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Risk of prostate cancer among cancer survivors in the Netherlands

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ABSTRACT

Background: 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.
Methods: Data from the Netherlands Cancer Registry were used to estimate standardized incidence ratios (SIRs) and 95% confidence intervals (CIs) 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.
Results: Out of 551,553 male patients diagnosed with a first primary cancer between 1989 and 2008, 9243 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 10 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).
Conclusions: Our data showed that cancer survivors have an increased prostate cancer risk in the first year following a first cancer diagnosis, which is most likely the result of active screening or incidental detection.

1. Introduction

The number of patients newly diagnosed with cancer increased substantially during the past decades and this trend is expected to continue in the 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 occurrence 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 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.

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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 analysis 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 while taking into account the first cancer sites and time since first cancer diagnosis. This approach allowed us to compare prostate cancer risk among different first cancer sites and to evaluate the possible effects of detection and treatment.

2. 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 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 grouped into six categories (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), metastases (M) stages and histological grade, but did not include PSA levels.

Standardized incidence ratios (SIRs) were estimated to compare incidence rates of prostate cancer as a 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 a 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 by subtracting the number of expected patients 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. In addition to estimates for all cancer sites together, results were provided for all sites excluding bladder cancer 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 effect 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 bladder cancer were not included in this analysis, because most patients who were not treated with pelvic radiotherapy were likely to undergo radical cystoprostatectomy and were therefore not at risk of developing prostate cancer in the long term. The subgroup analysis for patients treated without pelvic radiotherapy comprised all patients diagnosed with the aforementioned tumours located in the pelvic area (without bladder cancer), who were not treated with primary radiotherapy.

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

3. Results

The study population includes 551,553 male cancer patients diagnosed with a first primary cancer between 1989 and 2008. Of these, 9243 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 the time of first cancer diagnosis (Table 1). Clinical

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.

	Patients who were not diagnosed with prostate cancer as second primary cancer (n = 542,310)	Patients who were diagnosed with prostate cancer as second primary cancer (n = 9243)
Age at first cancer diagnosis		
Median (interquartile range, in years)	68 (58–75)	70 (64–76)
<50 years	71,116 (13%)	167 (2%)
50–74 years	327,929 (60%)	6338 (69%)
75+ years	143,265 (26%)	2738 (30%)
Period of first cancer diagnosis		
1989–1993	124,057 (23%)	2717 (29%)
1994–1998	128,434 (24%)	2694 (29%)
1999–2003	135,556 (25%)	2316 (25%)
2004–2008	154,263 (28%)	1516 (16%)
Time at risk[a]		
Median (interquartile range, in years)	1.3 (0.3–4.5)	2.3 (0.3–5.9)
<1 year	241,149 (44%)	3386 (37%)
1–10 years	248,943 (46%)	4946 (54%)
10+ years	52,218 (10%)	911 (10%)
Pelvic radiotherapy for first primary cancer[b]		
Yes	18,218 (27%)	202 (16%)
No	49,823 (73%)	1096 (84%)

[a] Time at risk is defined as the time between date of first primary cancer diagnosis until date of death, emigration, diