only group with an increased risk of CLL. This is another indication for the role of increased detection. In the general population, men under the age of 65 have the lowest average number of doctor's consultations[18]. Hence, the difference in number of clinical check-ups (and therewith the chances of CLL being detected coincidentally) between cancer survivors and the general population is largest in this group, creating a gap between observed (rates in survivors) and expected (rates in population) cases, leading to a substantial increased risk of CLL.

Our results on the risk of CLL according to prior cancer therapy confirmed the findings of previous studies that therapy for a prior cancer generally does not increase the risk of CLL.

Two earlier studies among patients with endometrium and prostate cancers showed that radiotherapy for these malignancies did not increase the risk of CLL[19,20].

The reduced risk among patients that received both chemo- and radiotherapy could be the consequence of very intense monitoring of this group in the first three months after diagnosis of FPM. In general, about 30% of the cases of CLL being a SPM are diagnosed within three months after diagnosis of the FPM. Among patients that received both chemo-and radiotherapy this is 58%. Detecting many patients at a certain period at a subclinical phase, will cause a temporary increase in incidence, followed by a decline, as all the cases that normally would be detected by the time the patient presented with symptoms are already diagnosed.

We found an increased risk of CLL ten years after the diagnosis of FPM, especially in males. Although the effect of radiation emerges earlier in haematological malignancies than in solid tumours[21], CLL could be an exception due to its very long latent period[7]. In our study we did not find any further evidence to support this hypothesis.

To our knowledge, this is the first study that uses national cancer registry data with good quality data and ample number of cases assuring the validity of the results. However, this study is limited by the lack of data on risk factors, stage of CLL and details of prior treatment (such as intensity of radiation or type of chemotherapy). Furthermore, we should bear in mind that due to the long indolent course of the disease and lack of pathology reports to signal new CLL cases, there is a possible delay in the detection and registration of CLL, causing CLL cases appearing to be the second malignancy while they actually were the first.

In conclusion, increased detection seems to be the main cause of the increased incidence of CLL among cancer survivors, especially in males younger than 65. As the number of cancer survivors is increasing, the number of patients with second CLL will follow the same trend. Further research on the increased incidence more than ten years after diagnosis of a FPM, the prognosis of second CLL and its influence on the FPM is warranted to support physicians and patients in decision making for this increasing group of complex patients.

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CHAPTER 2.6

Trends in risk of second primary melanoma amongst cancer patients in the Netherlands, diagnosed 1989-2008

L. Liu, I. Soerjomataram, T. Nijsten, M. van der Aa, R. van der Leest, J.W.W. Coebergh, E. de Vries

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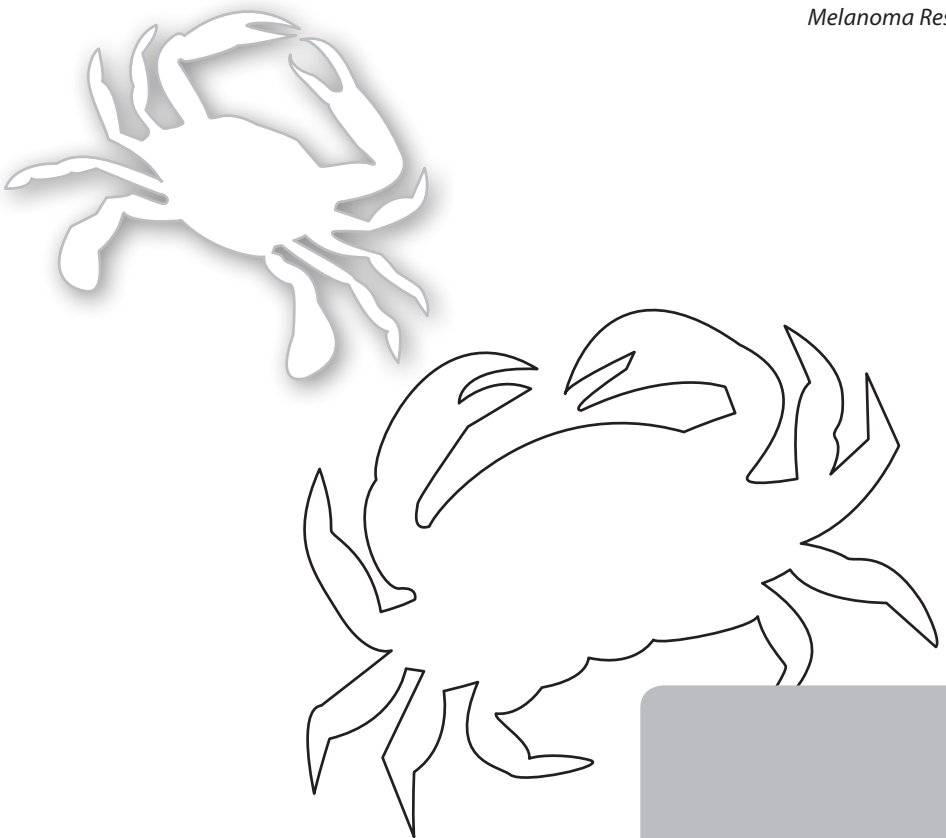


ABSTRACT

Objective: to assess time trends of risk of melanoma as a second primary cancer (MSPC) among cancer patients in the Netherlands during 1989-2008

Method: Data from the population-based Netherlands Cancer Registry (NCR) were used for an analysis of time trends in risk of MSPC in a fixed inception cohorts design (1989-1990, 1996-1997 and 2003), with similar length of follow-up. Standardized incidence ratios (SIR) and absolute excess rates (AER) were calculated to estimate relative risks and excess absolute risks of MSPC.

Results: Differential time trends of risk in MSPC were observed, i.e. decreasing for SIR and increasing for AER in both sexes, but not reaching significance. Over time, AER changed from 24 to 72 per 10,000 person years (p for trend=0.01) in male patients with a prior melanoma during 2-5 years of follow-up. Whereas, among females with a first squamous cell carcinoma of skin, AER sharply increased (p for trend=0.3) over time during the first year of follow-up, coinciding with a decrease during the 2-5 years of follow-up period (p for trend=0.1). MSPCs diagnosed later during follow-up were thicker than those diagnosed earlier this difference being only statistically relevant among male patients with a prior melanoma. The observed favourable risk trend among female patients coincided with thicker MSPCs than males'.

Conclusion: Differential risk trends were observed for MSPC among cancer patients during the past two decades in the Netherlands that did not seem to be affected by greater awareness of the disease. Since the stage distribution of MSPCs worsened during follow-up, efforts should be made to earlier diagnosis of MSPC.

Key words: Incidence, Melanoma, surveillance, Second Primary Neoplasm

INTRODUCTION

In the Dutch population, the incidence of cutaneous malignant melanoma (CMM) has been increasing with 4% annually between 1989 and 2005[1], most likely having two types explanations: higher exposure to exogenous risk factors (i.e. sunlight, sun-beds), together with changes in clothing and improved awareness of signs of the disease (partly reflected by Freckle Bus type of actions) , lower barrier to visit a dermatologist resulting in more diagnosis of relatively benign lesions [2].

Improved survival among cancer patients results in an increase in the number of patients alive thus amenable to second primary cancers, including melanomas (MSPC), diagnosed after any first cancer diagnosis [3-4]. MSPC ranked the 8th most prevalent multiple malignancy among cancer survivors in the Netherlands [5].

As melanoma is a potentially lethal cancer and a melanoma diagnosis has been shown to negatively impact health-related quality of life [6], analyzing time trends of MSPC in cohorts of cancer survivors is of both clinical and public health importance.

As MSPC and its precursor lesions occur on the skin, they can in theory be more easily recognized and diagnosed in early stages. Changes in awareness of melanoma in the population can affect incidence trends and stage at diagnosis of MSPC. A better understanding of trends in the occurrence of MSPC may facilitate both primary and secondary prevention of melanoma among cancer survivors.

The objective of current study is to evaluate time trends on risk of MSPC in the Netherlands between 1989 and 2008.

MATERIALS AND METHODS

Data

Population-based data from the nationwide Netherlands Cancer Registry (NCR), which was started in 1989 and is maintained and hosted by the Comprehensive Cancer Centers, were used[7]. The NCR is based on notification of all newly diagnosed malignancies in the Netherlands by the automated pathological archive (PALGA). Additional sources of patient identification is the national registry of hospital discharge diagnoses, which accounts for up to 8% of new cases[7]. Information on patient characteristics such as gender and date of birth, as well as tumor characteristics such as date of diagnosis, sub site (International Classification of Diseases for Oncology (ICD-O-3)[8], histology, stage (Tumor Lymph Node Metastasis (TNM) classification[9] and grade, are obtained routinely from the medical records at about 6-9 months after diagnosis. The quality of the data is high, due to thorough training of the registrars and computerized consistency checks at regional and national levels. Completeness is estimated to be at least 95%[10]. In addition to passive follow-up via the hospitals, date of death

is also retrieved from the Municipal Personal Records Database which contains all deaths or emigrations in the Netherlands since October 1994. For patients diagnosed before October 1994, follow-up was completed by merging the database with municipality death records or with the Central Bureau for Genealogy, which registered all deaths in the Netherlands.

Of note, in the Netherlands cancer registry, 96% of non-melanoma skin cancers are squamous cell carcinomas of the skin and 4% are rare skin cancer types [11]. Basal cell carcinomas are only registered in the south Netherlands Eindhoven Cancer Registry.

Definition of melanoma as a second primary cancer (MSPC):

We define a CMM (ICD-10: C43) following diagnosis of any type of invasive cancer that was recorded in the Netherlands cancer registry in 1989-2008 a melanoma as a second primary cancer (MSPC). We only included invasive MSPC in the analysis (N=388).

Fixed inception cohorts:

Cancer patients were grouped into 3 cohorts based on period of diagnosis of first cancer (1989-1990, 1996-1997, and 2003). We followed each of the cohorts for the same period of 1 day after first cancer diagnosis until a maximum of 5 years of follow-up time; i.e. follow-up years were 1989-1995 for the first cohort, 1996-2002 for the second cohort and 2003-2008 for the third cohort. Occurrence of MSPC, second other cancers, death or end of study (i.e. December 31 1994 and 1995, December 31 2001 and 2002, and December 31 2008), whichever came first, defined the end of follow-up. In this design we aimed to use maximum information on MSPC while taking both equal follow-up periods and avoiding overlapping in follow-up calendar years [12].

Statistical analysis used to assess changes in risk of MSPC

(1) Incidence number and rates.
Number of cases with an MSPC was described according to sex and cohorts. Crude incidence rates of MSPC were calculated as the number of cases divided by the person years at risk in each cohort. To correct for differences in age structure over cohorts, rates were adjusted to the European Standard Population. European standardized incidence rates of melanoma were computed for both single and total melanoma diagnosis (incl. single and multiple diagnoses) in 1989-2008.The difference between these two incidence rates is due to the occurrence of MSPC. Of note, this measure is prone to a bias from different follow-up duration: with longer follow-up, more MSPCs are expected to occur, resulting in a higher MSPC incidence and hence a bigger gap.

(2) Standardized incidence ratio (SIR) and absolute excess risk (AER).
SIR expresses the excess incidence relative to the background incidence, defined as the ratio between observed and expected number of patients with MSPC.

AER expresses additional incidence beyond the background rate in the general population, defined as the difference between the observed and expected number of patients with MSPC divided by the person years at risk and expressed in per 10,000 person years.

To compute expected numbers, person years at risk for each of the sex-, age- (5-year band) and calendar year-specific (1-year band) strata were multiplied by the corresponding incidence rate in the general population and then summed across strata[13]. Person years at risk in each cohort was calculated summing individual follow-up times at the date of first cancer diagnosis until the occurrence of the MSPC, of other second cancer, end of the cohort (December 31 1994 and 1995, December 31 2001 and 2002, and December 31 2008) or death, whichever came first. Therefore maximum individual follow-up time was five years and minimum follow-up is one day.

Patients with zero follow-up time (N=51; 10%) were deleted from SIR and AER analysis.

AER was presented in two follow-up periods post-first cancer diagnosis: in 0-1 year and in 2-5 years according to sex and type of first cancers.

Tests for linear trend in relation to period of diagnosis were performed by incorporating a parameter in the relevant Poisson regression model with consecutive nonnegative integer values corresponding to increasing or decreasing levels of the factor and comparing the deviance statistic with that of a model without the relevant parameter.

Statistical significance was defined as a 2-sided p-value of less than .05.

Results

During a maximum of 5 years follow-up time, 388 (181 males and 207 females) patients were diagnosed with a MSPC among the 298,218 cancer patients included in the 3 inception cohorts. Characteristics and MSPC incidence rates of the 3 cohorts are described in **Table 1**. The age-adjusted incidence rates of MSPC cases per cohort were 5.1, 7 and 8.6 per 10,000 person years for cohort 1989-1990, 1996-1997 and 2003, respectively. Median age at diagnosis in patients with a melanoma as first primary malignancy was 51 years (interquartile range (IQR): 36-64 years), for patients with a first non-melanoma skin cancer, 74 years (IQR: 64-79 years) and for other types of first cancer 62 years (IQR: 52-74 years). The time interval between diagnosis of the first cancer and MSPC significantly shortened over time among patients with a first squamous cell carcinomafrom 3.4 years in the first cohort (1989-1990) to 2.2 years in the 2003 cohort in men and from 2.6 to 0.7 years in women (p=0.06 and p=0.1, respectively). Among patients with a first melanoma, the diagnostic interval seemed to be around 1 year longer over time, however not statistically detected.

Table 1 Characteristics of cancer survivors with a second primary cancer (MSPC) and followed until 5th year after (any) first invasive cancer diagnosis according to sex and 3 inception cohorts (1989-1990, 1996-1997, and 2003) in the Netherlands (N=388)

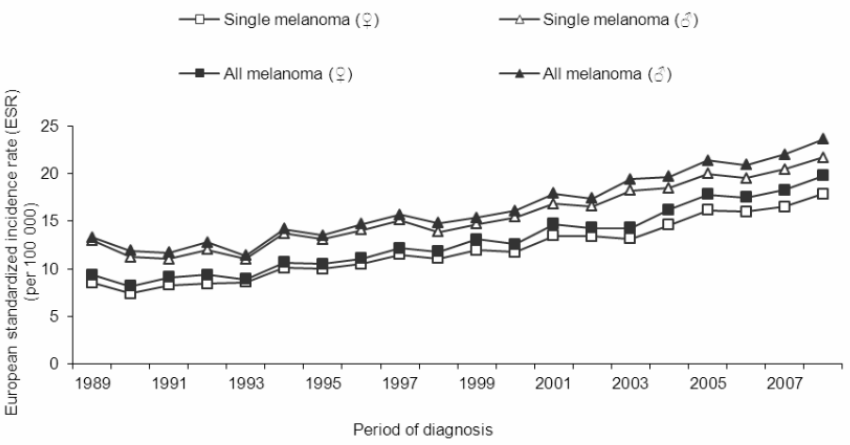
	Males				Females			
Period of diagnosis of first cancer	**1989-1990**	**1996-1997**	**2003**	**P for trend[1]**	**1989-1990**	**1996-1997**	**2003**	**P for trend[1]**
Number (%. row percentages)	40	77	64		61	83	63	
Person years at risk	83,007	112,599	72,847		118,507	146,896	90,661	
Age-adjusted rate (per 10,000 person years)	4.8	7.0	8.9		5.3	6.1	7.1	
Most common first cancers followed by a second primary melanoma								
Skin, Melanoma								
Number (% col[2])	14 (35)	27 (35)	22 (34)	0.1	21 (31)	21 (33)	25 (54)	0.8
Diagnosis interval (years) (median; interquatile range (IQR))	1.5 (0.3-2.4)	1.1 (0.1-3.0)	2.6 (1.4-3.6)	0.07	1.3 (0.4-2.6)	0.8 (0.4-1.9)	1.5 (0.3-3.4)	0.2
Age at first cancer diagnosis (years) (median; interquatile range (IQR))	34 (24-47)	51 (37-57)	55 (44-67)	0.03	40 (35-55)	50 (31-58)	58 (43-63)	0.2
Squamous cell carcinoma[3]								
Number (% col[2])	4 (10)	5 (6)	4 (6)	0.9	2 (7)	4 (8)	8 (13)	0.4
Diagnosis interval (years) (median; interquatile range(IQR))	3.2 (2.4-4.1)	2.7 (1.0-3.8)	2.5 (2.2-3.4)	0.03	2.6 (1.5-2.6)	3. 0 (1.1-3.9)	0.7 (0.4-1.1)	0.04
Age at first cancer diagnosis (years) (median; interquatile range(IQR))	71 (68-72)	66 (60-74)	72 (65-80)	0.3	72 (68-76)	76 (73-77)	69 (48-73)	0.09
Prostate cancer								
number (% col[2])	9 (23)	20 (26)	12 (19)	0.04	n.a.	n.a.	n.a.	n.a.
Diagnosis interval (years) (median; interquatile range(IQR))	1.7 (0.4-2.8)	1.4 (0.6-2.7)	2.0 (1.5-3.4)	0.1	n.a.	n.a.	n.a.	n.a.
Age at first cancer diagnosis (years) (median; interquatile range(IQR))	72 (67-75)	69 (61-74)	69 (66-71)	0.6	n.a.	n.a.	n.a.	n.a.
Breast cancer								
Number (% col[2])	n.a.	n.a.	n.a.	n.a.	18(30)	20(24)	21(33)	0.6
Diagnosis interval (years) (median; interquatile range(IQR))	n.a.	n.a.	n.a.	n.a.	1.9(0.7-3.8)	2.1(1.2-3.6)	2.3(0.8-3.3)	0.2
Age at first cancer diagnosis (years) (median; interquatile range(IQR))	n.a.	n.a.	n.a.	n.a.	52(46-65)	55(48-65)	59(55-66)	
Other cancers								
Number (% col[2])	13(33)	25(32)	26(41)	0.1	20(33)	38(46)	11(17)	0.02
Diagnosis interval (years) (median; interquatile range(IQR))	1.4(1.0-1.6)	2.4(0.9-3.3)	1.7(1.3-3.3)	0.3	1.5(0.7-3.4)	1.4(0.6-2.4)	2.2(1.0-4.0)	0.03
Age at first cancer diagnosis (years) (median; interquatile range(IQR))	64(52-68)	63(53-68)	60(51-71)	0.4	60(48-67)	58(50-68)	57(52-73)	0.4

Source: Netherlands Cancer Registry

Note: [1]. Test for heterogenity of frequency, Chi-square test is applied
Test for trend of medians, Kruskal-Wallis test is used.

[2]. Column percentage is for skin melanoma, squamous cell carcinoma and other non-skin cancers

[3]. Basal cell carcinomas were not registered in the Netherlands Cancer Registry

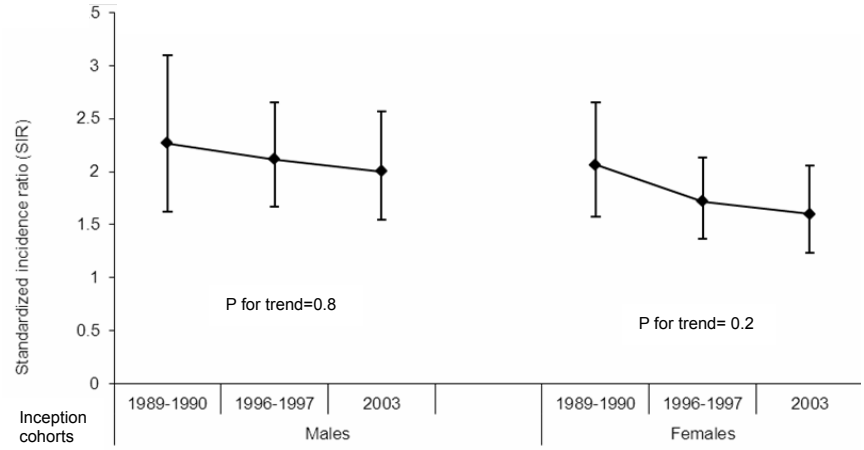


Source: Netherlands Cancer Registry

Figure 1 European standardized incidence rate of melanomas (Diagnosed with single melanoma vs with invasive melanomas (incl. SPM) according to sex (males ♂; females ♀), in period of 1989-2008

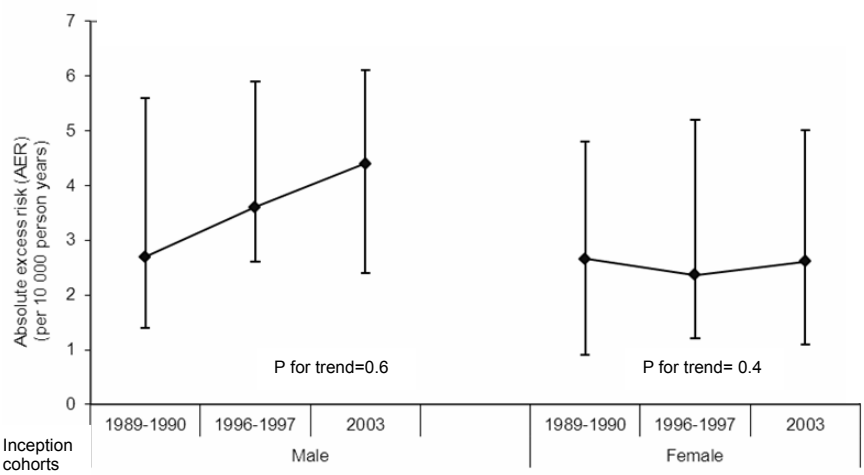
Over time, a growing difference between incidence rate of all melanoma diagnosis and single melanoma diagnosis was observed in both sexes indicating a growing proportion of MSPC in the total melanoma incidence (**Figure1**).

Between 1989 and 2008, trends in risk of MSPC were observed to decrease for SIR and to increase for AER in both sexes, but these changes did not reach statistical significance. The SIR for men changed from 2.2 (95% CI 1.6-3.1) to 2.0 (95%CI 1.5-2.6; p for trend=0.8). For women it changed from 2.1 (95%CI 1.6-2.7) to 1.6 (95%CI 1.6-2.7) (p for trend=0.2) (**Figure 2a**). AER varied from 2.7 (95%CI 2.6-6.1) to 4.5 (95%CI 2.4-6.1) per 10,000 person years (p for trend=0.6) in men and from 2.7 (95%CI 0.9-4.8) to 2.6 (95%CI 1.1-5.0) per 10,000 person years (p for trend=0.8) in women (**Figure 2**.b).



Source: Netherlands Cancer Registry

Figure 2.a Standardized incidence ratio (SIR) (95% CI) for melanoma as a second primary cancer (MSPC) in 3 inception cohorts (1989-1990, 1996-1997 and 2003) according to sex



Source: Netherlands Cancer Registry

Figure 2.b Absolute excess risk (AER, per 10,000 person years) (95%CI) for melanoma as a second primary cancer (MSPC) in 3 inception cohorts (1989-1990, 1996-1997 and 2003) according to sex

We observed that the highest SIR and AER of MSPC were among patients with a prior melanoma diagnosis, with SIR=19.6 (95%CI: 15.5-24.7) in men and 13.2 (95%CI: 10.8-16.1) in women. Corresponding AERs were 48 and 36 per 10,000 person years for men and women respectively. **(Appendix)**.

During 2-5 years of follow-up, AER for MSPC increased over time from 24 to 72 per 10,000 person years (p for trend=0.01) among male patients with a prior melanoma diagnosis. In the same group, there was a tendency for a decreasing trend of AER for MSPC over the cohorts in the first year post-first cancer diagnosis from 65 to 53 per 10,000 person years, although this did not reach significance (p=0.4). Among female patients with a prior squamous cell carcinoma diagnosis, a sharp increase in AER over time was observed in the first year after first cancer diagnosis (p for trend=0.3), tending to decrease over time in 2-5 years of follow-up period (p for trend=0.1) (**Table 2**.a-b).

Breslow thickness of MSPC was thicker in females than it was in males (0.8 VS 1.1 mm). In general it was higher among MSPCs that were diagnosed later in follow-up (i.e. 2-5 years) compared to those found earlier (i.e. 0-1 year follow-up). But this difference only became statistically significant, though marginal, among male patients with a first melanoma (0.5 VS 1.1 mm; p=0.05). (**Table3**)

Table 2.a Absolute excess risk (AER per 10,000 person years) (95%CI) for males according to follow-up time (0-1 year and 2-5 years follow-up) in 3 inception cohorts (1989-1990, 1996-1997, and 2003)

	AER (10,000 person years)							
	0-1 year				2-5 years			
Period of diagnosis of first cancer	1989-1990	1996-1997	2003	p for trend	1989-1990	1996-1997	2003	p for trend
Type of first cancers								
Melanoma	65 (42-137)	87 (58-158)	52 (26-140)	0.4	24 (16-62)	36 (22-56)	72 (53-107)	0.01
Squamous cell carcinoma [1]	0	5 (2-9)	13 (5-58)	0.4	15 (7-32)	8 (3-20)	10 (3-23)	0.5
Other non-skin cancers (including breast, prostate cancer, and other cancers)	3 (1-6)	5 (3-8)	3 (1-9)	0.5	3 (2-5)	4 (2-5)	9 (6-12)	0.002
All first cancers combined	3 (2-8)	5 (3-9)	4 (2-9)	0.3	4 (3-6)	4 (3-6)	8 (5-12)	0.004

Source: Netherlands Cancer Registry

Table 2.b Absolute excess risk (AER per 10,000 person years) (95%CI) for females according to follow-up time (0-1 year and 2-5 years follow-up) in 3 inception cohorts (1989-1990, 1996-1997 and 2003)

	AER (10,000 person years)							
	0-1 year				2-5 years			
Period of diagnosis of first cancer	1989-1990	1996-1997	2003	p for trend	1989-1990	1996-1997	2003	p for trend
Type of first cancers								
Melanoma	42 (24-96)	97 (65-147)	96 (58-160)	0.06	24 (15-40)	20 (12-33)	36 (23-57)	0.2
Squamous cell carcinoma [1]	0	6 (1-54)	39 (27-120)	0.3	8 (2-6)	13 (6-27)	0	0.1
Other non-skin cancers (including breast, prostate cancer, and other cancers)	4 (1-8)	8 (5-13)	6 (4-12)	0.2	3 (2-5)	4 (2-5)	4 (2-6)	0.8
All first cancers combined	4 (2-7)	8 (5-12)	9 (5-14)	0.07	3 (2-5)	4 (3-6)	3 (2-7)	0.7

Source: Netherlands Cancer Registry

Note: [1]. Basal cell carcinomas were not registered in the Netherlands Cancer Registry

Table 3 Average Breslow thickness (in millimeters) of second primary cancer (MSPC) according to sex and follow-up period (0-1 year and 2-5 years)

		Male			Female	
Over all		0.8			1.1	
Type of first cancers	0-1 year	2-5 years	P-value[1]	0-1 year	2-5 years	p-value[1]
Melanoma	0.5	1.1	0.05	0.5	0.7	0.3
Squamous cell carcinoma [2]	0.7	1	0.6	1	1.2	0.9
Other non-skin cancers	1.1	1.8	0.1	1.7	1.9	0.7
All first cancers combined	0.8	1.5	0.08	1.1	1.5	0.5

Source: Netherlands Cancer Registry

Note: [1]. p-value calculated by Wilcoxon-Mann-Whitney test due to lack of normality

[2]. Basal cell carcinomas were not registered in the Netherlands Cancer Registry

DISCUSSION

Age-adjusted incidence for MSPC among cancer patients diagnosed during 1989-2008 in the Netherlands increased from 5 to 9 per 10,000 person years. However, standardized incidence ratios (SIR) and absolute excess risks (AER) for MSPC remained unchanged, suggesting that the trend of MSPC paralleled that of melanoma incidence in the general population [1]. The AER for MSPC in patients with a first non-skin cancer was minimal (i.e. AER<10 per 10,000 person years). The time trend of AER for MSPC among males with a prior melanoma increased, especially in the 2nd to 5th year post-diagnosis of the first cancer. Among female patients with a prior squamous cell carcinoma of skin, the AER for MSPC increased in the first year of follow-up, coinciding with a non-significant decrease during 2 to 5 years of follow-up. In general, MSPC diagnosed earlier in follow-up were thinner than diagnosed later in both sexes. Females have thicker MSPC compared to males, which is in contrast with observations for first primary melanomas [1, 14-15].

In male patients with a prior melanoma, there seemed to be a prolonged diagnostic lag for MSPC over time from 1.5 to 2.6 years in the Netherlands between 1989 and 2008. This observation, together with the observed increasing excess risk over time later in follow-up time (i.e. in the period 2-5 years post-diagnosis of the melanoma), plus the probable decreasing trend for MSPC risk within the first year of follow-up after first melanoma, suggesting a delayed diagnosis of MSPC in this population. It is reported that many melanomas were patient-detected lesions [16-17]. A worsened risk trend of MSPC might reflect worsened self-examination skills among male melanoma patients. Also Francken et al found that melanoma patients may benefit from a regular review by their clinicians to reach early detection of MSPC because the prior melanoma diagnosis not necessarily increases the number of self-detected MSPC [17]. It seems that changes in their compliance to follow-up schedule may also play a role in forming the down-going trend. Interestingly, in both above-mentioned aspects, females perform better than males, which explain their optimal diagnostic trend for MSPC [6, 17].

Among female patients with a prior squamous cell carcinoma of skin, the rising AER trends for MSPC early in follow-up period (i.e. 0-1 year post-first cancer diagnosis) was accompanied by a declining AER trends later in follow-up (i.e. 2-5 years post-first cancer diagnosis), coinciding with a shortened diagnosis lag for MSPC from 2.6 to 0.7 years in the past 2 decades. A similar, but less pronounced trend was observed among males. These observations seem to point to increases in awareness of melanoma over time in this patient group and or among their treating physicians which might have led to a reduced incidence burden of MSPC later on. Unfortunately, notwithstanding these seemingly favorable time trends among women, Breslow thickness of their MSPC was higher compared to males.

Increased awareness of melanoma might arouse the suspicion of over-diagnosis especially for these second lesions, resulting in unnecessary worries among patients with limited benefit gain [2]. A recent study showed that Dutch women with thin melanomas (Breslow thickness<=1mm) have more follow-up exams than required by the Dutch guideline [18-19].

Any conclusion on a potential over-diagnosis of MSPC should be accompanied by data on cause-specific survival in the different patient groups. If over-diagnosis exists, the increased in incidence should be accompanied by a Table or even an increase of survival. Though, such data are not available, from our observations, over-diagnosis is unlikely for those second melanomas. For instance, MSPC in male melanoma patients diagnosed during 2-5 years after their first melanoma had a mean Breslow thickness of 1.1 millimeter (mm), whereas the Breslow thickness in early-found (i.e. 0-1 year) MSPC was 0.5 mm. Although statistically only marginal differences in Breslow distribution were detected, the impact on survival of several tenths of one millimeter might be substantial: the relative excess risk of dying of patient Breslow thickness 1-2 mm was about 5 times higher than those with a Breslow thickness <=1mm[1]. The same theory applies for patients with a first squamous cell carcinoma of skin. Instead of worrying on over-diagnosis, more efforts should be put to diagnose MSPC earlier during follow-up.

Upon interpreting these findings, we should be aware of changes of exposure to risk factors (e.g. UV sunlight) can also have influenced the observed time trends of MSPC risk[20]. However, as specific trends in relative risk (SIR) of MSPC were not observed, the pattern of risk factor exposure in cancer patients seems to be similar to that in the general population during the observing period, therefore are less likely to explain the observed differential trend[21].

To our knowledge, this is the first study to analyze trends of MSPC among cancer patients and relate them to melanoma awareness. The long-standing population-based Netherlands cancer registry (1989-2008) data guarantee the representativeness of Dutch population and validity of the estimates.

CONCLUSION

Excess risk for melanoma as a second primary cancer (MSPC) tends to increase in the past two decades in the Dutch cancer patients, though not reaching statistical significance. The worsening of stage distribution of MSPCs during follow-up should be addressed by better surveillance approaches.

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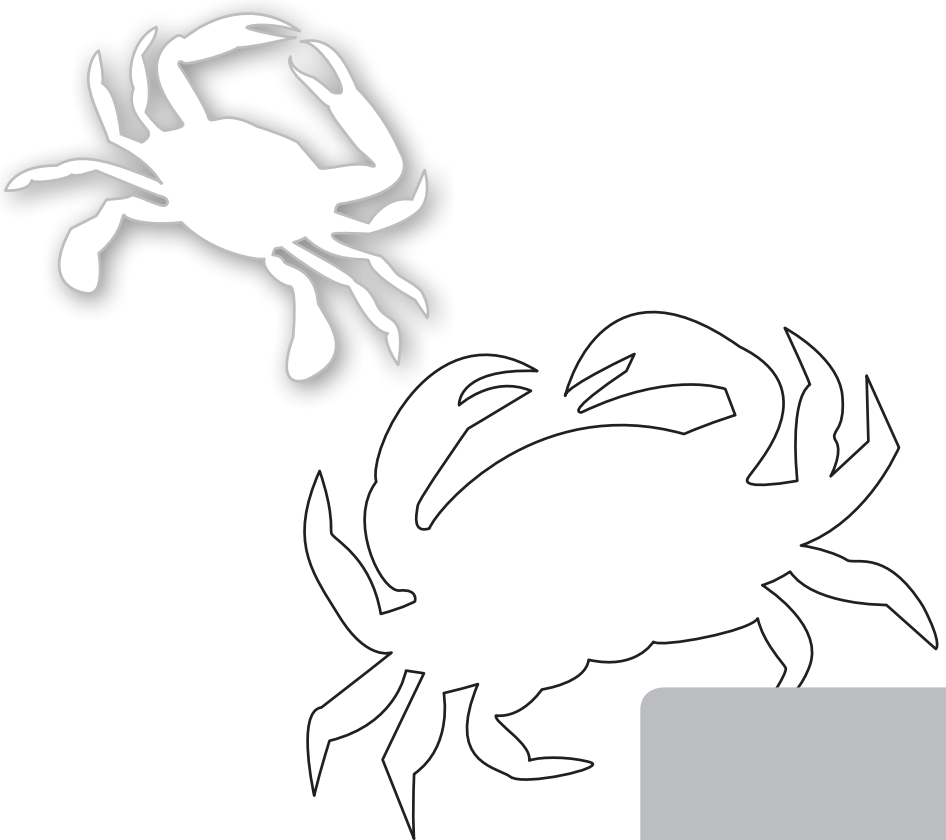
Appendix: Standardized incidence ratio (SIR) and Absolute excess risk (AER, per 10,000 person years) for melanoma as a second primary cancer (MSPC) among cancer patients in the Netherlands (1989-2008)

	Males		Females	
Type of fist cancer in	**SIR (95%CI)**	**AER (per 10,000 pyrs)**	**SIR (95%CI)**	**AER (per 10,000 pyrs)**
Colon and rectum	1.5 (1.3-1.7)	1.9	1.3 (1.1-1.5)	1
Skin, Melanoma	15.9 (14.6-17.3)	46.6	12.0 (11.1-12.9)	38.4
Skin,Suquamous cell carcinoma	3.9 (3.4-4.4)	12	3.2 (2.7-3.7)	8.8
Prostate	1.6 (1.4-1.8)	2.7	n.a.	n.a.
Breast	n.a.	n.a.	1.5 (1.4-1.6)	1.8

Source: Netherlands Cancer Registry
n.a. not applicable

CHAPTER 3

Prognosis in patients with multiple cancers

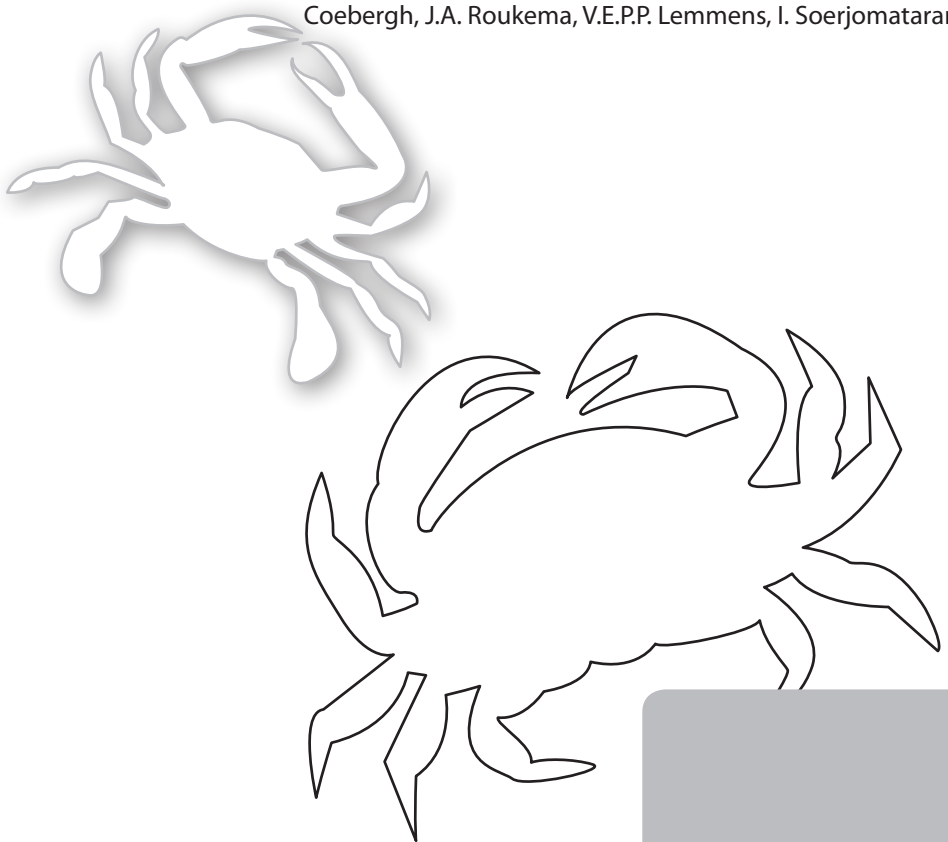


CHAPTER 3.1

Early detection of second colon cancer amongst colon cancer survivors might lower excess mortality: a 20-year study in the Netherlands

L. Liu, M.Murawska, L.Van Steenbergen, I. H.J.T. De Hingh, J.W.W. Coebergh, J.A. Roukema, V.E.P.P. Lemmens, I. Soerjomataram

Submitted



ABSTRACT

Aims: to examine the impact of second colon cancer risk of dying from any cause amongst patients with a previous stage I-III colon cancer.

Methods: From the Netherlands Cancer Registry, we retrieved data of 65,795 patients with stage I-III colon cancer who were 50 years or older, diagnosed between 1989 and 2008 followed until Feb 1st 2010. We computed hazard ratios (HR) comparing patients with and without a subsequent colon cancer using Cox proportional hazards modeling incorporating second colon cancer as a time-dependent covariate. Stratified analyses were performed according to age groups and stage of first cancer diagnosis. Prognostic factors, such as sex, age, stage, periods of diagnosis, subsite, treatment of the second cancer, and its association with the risk of dying from any cause was examined.

Results: In total, 2,911 (4%) patients were diagnosed with a second colon cancer which elevated overall mortality by 40% (HR=1.4 95%CI 1.3-1.5). The adverse impact of second colon cancer on overall survival decreased with age and stage at first cancer diagnosis: being HR=1.7, 95%CI: 1.3-2.1, amongst patients of 50-59 years versus HR=1.3 (95%CI: 1.2-1.5) amongst patients of 80+ years , and being HR=1.7 (95%CI 1.5-1.8) for patients with stage I colon cancer versus HR=1.2 (95%CI 1.1-1.3) for patients with stage III colon cancer. Advanced age at second colon cancer diagnosis (increasing to HR=4.4 (95%CI 3.5-5.6) in patients aged 80+years compared to 50-59 years old) and advanced stage (HR=1.9 (95%CI 1.6-2.2) for stage III versus stage I) strongly predicted poor survival. Sex, cancer subsite, lag-time, and period of diagnosis did not add to predictions of survival. Younger patients often had a second colon cancer 4 years (interquartile range 2-8 years) after the first and tend to receive two times aggressive treatment (e.g. resection+adjuvant chemotherapy) compared to the older patients.

Conclusions: A second colon cancer increased overall mortality amongst patients with a previous colon cancer, in particular amongst the younger age groups and those with localized disease. Whether increased toxicity of undergoing aggressive treatment twice affected survival negatively or aggressiveness of the underlying disease is a topic for further study.

INTRODUCTION

The markedly improved survival amongst cancer patients has generated a higher prevalence of second primary cancers[1]. Approximately 2% to 10% of all colorectal cancer diagnoses are subsequent lesions[2-5]. In 2007, it was estimated that more than 20% of colon cancer survivors live with a second colon cancer in the Netherlands[6]. A three-fold increased risk to develop a second cancer in the colon and rectum has been reported, which was possibly related to shared risk factors and increased surveillance after first cancer diagnosis[7-8].

We recently reported an increased risk for a second colon cancer amongst survivors of colorectal cancer that remains elevated in long-term survivors i.e. 5 years and longer[9]. This persistent elevated risk in combination with the worsened staging by longer follow-up indicates the need for enhanced surveillance in this survivor group[10]. A systematic review showed that more intensive follow-up after curative intent resection for colorectal cancer (CRC) improves survival[11]. Rosso et al have shown that including a second cancer diagnosis decreased relative survival by 0.5% amongst patients with a prior colon cancer[12]. But these studies did not assess prognostic factors which can facilitate communication between doctors and patients. Conditional survival amongst colon cancer survivors facilitates this communication and surveillance after cancer however, only a few prognostic factors can be separately explored[13].

Therefore, to understand important prognostic factors as well as to estimate the elevated magnitude of mortality after second colon cancer, we conducted the current study.

MATERIAL AND METHODS

Data and patient selection

We used population-based data from the nationwide Netherlands Cancer Registry (NCR). Data registration started in 1989 and is maintained and hosted by the Comprehensive Cancer Centers[14]. The NCR is based on notification of all newly diagnosed malignancies in the Netherlands by the automated pathological archive. An additional source of patient identification is the national registry of hospital discharge diagnoses, which accounts for up to 8% of new cases[14]. Information on patient characteristics, such as sex and date of birth, and tumor characteristics, such as date of diagnosis, subsite (International Classification of Diseases for Oncology (ICD-O-3)[15]) and stage (Tumor Lymph Node Metastasis (TNM) classification[16]) are obtained routinely from the medical records by the NCR at about 6-9 months after diagnosis. If pathological stage was missing, clinical stage was used. The quality of the data is high and completeness is estimated to be at least 95%[17]. In addition to passive follow-up via hospitals, date of death is also retrieved from the Municipal Personal Records Database that contains all deaths or emigrations in the Netherlands since October 1994. For patients diagnosed before October 1994, follow-up was completed through NCR by merging the database with municipality death records or with the Central Bureau for Genealogy, which registers all deaths in the Netherlands.

There were 107,958 new invasive colon cancer cases diagnosed between 1989 and 2008. Since patients aged younger than 50 years have a higher rate of hereditary syndromes (i.e. hereditary non-polyposis colorectal cancer (HNPCC)), we excluded them from analyses to avoid case-mixing with sporadic colon cancer cases[18]. We also excluded patients older than 95 years, patients with stage IV colon cancer of their first colon tumor, those with unknown stage of their first colon cancer, and patients with a second cancer other than a colon cancer (N=39,163). In total 68,795 patients were included in the analysis. Patients were followed until February 1st 2010 with respect to their vital status.

The NCR records multiple cancers according to International Association for Cancer Registries (IACR)[15]. In short, a second primary cancer must be in a different segment of the colon than the primary cancer irrespective of time interval between two cancers diagnoses. Cancers in the same segment of the colon are regarded as the same malignancy, and are counted as one primary cancer[15]. We included 2, 911 atients with a second colon cancer.

Statistical analysis

The overall mortality ratio between patients with two colon cancers and those with a single colon cancer was defined as the outcome of interest.

Reported patients' demographics were stratified by number of primary colon cancers. For patients with two colon cancers, treatment for the first and second colon cancer were reported according to age at first cancer diagnosis for metachronous cancers only because the patients with two tumors diagnosed long enough are less likely to be treated twice.

We used the Kaplan-Meier method to construct cumulative overall survival proportions. The survival curves for all-causes of death were plotted from the time of the first cancer diagnosis for those with only one colon cancer and from the time of diagnosis of the second cancer for those with two. The difference in survival curves was tested using log-rank tests at statistically significant level of *p-value*<0.05.

The mortality rate between patients with one cancer and patients with two colon cancers were compared in a Cox proportional hazard (CPH) model with the second colon cancer as a time-dependent covariate. Mortality ratios were also calculated stratified for four age groups (50-59, 60-69, 70-79 and 80+ years) and in three stages (I, II, III). We controlled for potential confounders including sex, age at first cancer diagnosis (50-59, 60-69, 70-79 and 80+ years), stage (I, II,III), location of the first cancer (proximal- and distal-colon), and initial treatment for the first cancer (resection alone, resection and adjuvant chemotherapy). 'Unknown' and 'other treatment' (including no treatment at all, radiotherapy alone, systemic therapy alone, systemic therapy + radiotherapy, systemic therapy + resection and systemic therapy + resection + radiotherapy) were presented as one group. In this analysis, patients were followed-up since first cancer diagnosis and second colon cancer was entered as time-dependent covariate. We assumed a linear relationship of lag-time. Interactions between age and stage, stage and treatment, as well as the interaction between age, stage and treatment were evaluated using likelihood ratio test.

Table 1 Characteristics of patients with one and two colon cancers (N=65,795), diagnosed in the Netherlands, 1989-2008

Patient characteristics	Two colon cancers N=2,911		One colon cancer N=62,884
	1st colon ca	2nd colon ca	
Median surviving time (years, IQR[1])	4.8 (2.1-9.6)	2.9 (1.3-6.6)	3.7 (1.5-7.6)
Sex (men, %)	1,467 (50)		29,159 (46)
Age at diagnosis, in years (%)			
Median (IQR[1])	72 (65-78)	74 (67-80)	72 (64-79)
50-59	318 (11)	227 (8)	8,662 (14)
60-69	807 (28)	716 (25)	16,845 (27)
70-79	1,181 (41)	1,157 (40)	22,951 (37)
80+	605 (21)	811 (28)	14,426 (23)
Period of diagnosis (%)			
1989-1993	737 (25)	451 (16)	12,884 (21)
1994-1998	761 (26)	668 (23)	14,154 (23)
1999-2003	699 (24)	778 (27)	16,002 (25)
2004-2008	714 (25)	1,014 (35)	19,844 (32)
Stage (%)			
I	610 (21)	929 (32)	11,802 (19)
II	1,426 (49)	896 (31)	19,581 (47)
III	875 (30)	530 (18)	21,501 (34)
IV	n.a.[4]	196 (7)	n.a.[4]
Unknown	n.a.[4]	360 (12)	n.a.[4]
Sub site (%)			
Proximal-colon	1,754 (60)	1,924 (66)	34,168 (54)
Distal-colon	1,157 (40)	987 (34)	28,716 (46)
Lag-time[2] (%)			
0-0.5 year	1,720 (59)		n.a.[4]
0.51-5 years	814 (28)		n.a.[4]
>5 years	377 (13)		n.a.[4]
Treatment (%)			
Resection only	2,488 (86)	2,311 (79)	51,076 (81)
Resection + adjuvant chemotherapy	388 (13)	460 (16)	10,088 (16)
Other+unknown[3]	35 (1)	140 (5)	1,720(3)

Source: the Netherlands Cancer Registry

[1] interquartile range

[2] interval between the first and second colon cancer diagnosis

[3] Other+unknown treatment including no tumor treatment, radiotherapy alone, systemic therapy alone, systemic therapy + radiotherapy, systemic therapy + resection, systemic therapy + resection + radiotherapy, and unknown

[4] not applicable

Furthermore, we assessed factors that might affect the risk of dying amongst patients with two colon cancers, namely lag-time, sex, age at second cancer diagnosis, and tumor characteristics of the initial colon cancer (i.e. stage, treatment, and sub sites) using CPH model. For this analysis, survival time was counted since diagnosis of the second colon cancer.

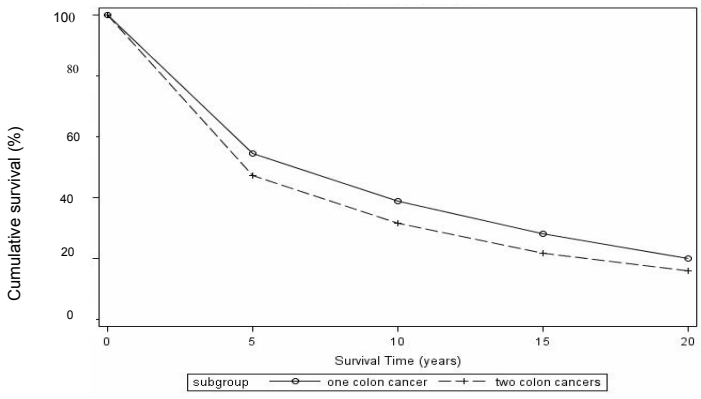
Model fit was evaluated using residual-based graphical methods and goodness-of-fit test statistics. All reported *p*-values were two sided, the statistical significance level was set at <0.05.

RESULTS

Among the 65,795 patients with a prior colon cancer, only 2,911 (4%) patients developed a second cancer in the colon. Median lag-time between the first and second colon cancer diagnosis was 1 month (Interquartile range (IQR) =0.1-26 months, **Table 1**).

Patients were on average 72 years old at diagnosis of the first colon cancer and 74 years at the second. Median surviving time from the first colon cancer was 3.7 years (IQR=1.5-7.6 years) in patients with one colon cancer only, and 4.8 years (IQR=2.1-9.8 years) in patients with two colon cancers. When comparing characteristics of the first colon cancer between these two groups of patients, we observed that patients with two colon cancers had more often proximal lesions (60% versus 54%), underwent h resection (86% versus 81%) and less often adjuvant therapy (13% versus 16%) or were diagnosed more recently (i.e. 2004-2008) as compared to those with one colon cancer only.

As for the second colon cancers, more than half (59%) was diagnosed within 6 months after the first colon cancer. Second cancers were more often diagnosed in the most recent study pe-



(log-rank test P<0.0001 reference=one colon cancer)

Source: Netherlands Cancer Registry

Figure 1 Cumulative survival in patients with one and with two colon cancers, diagnosed in the Netherlands 1989-2008

Note: follow-up started from the diagnosis of the first cancer for patients with one colon cancer, and from the diagnosis of the second cancer in case of two colon cancers.

Table 2 Death hazards from any cause between patients older than 50 years with one and two colon cancers using multivariate analysis, also stratified for age and stage (I-III) at diagnosis of the first colon cancer in the Netherlands 1989-2008 (N=65,795)

Number of colon cancers		**Multivariate HR[1,2]**	**95%CI**
	One	1.0	Reference
	Two	1.4	1.3-1.5

Stratified analysis	**Unadjusted**		**Multivariate HR[1]**	
	HR	95%CI	HR	95%CI
Age at diagnosis of 1st colon cancer (years)				
50-59	1.5	1.2-1.7	1.7	1.3-2.1
60-69	1.4	1.2-1.5	1.5	1.4-1.7
70-79	1.2	1.2-1.4	1.4	1.3-1.5
80+	1.2	1.1-1.4	1.3	1.2-1.5
Stage of 1st colon cancer				
I	1.8	1.6-2.0	1.7	1.5-1.8
II	1.2	1.1-1.3	1.3	1.2-1.4
III	1.3	1.2-1.4	1.2	1.1-1.3

Source: the Netherlands Cancer Registry

[1] Patients were followed-up since first cancer diagnosis, the second colon cancer being a time-dependent covariate

[2] Multivariate analysis adjusting for sex, age at first cancer diagnosis, stage, primary treatment and interaction between age and stage at cancer diagnosis

riod (35%, 2004-2008) and situated in proximal area of the colon (66%). The majorities of these cancers were stage I and stage II diseases, hence more likely to receive only resection (79%).

Comparing prognosis between patients with two and with one colon cancer

Overall survival of patients with one colon cancer was significantly better than those with two, 45% and 52% after 5 years (**Figure1**), irrespective of lag-time between the two colon cancers (data not shown).

In multivariate analysis, patients with two colon cancers experienced a 40% higher mortality rate (HR=1.4, 95% confidence interval (95%CI) = 1.3-1.5) compared to those with only one colon cancer. Mortality ratio was largest in the younger age group and declined with increasing age, HR=1.7 (95%CI=1.3-2.1) when the first cancer was diagnosed below 60 years, declining to 1.5 (95%CI=1.4-1.7), 1.4 (95%CI=1.3-1.5) and 1.3 (95%CI 1.2-1.5) in the 60-69, 70-79 and 80+ years age groups, respectively (**Table 2**).

Prognostic factors amongst patients with two colon cancers

Table 3 illustrates associations between potential prognostic determinants and all-cause death amongst patients with two colon cancers since the diagnosis of the second cancer. Risk of dying of any cause increased with advanced age and stage at second colon cancer diagno-

Table 3 Determinants of hazard of dying from all causes amongst patients with two colon cancers, in the Netherlands 1989-2008 (N=2,911): a multivariate analysis

	Univariate		Multivariate[3]	
	HR	95%CI	HR	95%CI
Sex				
Women	1.0	0.9-1.1	0.9	0.8-1.0
Age at diagnosis for 2nd colon cancer (years)				
50-59	1.0	Reference	1.0	Reference
60-69	1.5	1.2-1.9	1.5	1.2-1.9
70-79	2.3	1.8-2.9	2.2	1.8-2.8
80+	4.4	3.5-5.5	4.4	3.5-5.6
Stage of 2nd colon cancer				
I	1.0	Reference	1.0	Reference
II	1.1	1.0-1.3	1.1	1.0-1.3
III	1.6	1.4-1.8	1.9	1.6-2.2
IV	2.2	1.6-2.8	2.6	1.6-3.6
Sub site of 2nd colon cancer				
Proximal-colon	1.0	0.9-1.1	0.9	0.8-1.0
Distal-colon	1.0	Reference	1.0	Reference
Lag-time[2]				
0-0.5 year	1.0	Reference	1.0	Reference
0.51-5 year	0.8	0.7-1.0	0.9	0.7-1.0
>5 year	1.0	0.9-1.1	0.9	0.8-1.0
Period of diagnosis of 2nd colon cancer				
1989-1993	1.0	Reference	1.0	Reference
1994-1998	0.9	0.8-1.0	0.9	0.8-1.0
1999-2003	0.8	0.7-0.9	0.8	0.7-1.0
2004-2008	0.8	0.7-1.0	0.8	0.7-1.0
Treatment of 2nd colon cancer				
Resection alone	1.0	Reference	1.0	Reference
Resection + Adjuvant chemotherapy	0.7	0.6-0.8	0.8	0.6-0.9
Other+unknown[4]	2.6	1.7-4.0	3.0	2.0-4.7

Source: the Netherlands Cancer Registry

[1] Survival time is counted since diagnosis of the second colon cancer

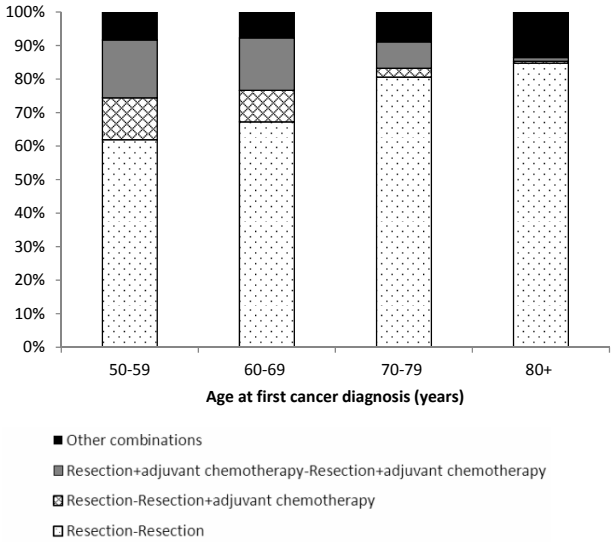
[2] Lag-time: time interval between the first and second colon cancer diagnosis

[3] Multivariate analysis included: age at diagnosis, stage, periods of diagnosis, and treatment, and interaction between age and stage

[4] Other+unknown treatment including no tumor treatment, radiotherapy alone, systemic therapy alone, systemic therapy + radiotherapy, systemic therapy + resection, systemic therapy + resection + radiotherapy, and unknown

sis. Patients receiving adjuvant chemotherapy in addition to resection for the first cancer had a 30% reduction in mortality rate (HR=0.7, 95%CI 0.6-0.8) compared to those receiving only

resection. Sex, sub site, diagnosis period of the initial cancer and lag-time between the first and second colon cancer did not affect significantly the prognosis after the second cancer.

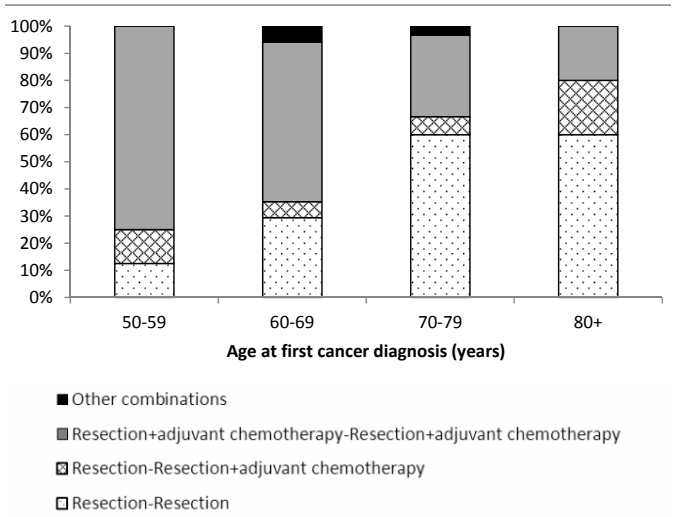


Source: Netherlands Cancer Registry

Figure 2 a Treatment combination of the first and second metachronous colon cancers (i.e. lag-time[1]>0.5 year) amongst patients with two colon cancers, according to age at first cancer diagnosis (N=1,191)

Treatment combinations for the first and second colon cancer according to age at first cancer diagnosis

We presented treatment combinations of first and second metachronous colon cancer (i.e. lag-time >6 months) according to age at first cancer diagnosis (50-59 years, 60-69 years, 70-79 years, and 80+ years). We chose metachronous cancers only because the intensive treatment for cancer often occurs in this period of time (6 months) and second cancers diagnosed in this period are less likely to be treated for two times. The lag-time between two colon cancer diagnoses decreased with higher age (**Figure 2**). Amongst patients younger than 60 years, the second colon cancer was often found 4 years after the index cancer, whereas, for older patients (60+) it was found around 2 years after the first colon cancer. Younger patients often received more aggressive treatment (resection and adjuvant chemotherapy) compared to the older patients (resection only).



Source: Netherlands Cancer Registry

Figure 2 b Combined treatments of the first and second metachronous colon cancer (i.e. lag-time[1] >0.5 year) amongst patients with stage III disease according to age at first cancer diagnosis (N=60)

DISCUSSION

We found that a second colon cancer elevated mortality by 40% in patients with colon cancer. The adverse impact of second colon cancer on overall survival was more pronounced amongst patients aged<60 years at diagnosis of first colon cancer and amongst patients with early stage first colon cancer. For patients with two colon cancers, advanced age and higher stage of the second cancer were associated with poorer survival, whereas, sex, lag-time between the first and second cancer, and period of diagnosis were not.

Our findings were comparable with previous results from a regional Dutch cancer registry where colon cancer patients with comorbidity (7.1% were previous malignancies) had 30% higher mortality risk (HR=1.3) compared to those without a comorbidity[19]. The small discrepancy of 10% in our study (HR=1.4) may be related to different inclusion criteria between these two studies. Moreover, we only included patients with stage I-III first colon cancer whereas this other study included patients with stage IV that could lower the HR.

In our study, being diagnosed in more recent years was not associated with improved overall survival. In contrast, van Steenbergen et al. observed an improved survival amongst patients who were diagnosed more recently with colon cancer in the Netherlands, which is mainly due to the increasing administration of chemotherapy to patients with stage II and III disease[20]. Older patients (75+ years) are less likely to receive adjuvant chemotherapy than younger patients[21]. Since patients in our study population were on average 74 years at second cancer diagnosis, this may explain why we did not observe significant improve-

ment in survival over time[20, 22]. Furthermore, 63% of patients with a second colon cancer was diagnosed with stage I or II disease who have a smaller improvement in survival[20].

We observed that a second cancer elevated overall mortality in particular amongst the younger age group (age 50-59 years). A possible chemotherapy-related toxicity effect might be associated with the poor survival amongst the younger patients. There is a clear increasing administration of aggressive treatment of both colon cancers (i.e. resection+adjuvant chemotherapy). Chemotherapy is associated with a large range of toxicity, like neutropenia and gastrointestinal toxicity. Although chemotherapy improves survival, severe toxicity (>WHO grade II) may negatively impact overall survival[23]. Only few studies have investigated the toxicity of chemotherapy on colon cancers and its relation with survival, especially in young patients[24-28]. Based on these previous studies one may suspect a higher mortality due to double dosage of chemotherapy.

We observed that lag-time (i.e. interval between the first and second cancer) is not significantly associated with survival, which is different from what was observed amongst women with contralateral breast cancer, whereby shorter lag-time was related to poorer survival. Hence authors suggest the needs for closer surveillance to patients with two cancers diagnosed shortly after each other[29]. Our study suggests follow-up of patients equally irrespective of lag-time between two cancers. Yet, our earlier study found that with longer follow-up, especially after 5 years since first cancer diagnosis, stage distribution of second colon cancer becomes less favorable possibly due to less intensive follow-up[9-10]. This in combination with continuous increased risk of second colon cancers after 5 years of follow-up (standardized incidence ratio (SIR) =1.6 95%CI 1.5-1.7, with absolute excess risk (AER) =15 per 10,000 person years) enhanced follow-up for should be considered to earlier detect the cancer.

The main limitation is the lack of cause-specific death data. We observed that the second colon cancer elevated overall death in particular amongst the younger patients (HR=1.7 versus HR=1.3 for patients aged <60 years and >80 years) and amongst those with early stage disease (HR=1.7 versus HR=1.2 for patients with stage I and stage III first colon cancer). Apart from the possible adverse effect of two times of treatment for two colon cancers, this elevated overall death could be caused by the low baseline mortality rate amongt younger patients and patients with stage I colon cancer (i.e. mortality of patients with only one colon cancer)[20]. The HR of patients with two cancers as compared to patients with one is a relative measure between the mortality after a second cancer and its baseline mortality. Even if after a second cancer mortality rate is the same across age or stage groups, the HR remained higher amongst those with lower baseline mortality: the young and the ones with early stage. In order to distinguish these differences, cause-specific death data is important.

Our study is the first nation-wide population-based study estimating mortality differences between patients with one and with two colon cancers, using the high quality data from the Netherlands Cancer Registry for a period of 20 years. Using second colon cancer as time-

dependent covariate in the Cox model adjusted for lag-time between two colon cancers, which increases comparability of patients with one and with two colon cancers.

CONCLUSION

The higher overall mortality of patients with a second colon cancer after a previous colon cancer occurred especially at middle age and amongst those with lower stage of disease of the first cancer. However, this also leads to more aggressive adjuvant treatment with potential harmful side effects. Further study on understanding the causes of death of these patients is necessary.

ACKNOWLEDGEMENT

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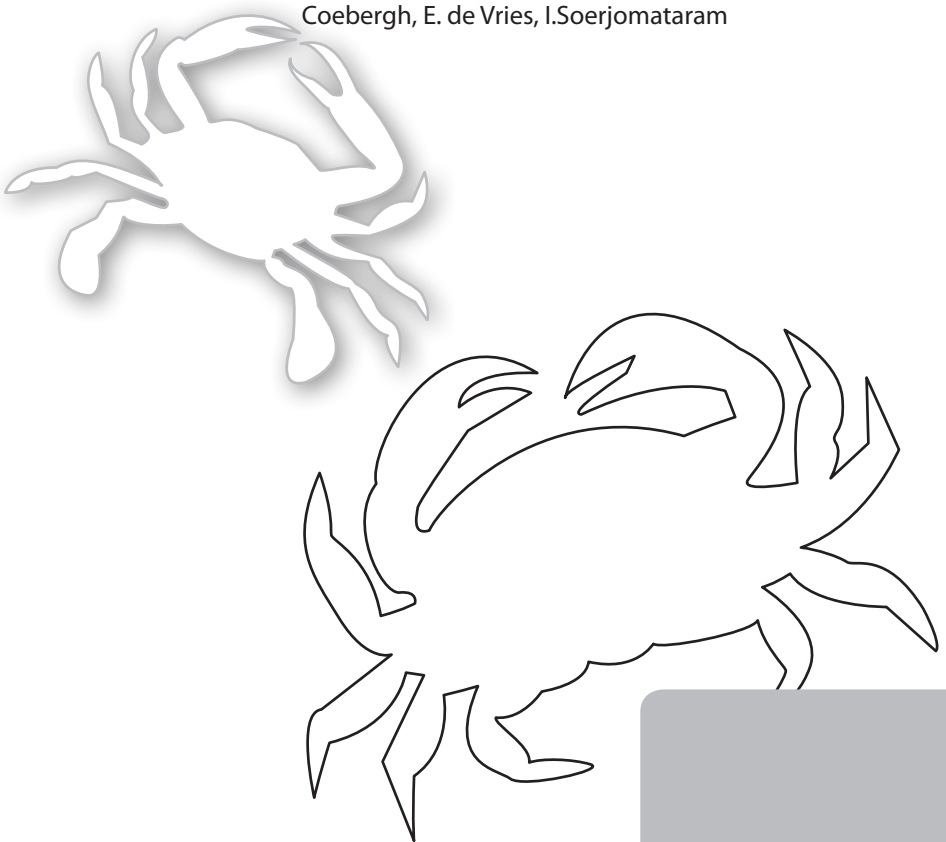
CHAPTER 3.2

Inferior survival for young patients with contralateral compared to unilateral breast cancer: a nationwide population-based study in the Netherlands

A.Font, L. Liu, A.C. Voogd, M.K. Schmidt , J.A. Roukema, J.W.W. Coebergh, E. de Vries, I.Soerjomataram

Submitted



ABSTRACT

Purpose: To compare overall survival between women with unilateral breast cancer (UBC) and with contralateral breast cancer (CBC).

Methods: Women with UBC (N=170,067; 95%) and CBC (N=8,835; 5%) recorded in the Netherlands Cancer Registry 1989-2008 were included and followed until 2010. We incorporated CBC as a time-dependent covariate to compute the overall mortality rate ratio between women with CBC and UBC. Prognostic factors at CBC diagnosis (i.e. time interval between first and second cancer, period of diagnosis, histology, tumour size, lymph node status and treatment) and their associations with overall death were examined according to age at first breast cancer.

Results: Absolute five-year survival for women with UBC and CBC was 78% and 71%, respectively (*p-value* <0.0001). Women with CBC exhibited a 40% increase in overall mortality (HR=1.4; 95%CI=1.3- 1.4) compared with UBC, decreasing with rising age at diagnosis of first breast cancer (≤49 years: HR=2.4 (95% CI 2.3-2.6) versus ≥70 years HR=1.1 (95 % CI 1.0-1.1)). Compared to CBC diagnosed < 2 years after the first breast cancer, women older than 50 years at a CBC diagnosis at 2 to 5 years exhibited a 20% higher death risk (HR=1.2 (95% CI 1.0-1.3), whereas in such women below age 50 the HR was significantly lower when the interval exceeded 5 years. Over time a clear improvement of the prognosis was observed for women with CBC at every age.

Conclusion: Women with CBC had a lower survival compared to women with UBC, especially those younger than 50 years, suggesting that some CBC tumours were metastases. Further explorations need to underpin a tailored follow-up strategy beyond current recommendations for young breast cancer patients without known familial risk before the start of population-based screening.

INTRODUCTION

Worldwide, breast cancer is a major burden for women's health[1]. In 2010, breast cancer was the most frequently diagnosed cancer among women in the Netherlands[2]. Marked improvements in survival have been achieved in the last 20 years due to a combination of earlier detection and improved treatment, resulting in 2% annual decrease in breast cancer mortality since 1995[3,4]. Mass screening was gradually introduced since 1990 for women aged 50-69, being extended to 75 years since 1998. Since 1995, familial risk based detection programme of mostly younger women was also introduced.

In the Netherlands the absolute annual number of newly diagnosed breast cancer patients has been predicted to increase from 13,257 in 2010[5] to over 19,000 in 2030, taking into account demographic changes and historical changes in rates[6]. This increase, combined with improved survival, will result in large increases in the number of breast cancer survivors, who have a 3.5-fold increased risk of being diagnosed with a contralateral cancer (CBC) compared to the risk of breast cancer in the general population[7].

Previous research addressed the influence of CBC on survival but results have been inconsistent. While some studies showed a negative effect on survival by CBC[8-17], others, mainly using hospital-based data and small numbers of patients, found a similar[18-21] or even better prognosis for CBC patients[22]. Some studies observed a better prognosis for CBC among long term breast cancer survivors[15, 23-25].

In order to study the impact of CBC on survival we performed a population-based study using data from the high quality Netherlands Cancer Registry (NCR). Our main aim was to compare survival of patients with unilateral breast cancer (UBC) with that of patients with CBC, taking into account the influence of age, stage, histology, type of treatment, and period of diagnosis of the first cancer. In addition, we explored prognostic factors for overall mortality among patients with CBC aiming to underpin adequate follow-up strategies.

METHODS

Data collection

The study cohort was obtained from the NCR that provided incidence data on all types of malignancies, except basal cell carcinoma, including multiple malignancies, diagnosed between 1989 and 2008. Vital status was updated through annual linkage of deaths through the Dutch Municipality Register. The NCR receives notifications of newly diagnosed cases from the different pathology laboratories, all participating in the Dutch nationwide network and registry of histo- and cytopathology of the Netherlands (PALGA)[26]. In addition, hospitals provide lists of newly diagnosed discharged cancer patients. Trained tumour registration clerks extract

data on patient demographic features, tumour characteristics and primary treatments. A high degree of accuracy and reliability of NCR data has previously been reported[27].

Unilateral disease was defined as one primary cancer in one breast and we defined CBC as a second primary breast cancer occurring in the opposite breast. We followed the guidelines from the International Association of Cancer Registries (IACR) on multiple primary neoplasms[28]. A primary cancer is defined as a malignant tumour originating at a primary site which is not an extension, neither a recurrence nor a metastasis. According to the definition from IACR, recognition of the existence of two or more primary cancers does not depend on time interval between cancer diagnoses.

Study population

In the NCR, we identified 204,438 women diagnosed with breast cancer diagnosed between 1989 and 2008, followed until Feb 1 2010. Women diagnosed with a new second non-breast cancer (N=12,192; 6%) and women who developed an ipsilateral breast cancer (N=547; 0.3%) were excluded from the analysis, resulting in 180,396 women diagnosed with UBC and 11,303 women with CBC. From the 191,699 women we further excluded patients with non-invasive (N=2,079; 1%) and stage IV (N=10,476; 5%) first breast cancer, as well as women older than 95 years at the time of first breast cancer diagnosis (N=235; 0.1%). Seven women were not included in the analysis due to a negative time interval between the first and second tumour, probably due to data entry errors. Finally, 170,067 and 8,835 women with UBC and CBC respectively were included for the analysis**.**

Statistical analysis

Demographic and tumour characteristics were presented for UBC and CBC as numbers and proportions of women in each sub-group. Significant differences in distribution of the variables were identified with Chi-square tests. Survival proportions of patients with UBC and CBC were calculated using the Kaplan-Meier method, applying the log-rank test to test differences between these two groups.

The overall mortality rate ratio between patients with UBC and CBC was the outcome of interest. Survival time was defined as the duration from diagnosis of first breast cancer until either date of death from any cause, or the date last known to be alive at the end of predetermined censoring date (i.e. Feb 1 2010). Survival was estimated using Cox proportional hazard regression models. The impact of CBC diagnosis was assessed in a univariate and multivariate model adjusting for age, histology, tumour size, nodal involvement, treatment and period of diagnosis of the first breast cancer. The models were constructed using CBC diagnosis as a time-dependent covariate. We also performed subgroup analyses by age at diagnosis (≤49, 50-69 and ≥70 years), tumour size (≤2.0, 2.1-5.0 and >5.0 cm) and nodal involvement (node-negative or positive) of the first cancer to explore potential differences in overall mortality of

CBC versus UBC in these subgroups, thereby using time-dependent survival analysis of CBC patients. This was done to avoid potential 'healthy patient' bias.

In the second stage of the analyses we explored factors that affected risk of death from all causes among patients with CBC only: age, period of diagnosis, tumour size, histology, nodal involvement and treatment of patients with CBC as well as the interval time between the first and second cancer. We used a Cox proportional hazard regression model with follow-up starting from diagnosis of CBC. In order to explore possible differences depending on age, we performed additional analyses in each age category group (≤49, 50-69 and ≥70 years). The proportional hazard assumption was not violated, as assessed by modeling the interaction between the covariates and (log) time.

For age, tumour size and nodal involvement, the same categories were used as for the subgroup analyses, mentioned earlier. Treatment variables were categorized into surgery alone (S) as well as combination of surgery with adjuvant treatment(s), i.e. surgery and radiotherapy (S+RT), surgery and radiotherapy and systematic treatment (immunotherapy, hormonal and chemotherapy, S+RT+ST) and surgery and systematic treatment (S+ST). Three follow-up intervals were defined: ≤2.0 years, 2.1-4.9 years and ≥5.0 years since diagnosis of the first tumour.

Statistical significance was set at *p-value* <0.05. Statistical analyses were performed using the statistical software programme SAS v 9.2.

RESULTS

Demographic and tumour characteristics of women who developed UBC and CBC are presented in **Table 1**. There was no significant difference in the distribution of age at the time of the first cancer diagnosis between women with UBC and CBC (median age of 59 versus 60 years). Most breast cancers had a size of 2.0 cm or less, 81% among women with UBC and 88% for first cancers of the CBC group. Women with CBC presented significantly more often with negative lymph nodes at first cancer diagnosis than women with UBC (54% versus 48%, p-value<0.001). A third (31%) of all UBC patients received surgery, radiotherapy and systemic therapy, compared with 23% of the first cancers of the CBC group. Twenty percent of the women with UBC received surgery alone, compared to 27% in the first cancer of the CBC group. The proportions of patients' receiving surgery and systemic treatment or surgery and radiotherapy were largely similar for patients with UBC as compared to the first cancer in patients with CBC. The vast majority of UBC (78%) and the first cancers in the CBC group (74%) were of ductal type. Forty-six percent of the CBC occurred within the first two years after the first breast cancer diagnosis.

Of the patients with CBC, 45% were between 50 to 69 years old at their CBC diagnosis. Given the fact that the mass screening programme had started in 1990 for women at this age,

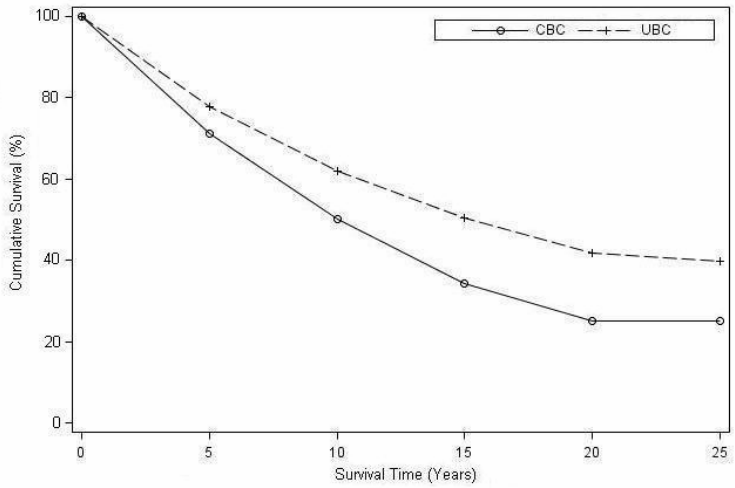
Table 1 Demographics, tumour characteristics and treatment of women diagnosed with unilateral and contralateral breast cancer (CBC) in the Netherlands, 1989-2008.

Patient characteristics	First and only breast cancer N (%) 170,067 (95)	Two breast cancers including contralateral N (%) 8,835 (5)	
		First of the two	Second of the two
Median age at diagnosis			
(inter quartile range (IQR))	59 (49-71)	60 (49-71)	64 (53-75)
Age (years)			
≤49	44,708 (26)	2,297 (26)	1,523 (17)
50-69	78,055 (46)	4,074 (46)	4,019 (45)
≥70	47,304 (28)	2,464 (28)	3,293 (37)
Tumour size (cm) [a]			
≤2.0	138,421 (81)	7,770 (88)	7,464 (84)
2.1-5.0	25,590 (15)	802 (9)	998 (11)
>5.0	3,883 (2)	178 (2)	213 (2)
Missing	2,173 (1)	85 (1)	160 (2)
Lymph node status [a]			
Negative	81,207 (48)	4,801 (54)	4,589 (52)
Positive	63,551 (37)	2,730 (31)	2,348 (27)
Unknown	25,309 (15)	1,304 (15)	1,898 (21)
Period of initial diagnosis			
1989-1993	32,987 (19)	2,719 (31)	987 (11)
1994-1998	38,404 (23)	2,680 (30)	1,864 (21)
1999-2003	46,134 (27)	2,151 (24)	2,667 (30)
2004-2008	52,542 (31)	1,285 (14)	3,317 (37)
Interval between 1st and 2nd tumour (years)			
≤2 .0	NA		4,088 (46)
2.1- 4.9	NA		2,448 (28)
≥5.0	NA		2,299 (26)
Primary treatment [b]			
S alone	33,901 (20)	2,365 (27)	2,550 (29)
S+RT	45,500 (27)	2,643 (30)	1,773 (20)
S+RT+ST	52,310 (31)	2,059 (23)	1,786 (20)
S+ST	28,136 (16)	1,300 (15)	2,014 (23)
Other/none/unknown [b]	10,220 (6)	468 (5)	712 (8)
Histology			
Ductal	133,049 (78)	6,534 (74.)	6,418 (73)
Lobular or lobular-mixed	24,435 (14)	1,560 (18)	1,675 (19)
Other/unknown [c]	12,583 (7)	741 (8)	742 (8)

Source: Netherlands Cancer Registry

[a] Includes only TNM stage I, II and III.

[b] S: Surgery alone, S+RT: Surgery with radiotherapy, S+RT+ST: Surgery with radiotherapy and systemic therapy, S+ST: Surgery with systemic therapy. Other/none/NK includes no treatment at all, unknown or not classified treatment [c] Includes tubular, medullary, Paget, mucinous and unknown.



Source: Netherlands Cancer Registry

Figure 1 Cumulative survival curves of women with contralateral breast cancer (CBC) (N=8,835) and unilateral breast cancer (UBC) (N=170,067), diagnosed in the Netherlands, 1989-2008.
Note: for patients with UBC, follow-up starts from first cancer diagnosis; for patients with CBC, follow-up starts from the second cancer.

being extended to 75 years since 1998, most of these patients (84%) were diagnosed with a small tumour (≤2 cm) and negative lymph nodes (52%).

Impact of Contralateral Breast Cancer on overall mortality

Absolute five-year survival for patients with UBC and CBC was 78% and 71%, respectively ($p<0.001$, **Figure 1**).

When comparing risk of death from all causes for women with CBC and with UBC adjusting for age, tumour size, nodal involvement, histology, treatment and period of diagnosis of first cancer, we found that women with CBC had a 40% higher risk of dying compared to UBC patients (Hazard ratio: HR 1.4, 95%, confidence interval (95%CI): 1.3-1.4), **Table 2**). When performing subgroup analysis by covariates, the HR for death due to any cause was more than twofold higher for women with CBC compared to UBC (HR: 2.4, 95%CI: 2.3-2.6): this only pertained to women aged 50 years or less at the time of first breast cancer diagnosis. CBC had an independent impact on overall mortality from nodal status and tumour size of the first breast cancer **(Table 2).**

Prognostic factors among women with Contralateral Breast Cancer

In the univariate analysis investigating prognostic factors amongst young (below 50 years) CBC patients, interval between the diagnosis of the first cancer and CBC, tumour size, lymph node status, histology and period of diagnosis significantly influenced survival (results not

Table 2 Hazard ratio (HR) and 95% confidence interval (CI) of overall mortality in women with contralateral (CBC) versus unilateral breast cancer (UBC), diagnosed in the Netherlands, 1989-2008, and according to age and stage at initial breast cancer diagnosis (N=178,902).

	Univariate HR	95%CI	Multivariate HR[b]	95%CI
Number of breast cancer				
1 (unilateral)	1	Reference	1	Reference
2 (contralateral)	1.5	1.45- 1.55	1.4	1.35- 1.45
Subgroup analysis:	Unadjusted HR	95% CI	Adjusted HR[c]	95% CI
Age at first cancer diagnosis (years)				
≤49	2.1	2.0-2.3	2.4	2.3-2.6
50-69	1.5	1.4-1.6	1.7	1.6-1.8
≥70	1.0	0.9-1.0	1.1	1.0-1.1
Tumour size of firsta cancer (cm)				
≤2.0	1.5	1.5-1.6	1.4	1.4-1.5
2.1-5.0	1.6	1.4-1.8	1.3	1.1-1.4
>5.0	1.3	1.0-1.7	1.4	1.1-1.7
Lymph node status of first cancer [a]				
Negative	1.7	1.6-1.8	1.5	1.4-1.6
Positive	1.4	1.3-1.5	1.3	1.2-1.4

[a] Includes only TNM stage I, II and III.

[b] Adjusted for tumour size, lymph nodes involvement, histology, treatment, age, and period of diagnosis of first breast cancer

[c] Hazard Ratios of CBC compared to UBC adjusted for age, histology, tumour size, lymph node involvement, treatment, period of diagnosis and at diagnosis of first cancer.

Source: Netherlands Cancer Registry

shown). In the older groups (aged ≥ 50 years), the variables mentioned above influenced survival with the addition of treatment and the exception of histology for women aged 70 years and above at diagnosis of CBC (results not shown).

In the multivariate analysis, large tumour size and a positive lymph node status conferred an increased risk of death from any cause (**Tables 3**). Size of CBC as a determinant of overall death had the highest impact among the younger group (HR: 3.3, 95%CI: 2.1-5.0). Similar observation was also observed for lymph node status (HR: 2.7, 95%CI: 2.1-3.4). An interval between cancers of more than 5 years in women diagnosed below the age of 50 years presented a decreased risk of death (HR: 0.7, 95%CI: 0.5-0.9). On the other hand, we saw a small increase in risk of death in the older age groups who were diagnosed with a CBC 2 to 5 years after the first breast cancer (HR: 1.2, 95%CI: 1.0-1.4 for the 50 to 69 years group; HR: 1.2, 95%CI: 1.0-1.3 for the above 70 years group) . Significant lower risks of death were seen among the younger group of women who received surgery and systematic treatment (HR: 0.6, 95%CI: 0.5-0.8) compared to surgery alone; but no significant increase was observed in the older group. A more recent year of diagnosis was associated with lower HR in all age groups as compared with earlier year of diagnosis.

Table 3 Determinants of hazard of dying from all causes amongst patients with two colon cancers, in the Netherlands 1989-2008 (N=1,523): a multivariate analysis

Variables	Univariate HR	95%CI	Multivariate HR[b]	95% CI
Age at diagnosis of CBC (years)				
≤49	1.2	1.1- 1.3	1.0	0.9- 1.2
50-69	1	Reference	1	Reference
≥70	2.3	2.1- 2.5	1.9	1.8- 2.1
Preceding interval between 1st and 2nd tumour (years)				
≤2	1	Reference	1	Reference
2.1- 4.9	0.9	0.8- 1.0	1.1	1.0- 1.2
≥5	0.7	0.7- 0.8	0.9	0.8- 1.0
Period of CBC diagnosis				
1989-1993	1	Reference	1	Reference
1994-1998	0.8	0.8- 0.9	0.8	0.7- 0.9
1999-2003	0.7	0.7- 0.8	0.7	0.6- 0.7
2004-2008	0.6	0.5- 0.7	0.6	0.5- 0.6
Size (cm) of CBC [a]				
≤2	1	Reference	1	Reference
2.1-5.0	1.1	1.0- 1.2	1.4	1.2- 1.5
>5	2.1	1.7- 2.5	2.3	1.9- 2.7
Lymph node status of CBC [a]				
Negative	1	Reference	1	Reference
Positive	1.8	1.6- 1.9	1.8	1.6- 2.0
Treatment of CBC [c]				
S alone	1	Reference	1	Reference
S+RT	0.7	0.6- 0.8	0.7	0.7- 0.8
S+RT+ST	1.1	1.0- 1.2	0.9	0.8- 1.0
S+ST	1.2	1.1- 1.3	1.0	0.9- 1.1
Histology of CBC				
Ductal	1	Reference	1	Reference
Lobular or lobular-mixed	1.0	1.0- 1.1	1.0	1.0- 1.1

Source: Netherlands Cancer Registry

[a] Includes only TNM stage I, II and III.

[a] Survival time counted since diagnosis of second breast cancer; [b] Analysis included all variables also missing values sub-categories; [c] S: Surgery alone, S+RT: Surgery with radiotherapy, S+RT+ST: Surgery with radiotherapy and systemic therapy, S+ST: Surgery with systemic therapy.

DISCUSSION

We observed that women with CBC had a 40% higher risk of dying from any cause than women with UBC during the 21 years of study follow-up. CBC diagnosis negatively impacted on the probability of dying from any cause, especially among women diagnosed with a first breast cancer before the age of 50 who had more than twofold higher risk of dying compared to women with UBC of the same age group. Tumours larger than 5 cm among women with CBC diagnosed before the age of 50 years were associated with a higher risk of death than in the older groups; explained probably by the presence of more rapidly growing tumours amongst the young. We also observed significant improvements in the prognosis of patients diagnosed with CBC since 1989, which is likely due to the introduction of mass screening for the older age groups and the increasing use of systemic therapies for the younger age groups.

Our findings on the impact of CBC on overall mortality are in line with previous Dutch studies. One, covering the north-western and south-eastern part of the Netherlands[13], also reported a HR of 1.4 (95%CI: 1.3-1.6) for patients with CBC compared to UBC. The patient population in this study originated from three large cancer registries in the Netherlands (45% of the population, also included in the present study) and more recent study period of diagnosis was established (from 1983 to 2002). The effects of implementing sentinel node biopsy as standard-of-care for breast cancer treatment, being described in literature as resulting in stage migration towards more positive axillary lymph nodes[29], were probably not reflected as much as in our study. Furthermore, in our study more patients will have received 5 years of hormone treatment than in the previous study[13], where the majority received 2 years of hormone treatment. Another small population-based study with similar period of diagnosis as the previous study[14], indicated a worse breast cancer-specific survival rate for patients with a CBC compared with an UBC (41% versus 84% at 10 years, p-value: 0.0045). In a Dutch study with the same cohort and period as the present study, CBC was an explanation for a small but significant excess mortality in long-term breast cancer patients studied by means of conditional 5-year relative survival[30].

The impact of a CBC diagnosis on the risk of death is mostly marked among those aged up to 50 years. Similarly, in Sweden a higher excess mortality was found among younger compared to older women with CBC[10]. Based on subgroup analyses, young age negatively affected the prognosis of CBC[8, 31]. Systemic treatment received for the first breast cancer might have unfavourably affected the biology of the CBC[10]. Another hypothesis is that in young patients the treatment of the CBC is less effective than the treatment of the first breast cancer. A change into a therapy-resistant phenotype after treatment of the first breast cancer might negatively affect CBC survival[10,32]. In addition, younger breast cancer patients also tend to present with more aggressive form and eventually also more aggressive CBC[31] i.e. oestrogen (ER) and progesterone (PR) receptor negative or HER2 positive tumours[33]. Furthermore, a genetic component might also be related to poor survival among the younger group of

patients[34]. More aggressive tumour characteristics are more likely to present in women with genetic predisposition to develop breast cancer[35].

The risk of death for women with CBC was higher for those with a shorter time interval between first and second breast cancer diagnosis, this was especially noTable among the older age groups. This finding concurs with those from other studies reporting a 1.7-3.0 increased mortality rate for an interval of less than 5 years[8,31,36]. This worse prognosis of CBC presenting shortly after the first breast cancer may be due to a misclassification of a metastasis from a true primary breast, due to the difficulty of distinguishing the two. In our study, a large proportion of the UBC and CBC cases presented with ductal carcinoma. Evidence of metastatic disease would have to come from the same histologic type, grade and positive lymph nodes[37]. However, standard pathological assessment often fails to provide unambiguous evidence for tumour origin, for which genetic analysis is likely to be more reliable[38]. Genetic studies of CBC have found that "CBC" are in fact not always two independent primary cancers[38-39]. The development of a CBC after a short interval is more likely to represent active systematic disease (metastasis)[40]. This might explain why overall mortality among the older age groups is highest for CBC diagnosed between 2 and 5 years after the first breast cancer. Another explanation is the possibility of less intensive diagnostic work-up of the CBC in these age groups. Differences in breast cancer management among older women compared to younger women been have reported[41]. This might suggest the need of adherence to diagnostic work-up guidelines for CBC among older breast cancer patients 2 to 5 years after first breast cancer diagnosis.

All in all, early detection of CBC in breast cancer survivors is of great importance, especially for women firstly diagnosed with breast cancer before the age of 50. In the Netherlands, national guidelines for follow-up care after breast cancer only recently include annual surveillance with mammography and clinical examination for patients below 60 years of age[42]. The effectiveness of mammography to detect CBC is still under debate[43], having shown low sensitivity for the detection of bilateral breast cancer in a Dutch study[44]. Magnetic resonance imaging (MRI) is recommended for women of the same age with known BRCA1 and BRCA2 mutations[42]. Research on more intense surveillance (with MRI or screening ultrasound) for women with elevated risks of breast cancer showed higher breast cancer detection rates but also increased false-positive findings, although the risk of false positives was lower among women with a previous history of breast cancer[45].

On the other hand, psychological distress, such as anxiety, plays an important role in women with an increased (genetic) risk of breast cancer when considering prophylactic mastectomy[46], psychological aspects might thus also need consideration in the setting of early detection of CBC. More research is needed to define the tailored follow-up strategy to earlier detect CBC among young women before they become eligible for the mass screening programme.

To our knowledge, our study is the largest population-based nationwide study for CBC survival. We benefit from using NCR data, which contains high quality detailed, data on a large number of unselected patients and with complete follow-up. In this study we took into account the time interval between first and CBC. The use of different cut-off points for the time intervals used in previous studies to define synchronous and metachronous bilateral breast cancer (range 0-60 months) might explain the contradictive findings on the impact of a CBC on mortality[17]. The time-dependent Cox proportional hazard model took into account the interval between the first and subsequent CBC for an accurately comparison of the impact of CBC and UBC on survival, although we did not have detailed information on tumour grade[47] or hormone receptor status. Another limitation was the lack of cause of death. The burden of co-morbidities among the older patients might have influenced their risk of overall death.

Conclusion

Women diagnosed with CBC had a worse survival estimated from their first cancer as compared to women with UBC, also after adjusting for tumour characteristics and treatment of the first tumour. This poorer survival was most pronounced among patients younger than 50 years, who might need tailored early detection strategy as mass mammography screening only starts at age 50 in the Netherlands. Further research needs to evaluate the potential benefits and harms of such approach.

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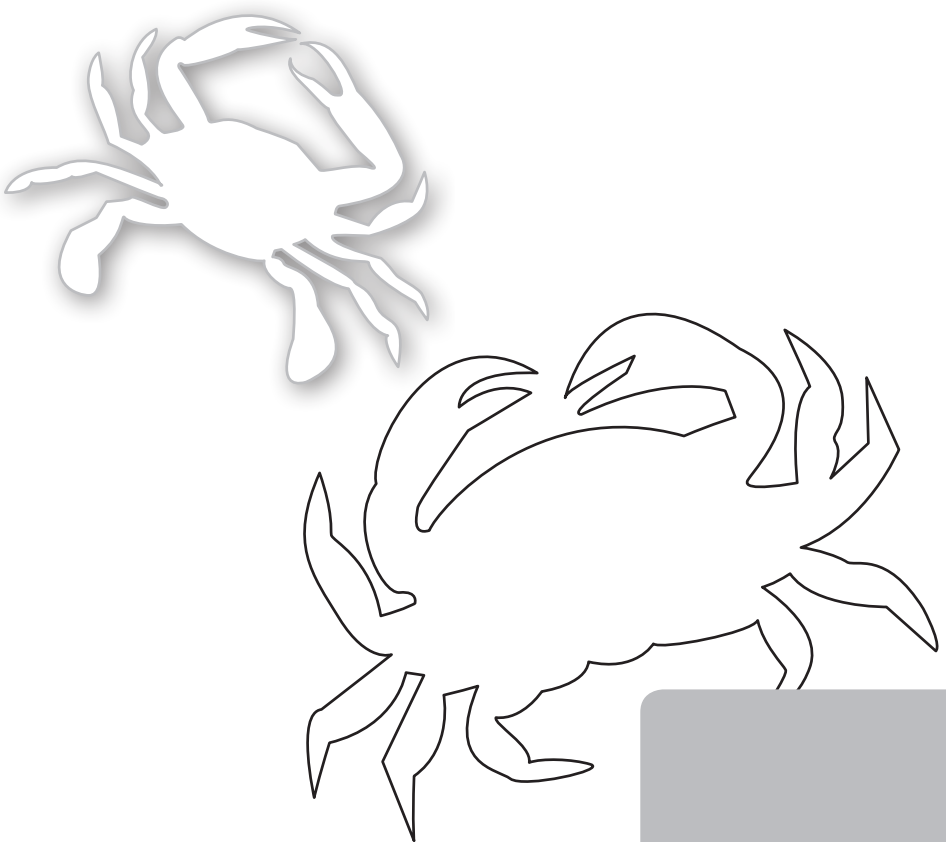
CHAPTER 4

General discussion



Due to the aging of the population and prolonged survival of cancer patients more and more patients are confronted with multiple cancers in a large variety of combinations, depending on the incidence of the primary cancer, its long-term survival and its direct or indirect determinants. This pertains particularly to nations with a well- functioning health care system like the Netherlands because survival is in many cases quite good and the good diagnostic facilities, making the likelihood of multiple cancers occurring and being detected within one patient high. This thesis provided estimates of the occurrence of multiple cancers in the past two decades (1989-2008) diagnosed in the Netherlands (with almost 17 million people having one of the largest cancer registries in the world), subsequently followed by analyses of survival. I hope the findings described in this thesis will provoke informed discussion on etiological and pathogenetic associations between first and subsequent cancers and help to underpin follow-up strategies amongst cancer patients.

This chapter consists of three parts,

i) Part I: main findings from **chapter 1.2-4** are summarized and discussed ,
ii) Part II: discussions on strengths and limitations of the studies
iii) Part III: clinical implications and future research directions followed by conclusions.

4.1. Research question 1:

What was the prevalence of multiple malignancies in the Netherlands in January 2007?

- What types of cancers often coexist within one patient?
- What are the characteristics of tumors and patients with multiple malignancies?

Part I: Main findings and interpretations

Prevalence data may give important but often ambiguous information to assess the need for care. In **Chapter 1.2**, the prevalence of multiple malignancies (MMs) in the Dutch population appeared to be more than 30,000 (or 7% of all cancer patients alive) on January 1st 2007. This population is relatively old with a median age of 74 years (IQR 71-76 years) being on average 3 years older than at the onset of the first cancer. Old age challenges treatment decisions at diagnosis, impairs survival, in particular when patients have comorbid conditions besides the cancers[1-5].

We found that the most common prevalent subsequent cancers were those located in paired organs (breast cancer) or in organs with a large surface (skin and colorectal cancer), which might be related to 'field-cancerization' and also because those cancers are common in the population[6-10]. The common cancer pairs of first and second cancers were as follow:

i) Female breast and genital cancers (any order),
ii) Urinary tract and prostate cancer (any order),
iii) Hodgkin's lymphoma and subsequent female breast cancer,
iv) Non-hodgkin's lymphoma and subsequent cutaneous squamous cell carcinomas.

Finding the most common subsequent cancers amongst cancer survivors triggers hypotheses for further research to find the explanations for the observed high prevalence of cancers and may be important information when deciding where to allocate health care resources.

With the growing population of cancer survivors, this prevalence of 30 000 cases in 2007 is expected to reach 100 000 by 2015, in the Netherlands[11].

Answer box 4.1:

i) On January 1st, 2007, 7% (30 000) of cancer survivors in the Netherlands were alive with more than one cancer.
ii) They were on average over 70 years at prevalence estimates.
iii) Multiple malignancies are often located in paired organs (i.e breast) and in organs with large surface such as in colon, rectum, and skin.

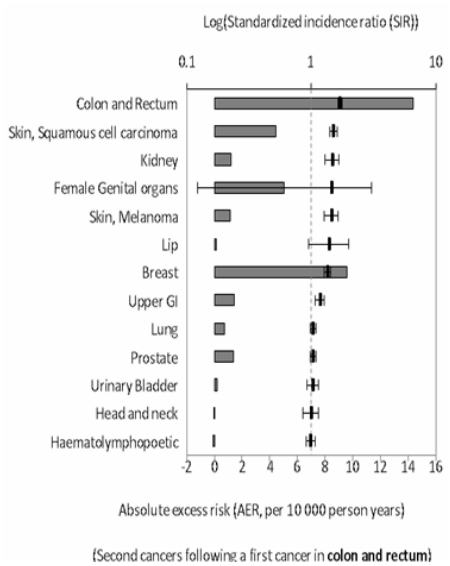
4.2. Research question 2:

i) Can we detect risk patterns with increased or decreased relative and absolute risks amongst cancer patients compared to the general population (i.e. people without a history of cancer)?
ii) Can these risk patterns inform us regarding potential underlying risk factors for the co-occurrence of certain types of cancer within one patient?

In **Figures 1a-1**d, I described risk of common cancers amongst patients with a previous cancer in breast, prostate, colon & rectum, and melanoma of the skin as compared to general population (i.e. people without a history of cancer). Detailed analyses on the most common subsequent cancers (e.g. colorectal cancer, breast cancer, prostate cancer, and cutaneous melanoma) were performed and presented in **Chapter 2**. Other analyses on less frequent cancers have been performed and published outside the scope of this thesis (other publications).

I used standardized incidence ratios (SIR) to estimate the relative risk for cancer between cancer patients and general population. Absolute excess risks (AER) were used to estimate how many extra cancer cases occurred as second cancer. Often, risks for cancers are increased amongst cancer patients compared to people without a history of cancer (i.e. SIR>1 and AER>0). However, it is also possible that cancer patients are at lower risk for certain cancers compared to the general population (i.e. SIR<1 and AER<0).

In this section, I will discuss the relative and absolute risk for second cancers, followed by 4.2.2 the impact of synchronous second cancers on SIR and AER estimates; 4.2.3 risk for second cancers amongst long-term cancer survivors with first cancers in colon & rectum, and melanoma of the skin, and 4.2.4: Time trends of subsequent melanoma of the skin amongst cancer patients between 1989 and 2008.



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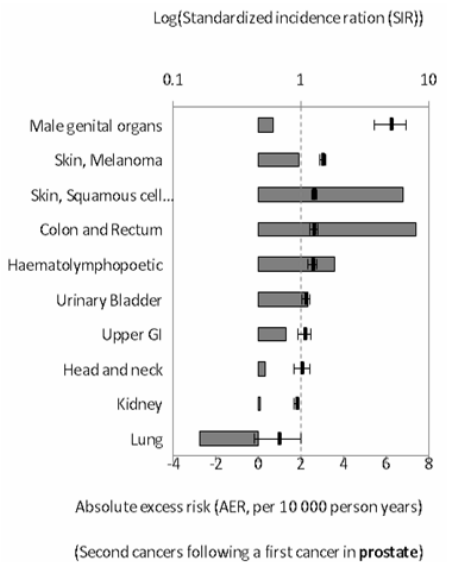

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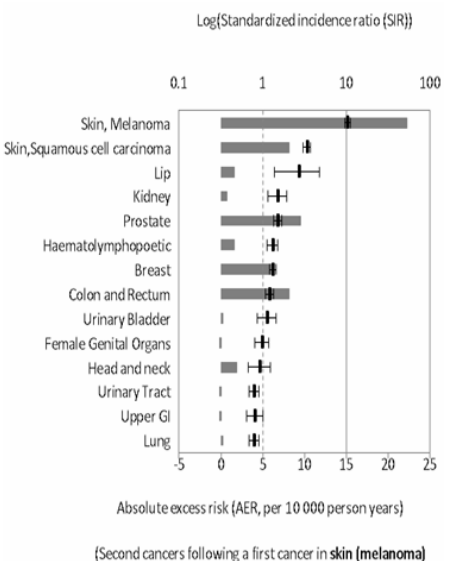

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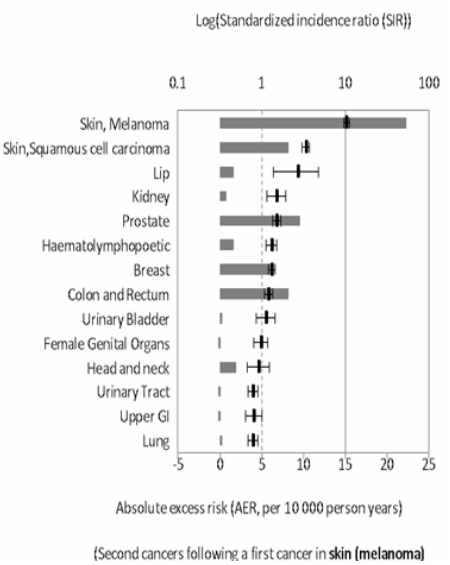

D

Figure 1 Standardized incidence ratio (SIR) and absolute excess risk (AER, per 10,000 person years) of second metachronous primary cancers amongst patients with a first cancer in breast, prostate, colon & rectum, and skin (melanoma) in the Netherlands between 1989 and 2008
Source: Netherlands Cancer Registry
Note: 1. Second cancers diagnosed within 6 months after the first were excluded.

4.2.1 Relative risk and absolute excess risk for second cancers

The occurrence of second primary cancers can be associated with

i) Shared lifestyle risk factors for the first and second cancer,
ii) Side effects from the treatment of the first cancer,
iii) Immune-suppression,
iv) Genetic predisposition,
v) a combination of the aforementioned factors[12].

Shared life style risk factors are likely responsible for a higher risk of second cancers which occur at the same anatomical site as the first one. Survivors of colorectal cancer experienced a three-fold increased risk for a second cancer in colon and rectum compared with the people without a history of cancer (**Chapter 2.1**); survivors of melanoma of the skin had a five- to ten-fold of higher risk for a second cutaneous melanoma (**Chapter 2.2**). Cancers occurring at different anatomical sites or of different subtypes may be related to common lifestyle features as well. High calorie diets, low levels of physical activity, and smoking may explain why the risk for cancers in breast and kidney are higher amongst patients with a first colorectal cancer (see also **Figure 1c**)[13]. Patients with melanoma of the skin experienced a higher risk for cancers in lip and skin (squamous cell carcinoma, SCC) which are probably due to high amounts of UV exposure (e.g. **Figure 1d**)[14]. Shared reproductive factors (e.g. low parity), hormone replacement treatment) or obesity as risk factors may associate cancers in breast and endometrium (**Chapter 2.3**). Sometimes, cancer patients have a decreased risk for subsequent cancers compared to the general population; for instance, patients with melanoma of the skin had a lower risk for lung cancer and cancers in the upper gastrointestinal (GI) tract cancers (esophagus, stomach, and small intestine) (**Figure 1d**, which might be explained by the high social economic status of melanoma patients where smoking prevalence is low[15-16]. Side effect of initial cancer treatment can be associated with either increases or decreases of risk for subsequent cancers. A higher risk for lung cancer amongst breast cancer survivors might be related to initial radiotherapy on the chest during treatment of breast cancer (see also **Figure 1a**)[17]. In line with this hypothesis, In **Chapter 2.3**, we observed that patients with contralateral breast cancer (CBC) experienced a higher risk for a lung cancer 5 years after radiotherapy was administrated for the first breast cancer. As low levels of ionizing radiation needs a 5-year lag period between radiation exposure and cancer induction, we suspect that the aforementioned increased risk is associated with radiotherapy from the first cancer[18]. Some *protective* effects from cancer treatment were also observed. Decreased risks for cancers of the lung, colon, rectum, ovary, and head and neck were observed amongst women with CBC receiving chemotherapy for the first breast cancer, hinting towards a potential preventative effect of chemotherapy (**Chapter 2.3**). Likewise, males receiving radiation in the pelvic region for first cancers (e.g. rectal, prostate, testis) showed a lower risk for a prostate cancer subsequent to the index cancer (**Chapter 2.4**), hinting that irradiation suppresses early and indolent prostate tumors[19-20]. Immune-suppression might be the explanation for the association between skin cancer (melanoma, SCC) and haematolymphopoietic malignancies (e.g. **Figure 1d**).

Cancer syndromes caused by inherited genetic mutations (e.g. BRCAI/II HNPCC) may underlie the observed associations between melanoma, breast cancer, and colorectal cancer, particularly amongst those patients who were very young (often before age 50) at first cancer diagnosis[21-22]. Colorectal cancer patients younger than 50 years at diagnosis had a more than five-fold increased risk for a second cancer in colon and rectum whereas for older patients the relative risk (SIR) was three-fold increased (**Chapter 2.1**). We suspect that a substantial proportion of the young patients were affected by the hereditary nonpolyposis colorectal cancer syndrome (HNPCC) as this is characterized by frequent occurrence of metachronous colorectal cancers[23]. Women with diagnosed with CBC before the age of 50 years experienced a ten-fold higher risk for an ovarian cancer, probably because many of them were affected by BRCA I/II[24]. (**Chapter 2.3**) Of note, these high risks will have been a bit inflated by the intensive screening which takes place in genetically affected populations.

Is a high SIR equivalent to a high excessive absolute risk (AER)?

A high SIR does not necessarily translate into a high absolute risk (AER) in rare cancers. For instance, patients with prostate cancer experience six-fold increased relative risk (SIR) for a cancer in other male genital organs (e.g. testis, penis) compared to the risk in the general population. However, absolute excess incidence (AER) due to second cancer is less than 1 in 10,000 person years. Likewise, the higher relative risk of cancers in lip translates to merely ~2 cases per 10,000 person years amongst patients with melanoma of the skin. On the contrary, SIRs for commonly occurring cancers, like colorectal cancer, breast cancer, and skin cancers are often relatively moderate, but AERs are high (**Figure 1a-1d).**

4.2.2 What is the impact of synchronous second cancers on SIR and AER estimates?

Around thirty-five per cent of all second cancers are found synchronously with the first due to the intensive workups around cancer diagnosis (data not shown). Because of the very short number of person years at risk (often just 1 day in between), SIR and AER estimates, especially for the time period shortly after first cancer diagnosis are elevated substantially, which may cause inflation of second cancer risk. In fact these synchronous cancers are probably prevalent cases that without the detection of the first cancer might have been detected later or maybe never (depending on their localization, tumor size or stage). For instance, in **Chapter 2.4** we observed that cancer patients were at increased risks of developing a prostate cancer. However, upon excluding lesions diagnosed within the first year after the first cancer, no excess risk was observed, suggesting that active surveillance after the first cancer elevated the risk of *detecting* a (second) prostate cancer which would normally have remained undetected or would have been detected later. Likewise, after excluding cases diagnosed around the index cancer (i.e. 3 months), the elevated risk for the second Chronic Lymphocytic Leukaemia (CLL) disappeared amongst cancer patients. (**Chapter 2.5**) Therefore, it's crucial to distinguish/

excluding synchronous lesions when estimating SIR and AER for second cancers to avoid over-estimation of risk for second cancers.

Worldwide, the definition of synchronous cancers varies: in the US, Surveillance, Epidemiology and End Results (SEER) Program defines second cancers as those detected within 2 months after the initial cancer[25]; The Victoria cancer registry (Australia) and the Netherlands cancer registry apply the coding rules of the International Association of Cancer Registries (IACR)) guidelines, where the recognition of the existence of second cancers does not depend on time but on location and morphology of cancers[26]. However, researchers also define synchronous lesions according to the aim of study. In this thesis, in general we use 6-month period as the cut-off point to distinguish synchronous and metachronous second cancers, because generally in this time period the intensive workup and initial treatment for the index cancer take place. In this thesis, I also applied 3-month and 1-year cut-off points according to the workup timeline of specific index cancers.

4.2.3 Risk for second cancers amongst long-term cancer survivors

Cancer patients who survive without recurrences or metastasis for 5 or more years are generally regarded as 'clinically cured'. However, we observed that long-term survivors of colorectal cancer and melanoma of the skin still have increased risks of developing a new cancer compared to the general population (**Chapter 2.1-2.2**). Likewise, other studies have showed that cancer patients are far from being 'cancer free' beyond this 5-year mark[27-30].

In **Chapter 2.1** we saw that amongst patients with an initial colorectal cancer the risk of getting diagnosed with subsequent cancers in the proximal-colon remained elevated after 5-years of follow-up. It is known that tumors or polyps in the proximal-colon are often missed (varying from 4-11%) during colonoscopy[31]. Likewise, in **Chapter 2.2** we have shown a persistently elevated risk for a second melanoma of the skin amongst melanoma (skin) survivors even up to 20 years. These long-existing increased risks may suggest the need to continue to follow patients beyond 5 years given the high relative and absolute risks of subsequent colorectal cancer and melanomas in the skin (for colorectal cancer SIR=1.6; AER > 15 / 10,000 person years, CI=4%; for melanoma of the skin SIR=10; AER=17/ 10,000 person years, CI=5%). However, benefits, adverse effects and costs should be carefully balanced when considering follow-up schedules and modalities.

4.2.4 How did the trend of occurrence of second cancer (e.g. melanoma of the skin) change over the past 20 years in the Netherlands?

The risk for second cancer in a population can decrease or increase over time because of

i) Changes in risk factors,
ii) Early detection programs,
iii) Awareness of cancers,
iv) and changes in cancer profile (i.e. incidence and survival) itself.

Within the framework of this PhD thesis I was able to assess the influence of detection by presenting changes of risk for second cancers according to clinical exam schedule (i.e. 0-1 year and 2-5 years).

To study variation over time in detection of second cancers, we investigated the diagnosis of subsequent melanoma as an example because of its high prevalence[32], combined with the increasing awareness of the disease over the past 20 years due to various preventive campaigns and attention from media. We expected an increasing detection rate for melanoma over time amongst cancer patients, with more subsequent melanomas diagnosed early in follow-up time in both sexes. Interestingly, we found that amongst male cancer survivors, over time, less subsequent melanomas were detected in the first year after the index cancer coinciding with a rising incidence trend later in follow-up (2-5 years after index cancer), whereas amongst female cancer survivors a clear trend towards earlier detection of melanoma over time was observed. As many second melanomas are patient-detected lesions[33-34], a worsened risk trend of second melanoma might reflect less perfect self-examination skills amongst male cancer survivors, which goes in line with the observation that females are more aware of skin lesions, more likely to seek physician examinations which leads to early detection of melanomas in skin[35-38]. It is also in line with the worse survival and higher mortality amongst (elderly) men[39].

Answer box 4.2

For 4.2.1

i) Shared life-style risk factors, initial cancer treatment, immune-suppression, and genetic predisposition underline the co-occurrence of second cancers with their index cancer.

ii) Risks for cancer could be either increased or decreased amongst cancer patients compared to people without a history of cancer.

iii) A high relative risk for second cancer does not necessarily translate into large absolute risks and therefore a commonly occurring problem.

For 4.2.2

iv) To include synchronous second cancer in estimating SIR and AER would over-estimate the risk for new incident second cancers.

For 4.2.3

v) Long-term (i.e. >5years) cancer survivors of skin melanoma and colorectal cancer are at increased risk for a second cancer.

vi) Before extending the surveillance schedule beyond the 5-year mark, trade-offs between health cost and gain should be carefully balanced.

For 4.2.4

vii) There is an increasing trend of occurrence of subsequent melanoma amongst cancer patients in the past two decades in the Netherlands.

viii) Despite the increasing awareness of disease, over time more subsequent melanomas were found later in follow-up time in males.

4.3. Research question 3:

What are the prognostic consequences of the diagnosis of a second cancer?

The prognosis of patients with two cancers can be estimated by various methods using different outcome measures (e.g. cancer-specific death, relative survival, hazard ratio)[40-42].
In the current project, we chose Cox proportional hazard model (CPH) to estimate the hazard ratio between patients with one and with two cancers by incorporating second cancer as a time-dependent covariate. We conducted studies on patients with colon and breast cancer. (**Chapter 3.1-2**)

For both patient groups we observed that diagnosis of a second cancer was associated with an increased overall death rate, particularly amongst younger patients: with 1.7 (HR=1.7 95%CI 1.3-2.1) times higher amongst colon cancer patients younger than 60 years and with 2.5 (HR: 2.4, 95%CI: 2.3-2.6) times higher amongst women with contralateral breast cancer younger than 50 years. Indeed, aggressive forms of cancers often occur amongst younger patients. Not only this aggressive nature of cancer accelerates the death of patients, but as

young patients more frequently receive intensive treatment than older patients, the chance that they have toxicity or resistance from the treatment is higher[43-46].

Besides the classic prognostic factors (i.e. stage, age, tumor size, and nodal status), the time-interval between the first and second cancer is associated with the risk of dying. For instance, women older than 50 years with contralateral breast cancer (CBC) diagnosed between 2 and 5 years after the first cancer had a 20% increased hazard of dying (HR=1.2 95%CI 1.0-1.3) compared to CBCs diagnosed within 2 years after the first breast cancer indicating a progress (e.g. metastasis) in the disease which negatively influences survival[47]. Another possible explanation is the less intensive diagnostic work-up of the CBC in these age groups. Differences in breast cancer management among older women compared to younger women been have reported. This might suggest the need of adherence to diagnostic work-up guidelines for CBC among older breast cancer patients 2 to 5 years after first breast cancer diagnosis.

Answer box 4.3

i) The occurrence of a second cancer negatively affects overall survival of patients with a previous cancer, especially amongst the young.
ii) A short time interval (e.g. <5 years) between cancers may indicate progress of disease hence decreases survival.

PART II STRENGTHS AND LIMITATIONS OF THE STUDY

Studies analyzing excess risk for a second cancer using data from a long-standing, good-quality population-based cancer registry as I preset in this thesis, generally have the advantages of

i) ample sample size;
ii) being representative for the general population;
iii) long-term follow-up; and
iv) using histologically verified cancers.

The data allows to identify high-risk populations and to capture the timing for development of certain subsequent cancer types.

However, some drawbacks and limitations should be considered.

First of all, risk patterns derived from cancer registry data, are rather 'detection patterns' than 'risk patterns' as we assumed. Unlike classical prospective cohort studies, observed 'risk patterns' can be influenced by detection behavior/frequency from both doctors and patients themselves. Therefore, when using these patterns to infer on follow-up strategies one should obtain information on *compliance to follow-up*.

Secondly, cancer registry data do not contain information on the resected precursors of cancers, such as polyps in colon and rectum. In **Chapter 2.1**, we observed an elevated risk

for a second cancer in the proximal-colon amongst survivors with colorectal cancer, probably due to a relatively high 'miss rate'(4-11%) for polyps in the proximal-colon during colonoscopy[31, 48-49]. Unfortunately, we could not test this hypothesis as we did not have (complete) data on the removed polyps. Hence, if our hypothesis is true, and if the doctors detected and removed polyps located in the proximal-colon better, the observed higher risk for cancer in the proximal-colon would be expected to diminish. It is, therefore, based on the observed increased risk, that the advice of extending follow-up focusing on this segment of colon should be made with caution.

Thirdly, cancer registries have not collected information on exposure to life style factors such as smoking, which could be confounders when examining the causal relationship between initial cancer treatment and occurrence of second cancers. In **Chapter 2.3** for instance, to examine the relation between initial radiotherapy and occurrence of lung cancer amongst women with breast cancer, we compared relative risks (SIR) for lung cancer between breast cancer patients who received radiotherapy versus those who did not. If the SIR is much higher amongst women who underwent /received radiotherapy than amongst those who did not, we suspect radiotherapy might play a role for the observed higher risk for lung cancer. However, we should realize that, unlike the situation in randomized controlled trials, the treatment that a patient receives is influenced by stage, age, and comorbid conditions at index cancer diagnosis. Hence, it is important to correct for potential confounders including those listed in the previous sentence and lifestyle factors (e.g. smoking). Due to the lack of lifestyle information we could not make strong conclusions regarding causal relations between treatment of our interest and occurrence of a certain second cancer.

Last, cancer registry data provide long-term risk patterns of second cancer which underpin, together with other prognostic and practical information, follow-up strategies for cancer patients. However, when explaining newly diagnosed cancer patients that they might be at long-term risk for getting a second cancer, one should realize that the currently observed patterns are in fact already outdated as they are derived from patients diagnosed many years ago. They might have a different underlying risk factor distribution than the new cancer patients, received a plethora of different types of treatments and the risk may be altered due to changes of lifestyle after cancer diagnosis[50]. Therefore, more studies, like the one conducted in **Chapter 2.6**, are needed to capture the most recent trends on occurrence of second cancer.

PART III STUDY IMPLICATIONS AND FUTURE STUDIES

4.3.1 Clinical implications: to underpin surveillance and therapeutic strategy for cancer patients

Firstly, our description on risks of second cancers that located non-adjacent from the first would facilitate to detect those lesions at earlier stage (**Figure1a-d, Chapter 2**). Via workups or follow-up screening second cancers that are adjacent to the first are often found, like second male genital cancers following a first cancer in prostate; subsequent skin squamous cell carcinoma (SCC) following a previous melanoma of the skin (**Figures 1b, 1d**). However, tumors located more distant from the index cancer may be missed. For example, subsequent breast cancer amongst patients with colorectal cancer may be missed during routine check-ups (**Figure 1c**).

Secondly, we observed an elevated risk for second cancers amongst long-term (e.g. > 5 years) cancer survivors (**Chapter 2.1-2.2**). This finding may alert patients and their treating doctors to perform surveillance for second cancers even after a patient is considered to be 'clinically cured' of the first cancer in order to find any second cancers in early stages. However, one should be conscious of the risk of 'over-diagnosis' of cancer which may result in increased anxiety, and even reduced health-related quality of life (HRQoL) of cancer survivors without gains in life-expectancy[51-52].

Thirdly, the risk estimates stratified by age and treatment as described in **Chapter 2.3 - 2.4** as well as the subgroup analysis on the impact of a second cancer on the overall survival of cancer patients (**Chapter 3.1-3.2**) can form an evidence base to underpin surveillance strategies in specific patient groups.

Last, analysis on associations between prognostic factors (e.g. stage, age, lag-time between first and second cancer, period of diagnosis) and outcome for second cancers also pin point groups that needs closer surveillance (**Chapter 3.1- 3.2**).

4.3.2 Future studies

As a sequel to the studies presented in this thesis, there are several aspects which deserve further study, further detailed below:

i) Studying more cancer pairs and clusters,
ii) Studying treatment dilemmas for patients with second cancers and consequences of these treatment decisions,
iii) Developing a surveillance strategy for second cancer,
iv) Study possibilities for primary prevention of second cancers through lifestyle changes.

4.3.2.1 More cancer pairs and clusters

In this PhD thesis, I described only a few etiological associations between first and subsequent cancers. In **Chapter 2.1-2.2**, common risk factors for the two cancers of the same type

Table 1 etiological associations between first and second cancers

	First cancers															
Second primary cancers	**Larynx**	**Oral and pharynx**	**Nasopharynx**	**Esophage (SCC)**	**Colon**	**Rectum**	**Lung**	**Female breast**		**Cervix uteri**	**Corpus uteri cancr(UCC)**		**Ovary**		**Vagina**	**Urinary bladder**
Larynx			■				■									■
Oral and pharynx	■	■	■	■			■			▒						
Nasopharynx				■												■
Esophagus	■	■	■													
Colon					▓	▓									▒	
Rectum					▓	▓					▒	▓	▓	▓		
Lung	■	■	■			■		■		■						■
Female breast											▒	▓	▓	▓		
Cervix uteri								■	■							
Corpus uteri								▓	▒							
Ovary								▓	▒							
Vagina										▒						
Urinary Bladder	■	■	■				■									

Notes for different etiological associations

■ smoking and /or alcohol

▓ lifestyle factors(SES,obesity,diet, physical activity)

▒ hormone factors(including parity status, hormone treatment)

▒ infection and immulogical susceptibility

Note: this summary is based on 'New malignancies among cancer survivors: SEER Cancer Registries, 1973-2000'[25]

(colorectal cancer and melanoma of the skin) were discussed; in **Chapter 2.3-2.4** associations between initial cancer treatment and occurrence of third/second cancer were investigated. However, other cancer pairs (clusters) which are mutually associated with lifestyle factors like smoking, alcohol, obesity, as well as infection-related cancer pairs have not been examined in this thesis. For instance, smoking and alcohol drinking may be the underlying reason why associate lung cancer and cancers of the upper aerodigestive tract (UADT) often occur in patients with laryngeal/hypopharyngeal carcinomas[53]. Similarly, as higher body mass index (BMI) is associated with an increased risk of breast cancer and also increases the risk for a second cancer in the breast, endometrium, and colon and rectum, overweight and obesity may be such a common risk factors[54-55]. More etiological associations are shown in **Table 1**. Identifying cancer types which frequently occur in pairs because of shared risk factor exposures may help to allocate high risk populations for certain cancers in order to optimize early detection.

Describing time trends of occurrence of such cancer pairs may reveal hints towards changes in exposure to risk factors and/or changes in surveillance over a period of time. We analyzed trends of second melanoma of the skin amongst cancer survivors in **Chapter 2.6.** However, as another quickly growing burden of skin cancer in the Dutch population, the basal cell carcinoma (BCC) which often appears as multiple cancers, its incidence has increased three fold in the past 30 years and it is expected to increase in the future[56-58]. The decreased risk of prostate cancer, breast cancer, and colorectal cancer hints to a protective effect of UV radiation for the aforementioned cancers[59-60]. Hence studies describing risk patterns and time trends of BCC of the skin will add valuable information for cancer surveillance and for cancer primary prevention.

4.3.2.2 Treatment delimmas regarding patients with second cancers

In the late 80s in the Netherlands, initial treatment of Hodgkin's disease and the occurrence of second cancers have been described by R. Somers and W.P. Breed[61-62]. Later studies on subsequent cancers and its relation with initial cancer treatment as well as its late toxic effects, increasing the risks of e.g. cardiovascular disease, has been thoroughly studied amongst long-term survivors of Hodgkin's disease, breast cancer, and testicular cancer[28, 63-67].

Yet, preferred treatments for second cancers or determinants of this treatment have been poorly studied. When a second cancer is diagnosed, there is often much discussion on how to treat patients for this cancer, especially if a patient also has other comorbid conditions. Lemmens et al. observed that patients received less aggressive treatment at a diagnosis of colorectal cancer when presenting with a history of cancer[4]. In **Chapter 3.1-3.2**, we also observed that patients with a second cancer often received less aggressive treatment than those with one cancer only especially amongst elderly. Most patients are old (average age >70 years) at diagnosed of a second cancer and it is known that doctors tend to administer less aggressive treatments to the old, the fragile, and to those presenting comorbid condi-

Table 2 Age at first diagnosis of patients with second primary cancers and diagnosis interval between cancers, the Netherlands Cancer Registry 1989-2008

Age at first cancer (years)	N	Proportion of patients diagnosed within 6 months after the first cancer	Time interval (median, Interquartile range (IQR) between the first and the second (years)[1]
<35	1,170(1%)	14%	5.4 (2.2-9.3)
35-50	8,665(10%)	12%	5.6 (2.7-9.8)
50-64	24,996(28%)	15%	5.1 (2.4-8.8)
65-74	33,948(38%)	18%	4.2 (2.0-7.3)
75+	20,165(23%)	25%	2.8 (1.5-5.0)

Source: The Netherlands Cancer Registry

Note: [1] only includes cancers diagnosed beyond 6-month following the first cancer.

tions (including previous malignancy)[3-5, 68]. Maas et al suggest to introduce Comprehensive Geriatric Assessment (CGA) before administrating (chemo) therapy in order to anticipate or estimate better the risk for drug toxicity[69]. However, there are no/few population-based data describing the aforementioned association.

Cancer patients (and or their family) already experienced one round of treatment before a second cancer, with potentially severe side effects, like nausea, fatigue, pain, fever, etc, from the previous treatment affect their compliance for treatment [70] and may hinder them from accepting the treatment for a second time. Decisions on treatment of second cancers may also be dependent on patients' (or their family's) opinion[71]. Further studies are, therefore warranted to investigate determinants of decisions on second cancer treatment, such as patient characteristics (age, stage of disease, social economic status, CGA score, etc) and patients' preferences.

We observed that younger patients (i.e. <60 years) more often had metachronous second cancers and often received aggressive treatment for both cancers. (**Chapter 3.1-3.2**) These young patients experienced a higher hazard ratio (of 1.7 versus 1.3 in colon cancer patients aged <60 years versus > 80 years; of 2.4 versus 1.1in breast cancer patients aged <50 years versus > 70 years) after a second cancer than the old to whom one round of treatment is often administered. Although it is unclear whether this higher impact on survival is because of high toxicity due to double dosage of therapeutic regimens or due to the more aggressive nature of tumors which occurred in this younger group, further studies on treatment decisions and their association with survival in this patients group are warranted.

4.3.2.3 Surveillance for second cancer amongst elderly cancer survivors

Patients who develop a second primary cancer are a heterogeneous group: the majority concerns people older than 65 years often having a second cancer shortly after the index cancer. (**Table 2**)

Current guidelines for surveillance of cancer patients have been made based on studies with younger and fitter subjects, but cannot be easily generalized to this older patient population. For example, in comparison to younger groups, older cancer patients are: i) less susceptible to the mutagenic effect of radiation, ii) less likely to be affected by a genetic cancer syndrome, iii) more likely to die of other diseases, iv) more likely to have an indolent cancer requiring less aggressive treatment, and v) less likely to develop a subsequent cancer because their life expectancy is shorter[72-75]. Further studies to develop and evaluate guidelines for this elderly patient group are needed[76].

The surveillance of patients with colorectal cancer and breast cancer may be combined with the mass screening programs for these cancers which are available in the Dutch health care system.

A challenge in the follow-up of these elderly cancer patients is to find the right surveillance tool. For instance, in **Chapter 2.1**, we saw a higher excessive risk for second cancer in colon and rectum amongst individual with a prior colorectal cancer years after the first cancer. This finding hints to the importance of monitoring this population at least for 5 years when patients reach an average age of 77 years (IQR 74-79 years). Use of invasive surveillance modalities such as colonoscopy in this age group would increase colonoscopy-induced adverse effects, like pulmonary complications and perforation. When taking into account their limited life-expectancy, this surveillance modality is likely to do more harm than benefit to those elderly patients[77]. Future research may aim to develop the most appropriate surveillance modality-tailored follow-up strategies-for this potentially fragile population.

4.3.2.4 Primary prevention for second cancers via changes of lifestyle

As described in **Table 2**, patients younger than 65 years often develop a second cancer 5 years after the first cancer, which suggests there is potential to prevent a second cancer by modifying lifestyle habits. Studies showed that cancer patients are willing to modify their health behaviour after cancer diagnosis than the healthy population: for example, men reduce tobacco and alcohol consumption, try to maintain a healthy body weight after cancer diagnosis[50]; and women with uterine cancer are empowered by healthy diet and being more physically active [78]; survivors of cancers in breast, colon-rectum, and prostate are willing to have a more active role in their health care and to know how to look after themselves after diagnosis[75, 79]. However, no study has ever been conducted to verify if such changes in lifestyle can prevent second cancers from occurring. It is possible that such primary prevention efforts of patients already diagnosed with a cancer are ineffective, because carcinogenesis is

a cumulative process and the damage may have already been done irreversibly at the moment of first cancer diagnosis.

CONCLUSIONS

The occurrence of second primary cancers (multiple malignancies) is largely the consequence of a prolonged survival of cancer patients. In 2007, one in six (16%) cancer patients had more than one cancer diagnosis and one in fifteen (7%) cancer survivors live with two or more cancers in the Netherlands. With the increasing number of cancer survivors, the number of patients with a second or higher-order cancer will increase in magnitude. I estimated that in 2012 we have about 75,000 people living with more than one cancer diagnosis in the Netherlands. Cancer survivors *often* are at higher risk for developing a cancer than the general population and second cancers negatively influence overall survival of patients. Detecting second cancers at early stages is *important* to improve survival but, due to the old age of this population, finding the right surveillance modality to balance the benefits and harm of early detection is *crucial*.

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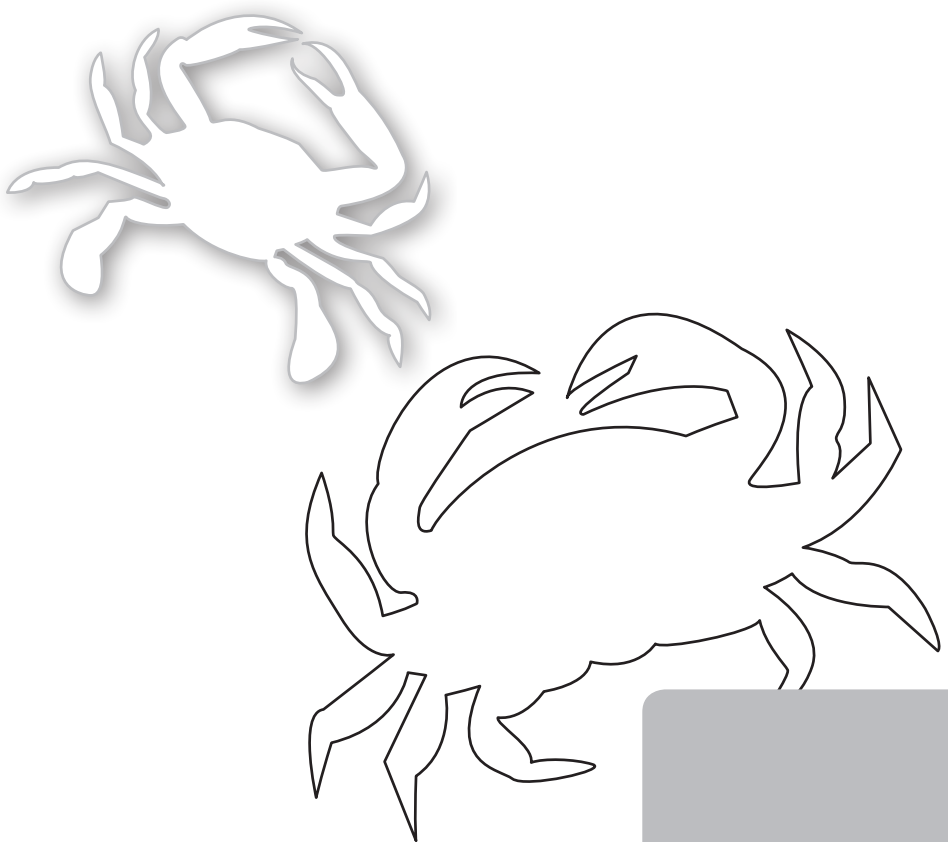
SUMMARY



Due to aging of the population and prolonged survival an increasing number of cancer patients develop multiple malignancies (MMs) in a large variety of combinations in differing orders, depending on the primary cancer, its curative treatments, its long-term survival and other direct or indirect determinants. In the Netherlands, the prevalence of MMs is expected to reach around 100,000 cases in 2015 which represents for ~15% of total cancer survivors, due to doubled number of cancer survivors since 2005.

Building upon earlier research of Soerjomataram (thesis) I aimed to answer the following **main research questions**:

i) What is the prevalence of multiple malignancies in the Netherlands?
- What types of cancers more or less often coexisted within one patient?
- What are the characteristics of tumors and patients with multiple malignancies?

ii) Are there any striking risk patterns with increased or decreased relative and absolute risks amongst cancer patients compared to the general population (i.e. people without a history of cancer)? Can these risk patterns inform us on potential underlying risk factors for the co-occurrence of certain types of cancer within one patient?

iii) Are there any amenable prognostic consequences of the diagnosis of certain second cancers?

The work in this thesis is based on a comprehensive research project funded by the Dutch Cancer Society named 'The increasing burden of second primary cancers in the Netherlands: trend in incidence, survival and causes-of-death since 1970 (EMCR 2008-4132) in which a variety of combinations of cancers in a patient has been studied and also a methodology was developed for these type of analyses of risk and prognosis. Most of these analyses were performed in collaboration with epidemiologists from the initially 8, now 2 comprehensive cancer centers (CCC's) and junior and senior specialized clinicians.

In the framework of the thesis, I selected the most common second cancers for detailed analyses on risk and survival. They are: colorectal cancer, breast cancer, prostate cancer, melanoma of the skin, and well as chronic lymphocytic leukemia (CLL).

Part 1: Prevalence of MMs

To determine the magnitude of problem of MMs and capture the available characteristics of patients with MMs in the cancer registry, we estimated the point prevalence on Jan 1st 2007 **(Chapter 1.2)**. On that date, there were more than 30,000 patients with MMs alive in the Netherlands, representing 7% of all cancer patients. This population is relatively old with a median age of 74 years (IQR 71-76 years) being on average 3 years older than at the onset of the first cancer. Old age often complicates treatment decisions at diagnosis, and impairs survival, in particular when patients have comorbid conditions besides the cancers. We found that the most common prevalent subsequent cancers were those located in paired organs (breast) or in organs with a large and extended surface (skin, colon and rectum). The common cancer pairs of first and second cancers were as follows:

i) Female breast and genital cancers (any order),

ii) Urinary tract and prostate cancer (any order),
iii) Hodgkin's lymphoma and female breast cancer,
iv) Non-Hodgkin's lymphoma and cutaneous squamous cell carcinomas.

Finding the most common subsequent cancers amongst cancer survivors triggers hypotheses for further research to find explanations for the observed high prevalence of cancers and may be important information when deciding on methods of surveillance. .

Part 2: Risk of cancers amongst cancer patients

Cancer risk amongst cancer patients could be either *higher or lower* compared to people without a history of cancer (i.e. general population) due to

i) Shared lifestyle risk factors for the first and second cancer,
ii) Side effects from the treatment of the first cancer,
iii) Immune-suppression,
iv) Genetic predisposition,
v) Combination of the aforementioned factors.

(1) Increased cancer risks

Often increased risk for cancer is observed amongst cancer patients compared to the general population. Survivors of colorectal cancer experienced a three-fold increased risk for a second cancer in colon and rectum compared with the people without a history of cancer (**Chapter 2.1**); survivors of melanoma of the skin had a five- to ten-fold of higher risk for a second cutaneous melanoma (**Chapter 2.2**). *Shared life style risk factors* are likely responsible for a higher risk of second cancers which occur at the same anatomical (sub)site as the first one, but also at other anatomical sites or and with similar subtypes (e.g. squamous cell or adenocarcinoma) may be subject to certain lifestyle features (like smoking or heavy alcohol). Shared reproductive factors (e.g. low parity), hormone replacement treatment) or obesity may act as risk factors for cancers in the breast and endometrium (**Chapter 2.3**). *Side effects of initial cancer treatment* might also be associated with an increased risk for subsequent cancers. Indeed, we observed in **Chapter 2.3** that patients with contralateral breast cancer (CBC) experienced a higher risk of lung cancer about 5 years after radiotherapy had been administrated for the first breast cancer. As low levels of ionizing radiation usually need a 5-year lag period between radiation exposure and cancer development, we assume that the aforementioned increased risk is associated with radiotherapy from the first cancer. Cancer syndromes caused *by inherited genetic mutations* (e.g HNPCC, BRCAI/II) may underlie the very high risk for cancer amongst the young patients compared to the general population. For instance, patients with colorectal cancer younger than 50 years at diagnosis had a more than five-fold increased risk of developing a second cancer in colon and rectum compared to general population, whereas for older patients the relative risk (SIR) was three-fold increased (**Chapter 2.1**). We suspect that a substantial proportion of the young patients were affected by a variant of the hereditary nonpolyposis colorectal cancer syndrome (HNPCC) as this is character-

ized by frequent occurrence of metachronous colorectal cancers. Women diagnosed with CBC before the age of 50 years experienced a ten-fold higher risk of ovarian cancer compared to the general population, probably because many of them were affected by BRCA I/II (**Chapter 2.3**).

The increased cancer risk may remain elevated beyond 5 years of follow-up (**Chapter 2.1-2.2**). In **Chapter 2.1** we saw that amongst patients with an initial colorectal cancer the risk of getting diagnosed with subsequent cancers in the proximal-colon remained elevated after 5-years of follow-up. Likewise, in **Chapter 2.2** we have shown a persistently elevated risk for a second melanoma of the skin amongst melanoma (skin) survivors even up to 20 years. These long-existing increased absolute and relative risks may suggest the need to continue to follow patients beyond 5 years. However, benefits, adverse effects and costs should be carefully balanced when considering follow-up schedules and modalities.

(2) Decreased cancer risks

Sometimes a decreased risk of subsequent cancers exists amongst cancer patients. For instance, decreased risks for cancers of the lung, colon, rectum, ovary, and head and neck were observed amongst women with CBC receiving chemotherapy for breast cancer, hinting towards a potential preventative effect of chemotherapy (**Chapter 2.3**). Likewise, males receiving radiation in the pelvic region for their first cancers (e.g. in the rectum, prostate or testis) showed a lower risk for a prostate cancer subsequent to the index cancer (**Chapter 2.4**), hinting that irradiation suppresses early and indolent prostate tumors. Also, patients from whom tissues were removed at treatment of the first cancer are at decreased risks of developing a second cancer. For instance, amongst patients with first cancer in rectum, the risk for a second cancer in rectum is lower compared to the general population (**Chapter 2.1**).

(3) Time trends of second cancers since 1989

The risk of second cancer in a population can decrease or increase over time because of

i) Changes in risk factors,
ii) Early detection programs,
iii) Awareness of cancers,
iv) Changes in the cancer profile (i.e. incidence and survival) itself.

To assess the influence of detection, we conducted a study on trends of second melanoma amongst all cancer patients in the Netherlands between 1989 and 2008, presenting changes of risk for second cancers according to clinical examination schedule (i.e. 0-1 year and 2-5 years). We expected an increasing detection rate for melanoma over time amongst cancer patients, with more subsequent melanomas diagnosed early in follow-up time in both sexes because of the increasing awareness of the disease over the past 20 years due to various preventive campaigns and attention from media. Interestingly, we found that amongst male cancer survivors, over time, less subsequent melanomas were detected in the first year after the index cancer, coinciding with a rising incidence trend later in follow-up (2-5 years after

index cancer), whereas amongst female cancer survivors a clear trend towards earlier detection of melanoma over time was observed. This worsening risk trend of second melanoma might also reflect suboptimal self-examination skills amongst male cancer survivors. Indeed, females usually are more aware of abnormal/changing skin lesions, and more likely to seek physician examinations which then lead to early detection of melanomas. It is also in line with the well-known worse survival and higher mortality amongst (elderly) men by Joosse et al..

Part 3: Prognostic consequences after diagnosis of second cancers

In the current project, we used Cox proportional hazard model (CPH) to estimate the hazard ratio between patients with one and with two cancers thereby incorporating second cancer as a time-dependent covariate. We conducted studies on patients with colon and breast cancer (**Chapter 3.1-3.2**). For both patient groups we observed that the diagnosis of a second cancer was associated with an increased overall hazard rate compared to patients with one cancer only, particularly amongst younger patients with 1.7 (HR=1.7 95%CI 1.3-2.1) times higher amongst colon cancer patients younger than 60 years and with 2.5 (HR=2.5, 95%CI: 2.3-2.6) times higher amongst women with contralateral breast cancer younger than 50 years. Not only does this aggressive nature of cancer accelerate the death of patients, but as younger/fitter patients more frequently receive intensive treatment than older patients, the chance that they suffer from treatment toxicity is higher, with negative effects on their survival.

The time-interval between the first and second cancer also seems to be associated with the relative risk of dying. Patients with contralateral breast cancer diagnosed between 2 and 5 years after the first cancer had a slightly increased hazard of dying (HR=1.1 95%CI 1.0-1.2) which seemed to indicate progress of the disease (e.g. metastasis), hence exhibiting worse survival.

We observed that second colon cancer decreased survival the most amongst patients with earlier stage disease compared to those with advanced disease (**Chapter 3.1**) which might be related to suboptimal follow-up amongst patients with localized disease. Because of the suboptimal follow-up, second cancers are often detected in more advanced stage which is associated with a poor survival.

The study implications as well as future studies were discussed in **Chapter 4.** Our studies have several implications in clinical practice:

i) to be aware of increased risk for second cancers located non-adjacent to the first cancer during work-up of the first cancer
ii) to realize long-term increased excess risk for certain second cancers amongst cancer survivors
iii) to realize different risk and prognostic pattern between subgroups of patients
iv) to identify important prognostic factors amongst patients with two cancers.

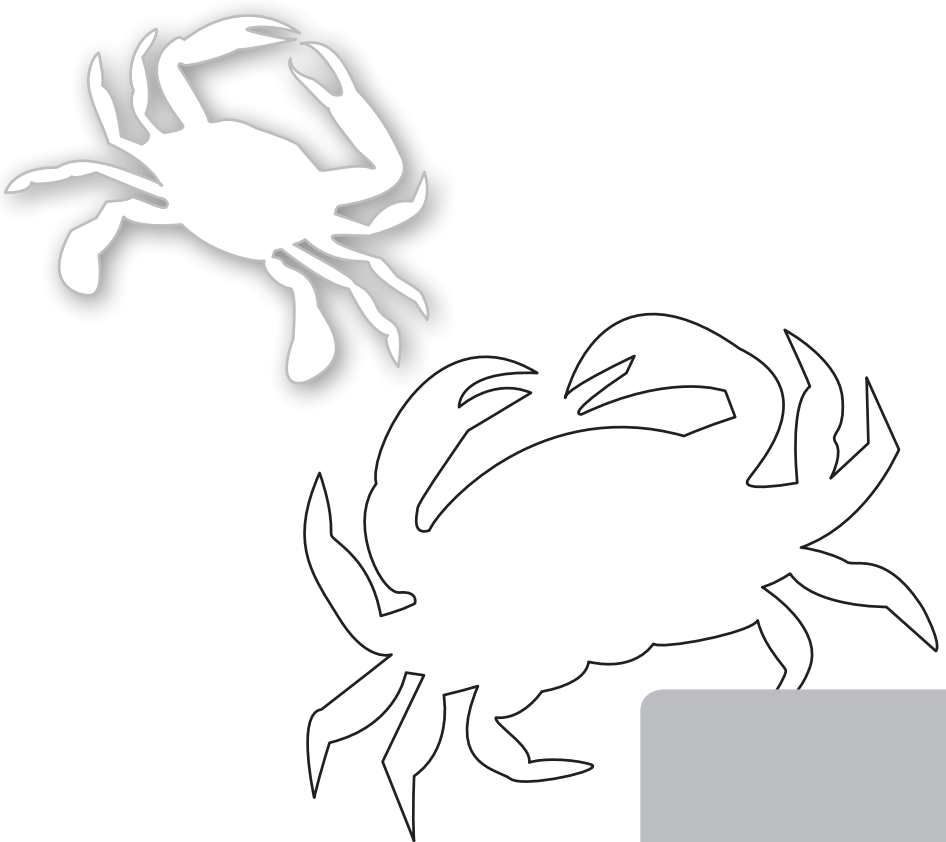
Overseeing our work and also emerging results from other studies in this project remaining outside this thesis we propose further studies on

i) explorations of more cancer pairs and clusters, especially those with share shared lifestyle factors, like smoking and heavy alcohol consumptions,
ii) developing a surveillance strategy for second cancer, especially when patients are old (i.e. >70years),
iii) determinants and outcome of treatment dilemmas for patients with second cancers, consequences of these treatment decisions, especially when patients are young or have comorbid conditions,
iv) possibilities for primary prevention of second cancers through lifestyle changes.

In conclusion, in the Netherlands with the increasing number of cancer survivors, the number of patients with a second or higher-order cancer will increase 3-fold from 30,000 reaching 100,000 in 2015, representing ~15% of total number of cancer survivors. Cancer survivors *often* have an increased risk of developing another malignancy (i.e. on average 2 times higher) compared to the general population. The persistently elevated cancer risk amongst long-term cancer survivors might suggest a continuation of follow-up in order to achieve early detection and or treatment for cancer. However, to avoid overdiagnosis and potential harms of extended follow-up might bring, one should weigh the benefit and harm with care. The risk association between first and subsequent cancers intrigues further studies to understand aetiology and possibilities for (primary) prevention of second cancers. We observed that the appearance of second cancers negatively influences overall survival of patients with breast and colon cancer, which might be related to adverse effects from double aggressive oncological treatments, and/or suboptimal follow-up for patients with localized disease.

Future studies on cause-of-death of these patients are warranted to find the appropriate explanation for the observed survival differences in subgroups of patients.

SAMENVATTING



Door de combinatie van de toename van het aandeel ouderen in de bevolking en het langer overleven van vele kankerpatiënten krijgen steeds mensente kampen met meerdere maligniteiten (MMs) (tweede primaire kanker). Ze komen voor in een grote verscheidenheid van combinaties afhankelijk van de incidentie van primaire kanker, de overleving op lange termijn en allerlei directe of indirecte determinanten daarvan. Verwacht wordt dat de prevalentie van MMs in Nederland in 2015 rond de 100,000 gevallen bereikt vanwege het dubbele aantal overlevenden van kanker sinds 2005.

In dit proefschrift heb ik de volgende **hoofdvragen** beantwoord:

i) Wat is de prevalentie van multipele maligniteiten (MMs) in Nederland?
- Welke type kankers komen in één patiënt voor?
- Wat zijn de kenmerken van tumoren en patiënten met MMs?

ii) Zijn er opvallende risicopatronen met verhoogde of verlaagde relatieve en absolute risico's onder kankerpatiënten vergeleken met de algemene populatie (mensen zonder een ziektegeschiedenis van kanker)? Kunnen deze risicopatronen ons meer leren over potentiële onderliggende risico factoren voor het samen vóórkomen van bepaalde typen kanker bij één patiënt?

iii) Zijn er beïnvloedbare prognostische consequenties van de diagnose van een tweede kanker?

Het werk in dit proefschrift is gebaseerd op een uitgebreid onderzoeksproject gefinancïeerd door het Nederlandse KWF Kankerbestrijding Fonds onder de naam 'The increasing burden of second primary cancers in the Netherlands: trend in incidence, survival and causes-of-death since 1970' (EMCR 2008-4132) waarin verscheidene combinaties van kankers werd bestudeerd en waarin een methodologie werd ontwikkeld voor dit type analyses en weergave van risico en prognose. De meeste van deze analyses werden ontwikkeld met epidemiologen van 4 van de aanvankelijk 8, nu 2 integrale kankercentra en met arts-assistenten en ervarengespecialiseerde artsen.

Vanwege dit proefschrift heb ik de meest voorkomende tweede kankers geselecteerd voor gedetailleerde analyse van risico en overleving, namelijk: dikkedarmkanker, borstkanker, prostaatkanker, huidkanker en chronische lymfatische leukemie (CLL).

Deel 1: Prevalentie van MMs

Om de grootte van het probleem van MMs en de kenmerken van patiënten met MMs te bepalen, hebben we de puntprevalentie op 1 januari 2007 bepaald**(hoofdstuk 1.2)**. Op dit datum waren er in Nederland meer dan 30,000 patiënten met MMs in leven, ongeveer 7% van alle kankerpatiënten. Deze groep patiënten is relatief oud, met een mediane leeftijd van 74 jaar (IQR 71-76 jaar), gemiddeld 3 jaar ouder dan bij de diagnose van de eerste kanker. Deze oudere leeftijd maakt beslissingen voor behandelingen na diagnose doorgaans meer complex, verkleint de overlevingskansen, vooral in geval van bijkomende ziekten naast de kankers. We hebben aangetoond dat de meest prevalente opvolgende 2de kankers geloka-

liseerd waren in gepaarde organen (borst) of in organen met een groot oppervlak (huid en darm). De meest voorkomende kankerparen van eerste en tweede kankers waren als volgt:

i) vrouwelijke borst- en genitale kanker (willekeurige volgorde),
ii) plasbuis- en prostaatkanker (willekeurige volgorde),
iii) Hodgkin-lymfoom kanker en opvolgende vrouwelijke borstkanker
iv) Non-Hodgkin-lymfoom kanker en opvolgende plaveiselcelcarcinomen.

Het vinden van de meest voorkomende opvolgende kankers onder overlevenden van kanker roept hypothesen op voor vervolgonderzoek naar verklaringen voor de geobserveerde hoge prevalentie van 2de kankers. Ook kan kennis over deze veel voorkomende kankerparen belangrijk zijn bij beslissingen omtrent de inrichting van de organisatie van gezondheidszorg.

Deel 2: Risico van kanker onder kanker patiënten

Kanker risico kan *hoger* of *lager* zijn onder kankerpatiënten vergeleken met patiënten zonder geschiedenis van kanker (de algemene populatie) door

i) gedeelde levensstijl risicofactoren voor de eerste en tweede kanker,
ii) neveneffecten van de behandeling van de eerste kanker,
iii) immuunsuppressie,
iv) genetische vatbaarheid, en
v) combinatie van de voorgenoemde factoren.

(1) Verhoogde kankerrisico's

In het algemeen wordt een verhoogd risico voor kanker waargenomen onder kankerpatiënten in vergelijking met de algemene populatie. In onze studies hadden overlevenden van darmkanker een drievoudig verhoogd risico op een tweede kanker in darm en rectum vergeleken met mensen zonder geschiedenis met kanker **(hoofdstuk 2.1)**; overlevenden van huidkanker hadden een vijf- tot tienvoudig hoger risico op een tweede huid melanoom **(hoofdstuk 2.2).** *Gedeelde levensstijl risicofactoren* zijn waarschijnlijk verantwoordelijk voor een hoger risico op tweede kankers welke vóórkomen op dezelfde anatomische plaats als de eerste. Kankers die vóórkomen op andere anatomische plaatsen of van verschillende subtypes kunnen eveneens aan veel voorkomende levensstijlen worden gerelateerd. Gedeelde reproductieve factoren (bijv. lage pariteit), hormoontherapie) of obesitas kunnen risico factoren zijn voor kankers in de borst en endometrium **(hoofdstuk 2.3)**. Een verhoogd risico op opvolgende kankers kan een bijwerking zijn van de eerste kankerbehandeling. In hoofdstuk 2.3 zagen we dat patiënten met contralaterale borstkanker (CBC) een hogere kanshebben op longkanker na bestraling voor de eerste borstkanker. Omdat er bij lage niveaus van ioniserende straling een periode van 5 jaar is tussen blootstelling aan straling en kanker detectie, vermoeden we dat radiotherapie van de eerste kanker dit verhoogde risico veroorzaakt.

Kanker syndromen veroorzaakt door erfelijke genetische mutaties (bijv. HNPCC, BRCA I/II) kunnen het zeer hoge risico voor kanker bij sommige jonge patiënten verklaren. Bijvoor-

beeld, dikkedarmkankerpatiënten jonger dan 50 jaar bij diagnose hadden een meer dan vijfvoudig verhoogd risico voor een tweede kanker in de dikkedarm en endeldarm, terwijl het relatieve risico (SIR) drievoudig verhoogd was voor oudere patiënten **(hoofdstuk 2.1)**. We vermoeden dat een aanzienlijk deel van de jonge patiënten leed aan het syndroom van erfelijke non-polyposis dikkedarmkanker, doordat dit wordt gekenmerkt met het frequent vóórkomen van metachrone dikkedarmkanker, dwz na 6 tot 12 maanden.

Vrouwen gediagnosticeerd met CBC vóór de leeftijd van 50 jaar ervaren een tienvoudig hoger risico voor eierstokkanker, waarschijnlijk omdat velen van hen BRCA I/ II hadden. **(hoofdstuk 2.3)**. Het verhoogde kankerrisico blijft overigens bestaan na meer dan 5 jaar follow-up **(hoofdstuk 2.1-2.2)**. In hoofdstuk 2.1 zagen we dat bij patiënten met een eerste dikkedarmkanker het risico om gediagnosticeerd te worden met daaropvolgende kankers in de proximale dikkedarm verhoogd bleef na 5 jaar follow-up.

Ook in hoofdstuk 2.2 hebben we onder (huid) melanoom overlevenden een aanhoudend verhoogd risico voor een tweede melanoom van de huid aangetoond, zelfs tot 20 jaar.

Uit het hoge relatieve, maar vooral het absolute risico van latere dikkedarmkanker en huidmelanomen ,blijkt de noodzaak om patiënten te blijven volgen na 5 jaar.

Voor- en nadelige effecten en kosten moeten worden afgewogen bij het overwegen van follow-up schema's en modaliteiten.

(2) Verminderde risico's op 2de kanker

Soms kan een verlaagd risico op kanker bij kankerpatiënten worden waargenomen. Zo hadden vrouwen die chemotherapie voor de eerste borstkanker ondergingen een verlaagd risico voor kanker in de long, dikke darm en endeldarm eierstok, en in het hoofd-halsgebied. Dit wijst op een mogelijke preventief effect van chemotherapie **(hoofdstuk 2.3)**.

Ook mannen die bestraald zijn voor een eerste kanker in het bekken (b.v. in de endeldarm, prostaat en zaadbal) toonden na de index kanker een lager risico voor prostaatkanker **(hoofdstuk 2.4);** mogelijk onderdrukt bestraling vroege en indolente prostaat tumoren.

Een verlaagd risico op kanker onstaat ook als bij de behandeling van de eerste kanker weefsels zijn verwijderd. Bij patiënten met een eerste kanker in de endeldarmis het risico voor een tweede kanker in de endeldarmbijvoorbeeld lager dan in de algemene bevolking, waarschijnlijk doordat een deel van de endeldarm verwijderd werd als onderdeel van de behandeling van de eerste kanker **(hoofdstuk 2.1)**.

(3) Trend-ontwikkelingen van de tweede kanker in de laatste 20 jaar

Het risico op tweede kanker kan na verloop van tijd in een populatie lager of hoger worden vanwegeveranderingen in de risicofactoren, vroege opsporing programma's en/of een ander niveau van bewustzijn van kanker, leidend tot meer of minder detectie, enwijzigingen in de incidentie en overleving van kanker.

Om de invloed van detectie te beoordelen door het presenteren van veranderingen van risico's voor tweede kanker naar de periode van klinisch naonderzoek(d.w.z. 0-1 jaar en 2-5 jaar) bekeken we de trends van tweede huid melanoom onder alle kankerpatiënten in Nederland tussen 1989 en 2008.

We hadden een toenemende detectie van melanoom verwacht na verloop van tijd onder kankerpatiënten, met meer dunne melanomen gediagnosticeerd vroeg in de follow-up tijd bij beide geslachten vanwege de verhoogde bewustwording van de ziekte in de afgelopen 20 jaar als gevolg van preventieve campagnes en media-aandacht. Verassend bleken bij mannelijke kanker overlevenden na verloop van tijd minder latere melanomen te worden ontdekt in het eerste jaar na de index kanker, wat samenviel met een stijgende trend van de incidentie laterin de follow-up (2-5 jaar na index kanker). Bij de vrouwelijke kanker overlevenden bleek daarentegen wel een duidelijke tendens naar eerdere detectie van melanoom na verloop van tijd. Deze slechtere risicotrend van tweede melanoom bij mannen zou dan te verklaren zijn door de minder goede zelfonderzoek vaardigheden bij de mannelijke kanker overlevenden, ten opzichte van vrouwen. . Het is ook in overeenstemming met de slechtere overleving en hogere sterfte onder (oudere) mannen.

Deel 3: Prognostische gevolgen na diagnose van tweede kanker

In het huidige project hebben we het "Cox proportional hazard model" (CPH) gekozen voor het schatten van de hazard ratio tussen patiënten met één en met twee vormen van kanker door de tweede kanker op te nemen als een tijd-afhankelijke covariabele. We hebben studies uitgevoerd voor patiënten met dikkedarm- en borstkanker **(hoofdstuk 3.1-3.2)**. Voor beide groepen patiënten bleek de diagnose van een tweede kanker samen te vallen met een verhoogd totaal sterftecijfer. Met name bij jongere patiënten was dit hoger70% hoger(HR = 1.7 95% CI 1.3-2.1) bij patiënten met dikkedarmkanker jonger dan 60 jaar en 2.4 maal (HR: 2,4, 95% CI: 2.3-2.6) hoger bij vrouwen jonger dan 50 jaar met contralaterale borstkanker vergeleken met oudere patiëntengroepen. Niet alleen deze agressieve uiting van kanker verhoogt de overlijdenskans van deze patiënten, ook de vaak intensievere behandeling van jongere/fittere patiënten ten opzichte van oudere patiënten, kan deze kans verhogen.

Het tijdsinterval tussen de eerste en de tweede kanker kan ook een aanwijzing geven voor het overlijdensrisico. Patiënten met contralaterale borstkanker gediagnosticeerd tussen 2 en 5 jaar na de eerste kanker hadden een licht verhoogde hazard ratio (HR = 1.1 95% CI 1.0-1.2), hetgeen ook kan duiden op progressie van de eerste tumor (bijvoorbeeld metastase).

Op basis van onze bevindingen, zou men in de klinische praktijk:

i) zich meer bewust moeten zijn van een verhoogd risico op een tweede kanker die niet aangrenst bij de eerste kanker tijdens het behandelen van de eerste kanker,
ii) zich moeten realiseren dat er bij overlevenden van kanker op lange termijn een verhoogd risico is voor bepaalde tweede kankers,
iii) zich moeten realiseren dat er verschillende risico- en prognostische patronen zijn tussen subgroepen van patiënten en

iv) belangrijke prognostische factoren onder patiënten met twee vormen van kanker moeten identificeren.

Wij stellen voor om verder onderzoek te doen op

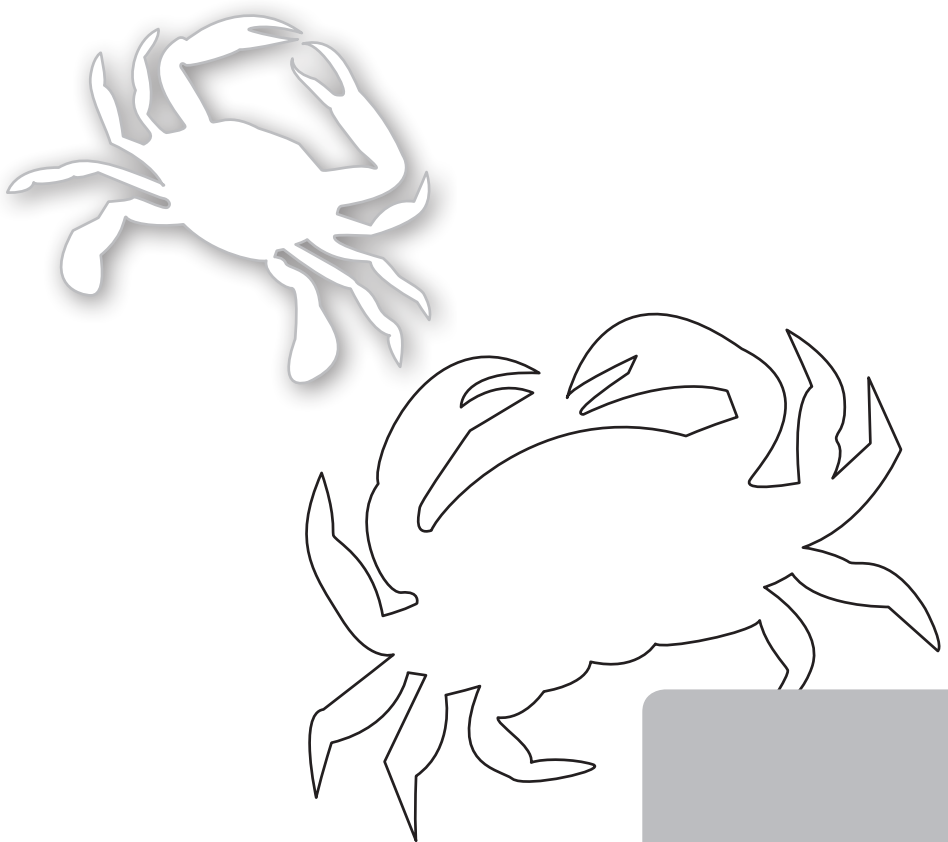
i) focussen op meer kankerparen en clusters,

ii) behandel dilemma's voor patiënten met tweede kanker en de gevolgen van deze beslissingen over behandeling (bijvoorbeeld: moeten patiënten wel of niet behandeld worden, hoe intensief kan die behandeling zijn, wat willen de patiënten zelf) ontwikkelen van een observatie strategie voor tweede kanker,

iii) mogelijkheden voor primaire preventie van metachrone tweede tumoren door veranderingen in levensstijl.

In conclusie, met het toenemende aantal overlevenden van kanker in Nederland zal het aantal patiënten met een tweede of hogere-orde kanker 3-voudig toenemen van 30.000 naar 100.000 in 2015; ongeveer 15% van het totaal aantal overlevende kankerpatiënten in Nederland zal dan meer dan één kanker hebben.. In vergelijking met de algemene bevolking hebben overlevenden van kanker vaak een verhoogde kansop een ander maligniteit (gemiddeld 2 keer hoger). Hetaanhoudend verhoogde kankerrisico bij lange-termijn overlevenden van kanker zou kunnen aangeven dat een voortzetting van follow-up zou kunnen leiden tot vroegtijdige opsporing en/of behandeling van kanker. Echter, om over-diagnose en de potentiële nadelen die uitgebreide follow-up met zich mee kan brengen te voorkomen moeten de voor- en nadelen worden gewogen. De associatie van risico tussen de eerste en volgende kankers vraagt om nader onderzoek om de etiologie en mogelijkheden voor (primaire) preventie van tweede kankers te begrijpen. Het vóórkomen van tweede kankers bleek de totale overleving van patiënten met borst- en dikkedarm kanker negatief te beinvloeden, wat soms gerelateerd zou kunnen zijn aan de schadelijke effecten van meervoudige agressieve oncologische behandelingen maar ook aan bv bij dikke darmkanker suboptimaal follow-up voor patiënten met gelokaliseerde ziekte. Toekomstige studies over de doodsoorzaakvan deze patiënten zijn belangrijk om de juiste verklaring te vinden voor de waargenomen overleving verschillen in subgroepen van patiënten.

综述



由于人口老龄化及癌症患者生存期的延长，越来越多的癌症患者面临着多个肿瘤（MMs）及次生癌（second primary cancer）的问题。首发肿瘤和其次生肿瘤的组合取决于癌症的发生率，生存率，还有其直接，间接的决定因素。由于从2005 年以来癌症生存者的数量翻了一番。在荷兰预测，将有10万癌症患者患有次生癌及多个肿瘤。

在本人的论文中，我主要关注一下几个研究课题:

i） 在荷兰有多少癌症存活者患有多个肿瘤?

- 那些是常见的和罕见的首发和次发肿瘤的组合?
- 患有多个肿瘤的患者的特征是什么?

ii）相对于没有癌症病史的人群，癌症生存者（患次生）癌的发生率有没有什么奇特的特征， 即， 是不是比无癌症病史的人群有更高或更低的癌症发生率? 如果有，这些不同于无癌史人群的发病率，会不会告诉我们，首发癌和次生癌之间的病因学联系?

iii）患有次生癌之后，有什么因素能影响预后? 哪些是可以变更的，从而改善预后?

本论文由荷兰癌症协会（KWF）的综合性研究项目‘荷兰逐渐上升的次生癌问题: 自70年代开始的发病率，生存率，和死亡原因的趋势描述’ 资助。在本项目中，我们研究了多种首发癌和次生癌的组合情况。 另外，关于次生癌的发病率和预后数据分析的方法论也进行了深刻讨论和应用。产生的学术性文章，是由全荷兰癌症登记所（cancer registry; 原8个分所，现2个分所）的流行病学家和资深的临床医生合作完成。

在本研究课题的架构中，我选择了几种多发次生癌—直肠结肠癌，乳腺癌，前列腺癌，皮肤黑色素瘤，和慢性淋巴瘤--的发病率和预后进行了详尽的分析。

第一部分: 多发肿瘤生存者分析

我们估算了于2007年1月1日在荷兰患有多个肿瘤的癌症生存者的数量 （第一章第二节）。根据我们的测算，约3万癌症患者于（相当于7%所有的癌症存活者）患有多个肿瘤。这个人群偏高龄: 平均年龄为74岁（四分位数间距 71–76岁），较比于首发癌的发病年龄高3岁。这个高龄的人群，使得在确诊后在治疗方案的制定上非常困难，也使得这些病人预后不容乐观，尤其是在合并其他并发症（如，糖尿病，心血管疾病）的时候。我们还发现大多数多发肿瘤发病于成对的器官，比如，乳腺。或多发于那些具有非常大表面组织的器官，例如，皮肤组织和直肠结肠。常见的多发肿瘤的组合有: i） 女性乳腺癌和女性生殖器官肿瘤，ii） 尿道肿瘤和前列腺癌，iii） 霍杰金氏病和次生的女性乳腺癌，iv)非霍杰金氏病和次生的皮肤鳞状细胞癌。找出这些常见的肿瘤组合能够启发后续对于病因学的研究，另外，还可以帮助规划医疗资源的分配。

第二部分: 癌症患者的癌症发病模式

癌症患者癌症的发病率可能高于或低于无癌症病史的人群。这是因为i） 首发癌与次生癌有共同的致病因素， ii）首发癌的治疗和次生癌的发生有关， iii）病人免疫功能不全或者受抑制，iv)病人有遗传性癌症基因引起的多癌综合征，v）或者上述综合的几项。

（1）癌症病人癌症发病率高于无癌症史人群

这是一种常见的发病模式。 例如，直肠结肠癌的患者，相比于一般人群，其发生次生 结肠直肠癌的可能要高出3倍 （第二章，第一节）。 又例如，皮肤黑色素瘤患者有5–10倍高于一般人群患有次生皮肤黑色素瘤的可能 （第二章，第二节）。共同的致病因素可能解

释了这些癌症同解剖位置癌症并发的原因。另外，共同的致病因素也可能导致肿瘤发病于不同的解剖位置。例如，由于低或无生育史，荷尔蒙代替治疗，和肥胖，这几种因素，可能解释了为什么乳腺癌和子宫内膜癌常共同发生与一个个体 （第二章，第三节）。另外，对于首发癌的治疗可能升高次生癌的几率。在（第二章，第三节）中我们观察到有双侧乳腺癌的患者，经历放射治疗，生存5年后，患有肺部肿瘤的几率要高于一般人群。这可能与放射治疗中的电离辐射有关， 因为这种电离辐射要一般经历5年的诱导时间产生肿瘤。遗传性癌症综合征也可以导致多肿瘤的发病 （例如 遗传性非息肉型直肠结肠癌，和BRCA I/II 变异引发的乳腺癌）。较为年轻的患者（常常50岁前）常有这个原因致病。比如，在第二章，第二节中我们发现在50岁前发病的直结肠癌病人中，发生次生直结肠癌的危险是普通人群的5倍，然而，在年龄高于50岁的病人中，其直结肠癌的发病率仅为3倍。我们估计，这种在青年群体中的高发病率和遗传性非息肉型直肠结肠癌有关。其特征为次生癌发于首发癌诊断后若干年。另外，我们在第二章，第三节中发现双侧乳癌的年轻女患者，其卵巢肿瘤的发病率为普通人群的10倍。这也许和BRCAI/II基因变异有关。

癌症患者生存5年之后，其癌症发病危险还有可能高于普通人群（第二章，第一，二节）。在第二章第一节中，我们发现在生存5年后，直肠结肠癌患者，在升结肠部的癌症发病率高于普通人群。同样，在皮肤黑色素瘤的生存者中，即使在发病后20年，其皮肤黑色素瘤的发病率还是高于普通人群。这些现象提示我们即使在癌症生存5年后（一般认为为临床治愈阶段）我们还要警惕次生癌的发生。但是由于5年生存者的数量不多，而且过多的检查可能造成不必要的焦虑和医疗资源浪费，我们需要非常谨慎的制定合适的随访方式和随访间期。

（2）癌症病人的癌症发病率低于正常人群

有些情况，癌症病人患有癌症的几率小于正常人群。例如，在接受化学治疗的双侧乳癌女性患者中，其，肺部，结肠，直肠，卵巢，颈项部肿瘤的发病率要低于普通人群。这也许和化学治疗对这些肿瘤有预防作用（第二章，第三节）。类似现象发生于接受盆腔放射性治疗的癌症患者。他们患有前列腺癌的几率要小于普通无癌症史的病人。这也许和放射线对于早期潜在性前列腺癌细胞的抑制作用有关。（第二章，第四节）。同样，由于首发癌对于病灶的切除，次生癌在原病灶的发生率也大大减低， 如，结肠癌患者，次生结肠癌发生率低于普通人群（第二章，第一节）。

（3）在过去的20年中，荷兰次生癌的发病趋势的变化是什么样的?

次生癌的发病率和i） 其致病因素的变化，ii)早期诊断模式的改进，iii)人们对疾病的认识，还有iv)癌症发病率，生存率的变化有关。为了分析自在荷兰1989年以来20年临床上日趋皮肤黑色素瘤的认识，我们分析了在肿瘤患者中次生皮肤色素瘤的发病率变化。我们预计在过去的20年里，由于人们对本病的认知提升，越来越多的黑色素瘤将在早期的随访中（即首发癌诊断后0–1年中）被发现。然而我们的结果不完全和预测相符。在男性癌症病人中，越来越多的皮肤黑色素瘤在后期随访（即首发癌诊断后2–5年）才被诊断。这种趋势说明了在男性癌症病人中对本病的认识， 和自查技能并不如女性，从而导致黑

色素瘤不能在早期被诊断治疗，也就从另一个方面解释了为什么黑色素瘤的生存率在女性要高于男性。

第三部分：患有次生癌病人的预后

在本来论文架构中，我们选择Cox proportional hazard model（CPH)来分析次生癌发生后对患者预后的影响。我们将次生癌作为时间变量植入此模型。我们对两个癌症患者群体做了分析：结肠癌和乳腺癌患者（第三章）。我们观察到，在这两个病人群体，次生癌的发生，提升了病人的死亡率。而且此现象在青年癌症病人中尤为显著。比如，在结肠癌患者中次生癌使得青年患者的死亡率提升70%（HR=1.7 95%CI 1.3–2.1)； 在乳腺癌患者中，死亡率甚至翻了一倍（HR=2.5 95%CI: 2.3–2.6)。 这种在年轻人群中高的死亡率不仅和癌症在年轻人群中快速发展的自然属性有关，他们更容易对癌症治疗抵抗，所以治疗效果不佳；也可能也许也因为他们年轻，经常接受两次彻底癌症治疗有关，由于癌症治疗有相应的毒性反应，两次叠加的结果可能会使机体不耐受，从而死亡率增加。除了年龄，两个肿瘤诊断的间隔也是一个重要的预后因素。我们在第三章，第二节中观察到， 如果乳癌妇女在首发癌诊断后2–5年内发现次生癌，他们的死亡率比那些5年后发现次生癌的妇女高出10%(HR=1.1 95%CI 1.0–1.2)。这也许说明了，如果在2–5年发现次生癌，这也许是一个疾病发展恶化的信号，值得临床医生注意。

第四部分：总体讨论

在第四章，我们将以上几部分的阎捷结果总结讨论，并且讨论了将来的研究方向。根据我们的主要结论，在临床上，我们可能需要注意i)在诊断首发癌的时候，对于身体其他部位的全面检查，以便于早期发现并存的次生癌,ii）需要意识到在癌症长期存活者中，次生癌的发病率还是高于一般人群的，iii）认识到在不同的病人群体（比如，不同的年龄，治疗方案等），他们患有次生癌后对预后的影响是不同的，iv）了解在诊断次生癌后预后因素对死亡率的影响是非常重要的。

我们建议未来的研究方向集中在:

i） 研究更多的首发癌和次生癌组合，从而更加深刻了解其发病关联

ii）研究如何制定对与次生癌的治疗方案，以及这些方案对于预后的影响,

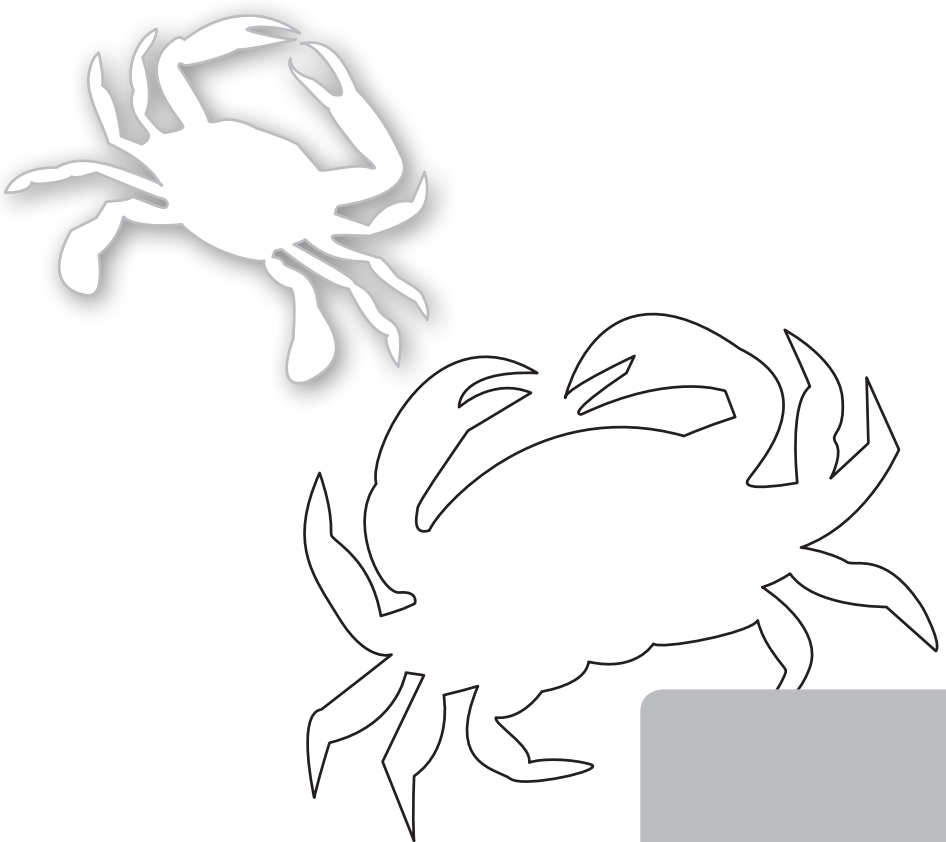
iii）建立适宜的对癌症病人的随访制度，以便于早期发现和治疗次生癌,

iv）讨论通过改变生活方式预防次生癌发生的可能性。

总结

次生癌的发生时人口老龄化，癌症病人生存率，和人们对于癌症认知度提高的综合产物。随着癌症生存者越来越多，患有第二个癌症的人的几率和总量将会不断升高。癌症患者一般来讲，相对于普通人群有更高的患癌几率，并且次生癌发病后，影响预后。对于次生癌的早期发现和治疗非常重要，但是也要注意到平衡对于早期发现是否对病人带去不必要的焦虑和对医疗资源的浪费。

DANKWOORD/ ACKNOWLEDGEMENTS



Yes, yes, finally I reached this section which I like to write the most. Here I write with a smile, a laugh, a frown, and sometimes with two moist eyes. **Thank**, is such a pale word to express my gratitude towards all of you.

Jan Willem, jw, Prof. Coebergh (though seldomly I call you as such), you are the most fatherly and knowledgeable professor I have ever met. With you, I am with a library. How lucky I am: with nice chocolate, discussions on cancers, history/politics of countries, I got the PhD degree. Isabelle, thank you for building up such a wonderful project on which I worked in the past four years. Thanks for letting me wander my way and stopping me when I am getting too far. You are never a teacher telling what to do and what not to but to ask all the time 'what do you want? Why?'. And your 'Isabelle-style' of comments just portray you as a smart and interesting person. I learnt so much from you. Esther, you are just wonderful! You always know the right way to explain things to me and being ALWAYS there when a talk, a coffee, or even a hug is needed. I admire your intelligence and efficiency. I am sure, without your guidance I would not have finished the thesis by now. Your loving and caring character can just easily bring warmth in the heart of everyone, of course including me.

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Britt and David, you are amazing roommates! Britt, thank you for sharing travel, shopping, and other tips. Please keep pushing me to speak Dutch, especially when I am getting lazy.

Dear friends and colleagues, thank you for appearing in my life. Elisabeth, you are special. Your wisdom is certainly beyond your age and what makes it even more appreciable is that

you are always there when I am in need. Maggie, with your travel stories, I almost reached every corner of the world. It is fun talking with you! Melissa, my paranymph, thanks for the chats, food, and shopping together. 谢谢你。Jacques, thank you dropping when I look desperate in front of my computer. Carlijn, my ex-roommate, thank you for willing to share your tips in surviving PhD thesis as well as now in sharing experience in surviving pregnancy.

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很难用感谢来表达我对先父,刘永柱, 的感恩，您成就了我的灵魂，我延续了您的生命。我想大概如此吧。我想您的在天之灵会为我感到骄傲吧，不止此刻，愿直到永远。

妈妈哥哥，您们成就了我的今天，我们一起走向未来，我爱你们！

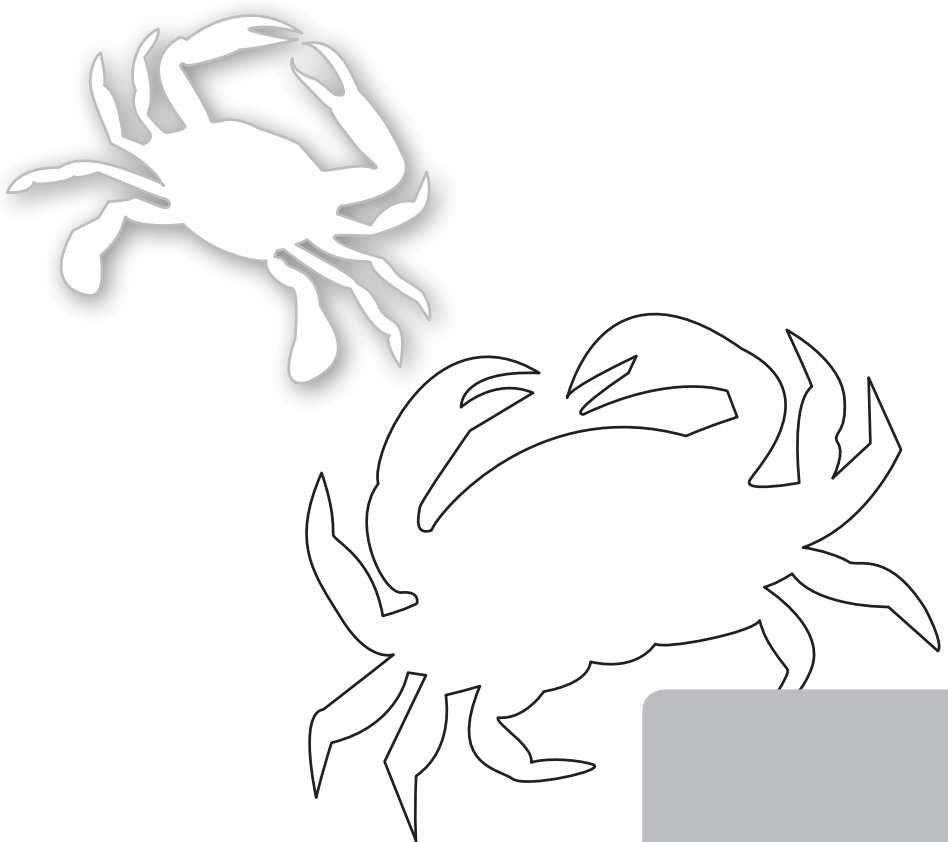
嫂子，小昱伯，对你们的爱不能言表。

澳洲和天津的刘氏亲属，非常感激您们对我们的帮助，没有您们也就没有今天的这一切。

演明师，正如您说的，您是师也是父，我非常感恩您出现在我的生命里—悉茗。

Lu, how can I express in words my love and gratitude towards you. Anyhow, I will try. Thank you for changing your path to follow me here in the Netherlands. It was not an easy choice, but you did it, for me. I know and I appreciate it. You let me know that there is always a shoulder I can rest on. Now we are going to have a family of three (or even more in the future). I have no idea what it will change but as we said before: 执子之手，与子偕老。

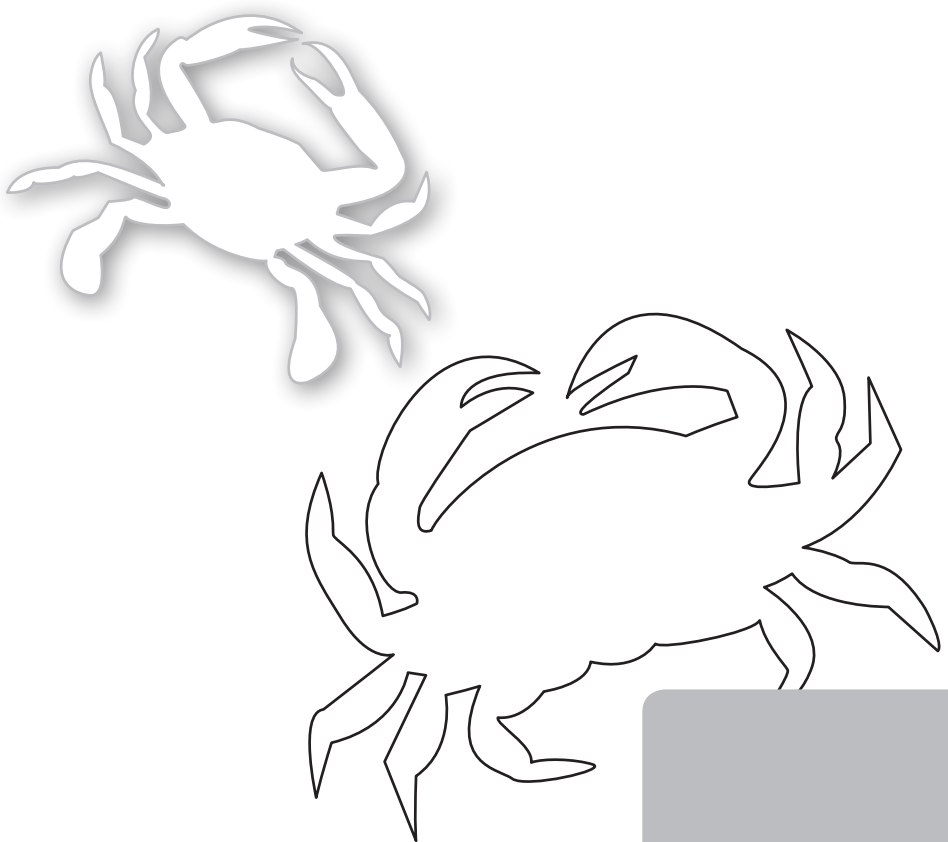
CURRICULUM VITAE



Lifang Liu was born on September 21st 1979, ZhangZhou, China, where is famous for narcissus. She moved to Tianjin, one of the four provincial cities, and started education there at age of 6 years.

In June 2003, she received medical degree from Tianjin Medical University major in clinical medicine. Afterwards she started practicing medicine in NanFeng Hospital (China) until June 2006. In September 2006, she moved to the Netherlands and started her training in master of science in Wageningen University, department of human nutrition and obtained her master degree in 2008. From November 1st 2008, she was appointed as a PhD student conducting KWF project 'Increasing burden of multiple malignancies in the Netherlands since 1970s' under the supervision of Prof. Jan Willem Coebergh, Dr. Isabelle Soerjomataram, and Dr. Esther de Vries. In the project, she focused on analysis of prevalence, risk patterns for second cancers in major anatomical sites and the prognostic consequences. In September 2012, she was awarded fellowship (Medical Research Fellow) from European Organization for Research and Treatment of Cancer (EORTC). She is currently continuing working on the project of multiple cancers and will start her fellowship in 2013.

LIST OF PUBLICATIONS



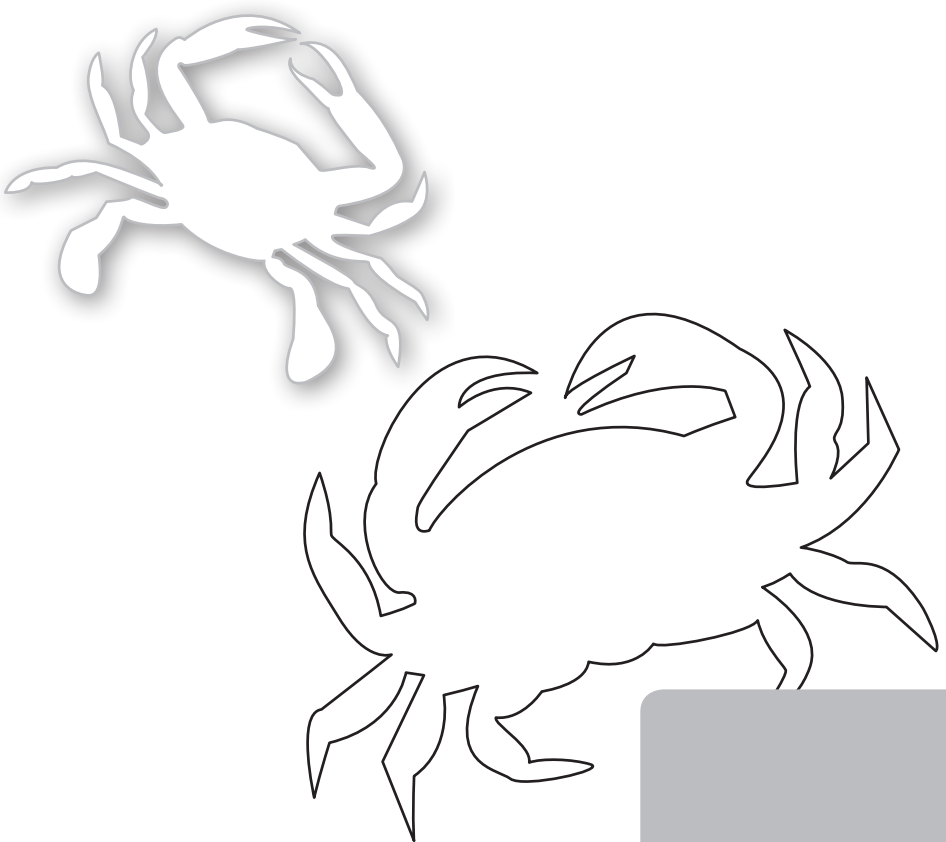
In this thesis

1. **L. Liu**, E. de Vries, M. Louwman, K. Aben, M. Janssen-Heijnen, M. Brink, J.W.W.Coebergh, I. Soerjomataram. Prevalence of multiple malignancies in the Netherlands. Int J Cancer. *2011;128:1659-67.*
2. **L. Liu**, V.E. P. P. Lemmens, I. H.J. T. De Hingh, E. de Vries, J. A. Roukema, M. van Leerdam, J.W.W. Coebergh, I. Soerjomataram. Second primary cancers in proximal-colon, distal-colon, and rectum among patients with a prior colorectal cancer *Dis Colon Rectum 2012, in press*
3. R.J.T. van der Leest, **L. Liu**, J.W.W. Coebergh, H.A.M. Neumann, W.J. Mooi, T. Nijsten, E. de Vries. Risk of second primary in situ and invasive melanoma in a Dutch population-based cohort: 1989-2008 *Br J Dermat 2012, epub*
4. A.B.G. Kwast, **L. Liu**, J.A. Roukema, A.C. Voogd, J.J. Jobsen, J.W.W. Coebergh, I. Soerjomataram, S. Siesling. Increased risks of third primary cancers of non-breast origin among women with bilateral breast cancer *Br J Cancer 2012, epub*
5. D.E.G. Kok, S.A.M. van de Schans, **L. Liu**, E. Kampman, J.W.W. Coebergh, L.A.L.M. Kiemeney, I.Soerjomataram, K.K.H. Aben. Risk of prostate cancer among cancer survivors in the Netherlands *Cancer Epidemiology, in press*
6. E.C. van den Broek, **L. Liu**, E.F.M. Posthuma, M.L.G. Janssen-Heijnen, J.W.W. Coebergh, I. Soerjomataram. High incidence of Chronic Lymphocytic Leukaemia among cancer survivors in the Netherlands due to increased detection. *Submitted*
7. **L. Liu**, I. Soerjomataram, T. Nijsten, M. van der Aa, R. van der Leest, J.W.W. Coebergh, E. de Vries. Trends in risk of second primary melanoma amongst cancer patients in the Netherlands, diagnosed 1989-2008 *Melanoma Res 2012, in press*
8. **L. Liu**, M.Murawska, L.Van Steenbergen, I. H.J.T. De Hingh, J.W.W. Coebergh, J.A. Roukema, V. E. P.P. Lemmens,I. Soerjomataram. Early detection of second colon cancer amongst colon cancer survivors might lower excess mortality: a 20-year study in the Netherlands
9. A. Font, **L. Liu**, A.C. Voogd, M.K. Schmidt , J.A. Roukema, J.W.W. Coebergh, E. de Vries, I.Soerjomataram. Inferior survival for young patients with contralateral compared to unilateral breast cancer: a nationwide population-based study in the Netherlands *Submitted*

Other publications

10. M.S.Y. Thong, F. Mols, R.H.A. Verhoeven , **L. Liu**, M. A. Andrykowski, J.A. Roukema, L. V. van de Poll-Franse Multiple primary cancer survivors have poorer health status and well-being than single primary cancer survivors: a study from the population-based PROFILES registry *Psycho-Oncology 2012 in press*
11. C. Schotborgh, **L. Liu**, V.E.P.P. Lemmens, I. Soerjomataram, J.W.W. Coebergh, J.J.G.H.M. Bergman, E. J. Schoon High incidence of second primary esophageal squamous cell carcinoma in patients with previous head-and-neck cancer: a nationwide population-based study *To be submitted*
12. D.Boll, H.E. Karim-Kos, R.H.A. Verhoeven, **L. Liu**, L.V. van de Poll-Franse, C.W. Burger, J.W. Coebergh, H.C. van Doorn. Progress against endometrial cancer in the Netherlands since the 1970s: incidence, survival and mortality *To be submitted*

PhD PORTFOLIO



Erasmus MC
Universitair Medisch Centrum Rotterdam

SUMMARY OF PhD TRAINING AND TEACHING

Name PhD student:	Lifang Liu	PhD period:	Nov 2008-Oct 2012
Erasmus MC Department:	Public health	Promotor:	Prof. Jan Willem Coebergh
Research School:	Cancer Surveillance	Supervisors:	Dr. Isabelle Soerjomataram, Dr. Esther de Vries

1. PhD TRAINING

	Year	Workload (Hours ECTS)
Research skills		
1. Epidemiological analysis on cancer prevalence, incidence, survival	2008-2012	40 hours (1.4 ECTs)
2. Analysis on second primary cancers	2008-2012	40 hours (1.4 ECTs)
3. Analysis on population based cancer registry data	2008-2012	40 hours (1.4 ECTs)
Other skills		
Organization skills - Organizing cancer working groups	2008-2012	40 hours (1.4 ECTs)
General courses		
- Biomedical English Writing and Communication, NIHEs course, ErasmusMC, The Netherlands	2009	112 hours (4 ECTs)
- Basic courses on oncology,	2011	40 hours (1.4 ECTs)
Specific courses		
Planning and evaluation of screening programmes, NIHEs course, ErasmusMC, The Netherlands	2009	43 hours (1.4ECTs)
- Essentials of descriptive epidemiology, karolinska institutet, Sweden	2009	40 hours (1.4 ECTs)
- Conceptual foundation in epidemiology, NIHEs course, ErasmusMC, The Netherlands	2009	20 hours (0.7 ECTs)
- Survival analysis for clinicians, , NIHEs course, ErasmusMC, The Netherlands	2009	54 hours (1.9ECTs)
- Cancer epidemiology, Netherlands Cancer Institue (NKI), Amsterdam, The Netherlands	2010	40 hours (1.4 ECTs)
- Regression analysis, NIHEs course, ErasmusMC, The Netherlands	2010	30 hours (1.9 ECTs)
- Introduction to public health, NIHEs course, ErasmusMC, The Netherlands	2010	15 hours (0.7 ECTs)

- Principles in data analysis, NIHEs course, ErasmusMC, The Netherlands	2011	15 hours (0.7 ECTs)
- Cancer survival: principles, methods and analysis, London, UK	2011	40 hours (1.4 ECTs)
- Advanced workshop in estimating relative survival using cancer registry data, London, UK	2011	30 hours (1 ECT)

Seminars and workshops

- Up-to-date estimates and projections of cancer survival using period and other methods	2010	2 hours
- Eurocadet (Key determinants of the future incidence of cancer across Europe: impact of prevention)	2010	2 hours
- Life-course inheritances, wealth and health:Examining causal effects in 11 European countries	2010	2 hours
- Discounting in Cost-Effectiveness Analysis: should we step away from convention?	2010	2 hours
- The Hospital Standardized Mortality Ratio: (non)sensical?	2011	2 hours
- The burden of disease among immigrant groups in the Netherlands: a synthesis	2011	2 hours
- Which questionnaire for my research?	2012	2 hours
- Health Expectancy: tools to increase its policy relevance	2012	2 hours
- Towards a better understanding of magnitude of risk prediction model increments	2012	2 hours
		Subtotal
		8 hours (0.3 ECTs)
- Semimars at the department of public health	2008-2012	100 hours (3.6 ECTs)
- How to write successful grant proposals?	2012	8 hours (0.3 ECTs)
- Predict absolute risk	2012	8 hours (0.3 ECTs)

Oral Presentations

- Research meeting, prevalence of multiple malignancies in the Netherlands in 2007, department of public health, ErasmusMC, The Netherlands	2009	28 hours (1 ECT)
- Conference of association of epidemiologist of the Netherlands (WEON), location of second colorectal cancers, Nijmegen, The Netherlands	2010	28 hours (1 ECT)

- VIKC meeting, project on multiple malignancies in the Netherlands, Utrecht, The Netherlands	2011	28 hours (1 ECT)
Poster presentation at (Inter)national conferences		
- Conference of association of epidemiologist of the Netherlands (WEON), The Netherlands	2009 -2011	120 hours (4.2 ECTs)
- IEA world congress of epidemiology, Edinburgh, Scotland	2011	168 hours (4.2 ECTs)
- International Association of Cancer Registries	2012	40 hours (1.4 ECTs)
International peer review	2010-2012	32 hours (1.1 ECTs)

2. TEACHING

Supervising work performed by

- Robert van der Leest (PhD student)	2010-2012	80 hours(2.8 ECTs)
- Anna Font (MSc student)	2011-2012	80 hours(2.8 ECTs)
- Charlotte Schotborgh (PhD student)	2011-2012	80 hours(2.8 ECTs)

3. OTHER

Estimate point prevalence of Hepatocellular carcinoma (HCC) in Europe	2009	28 hours (1 ECTs)
TOTAL		1,587 (57 ECTs)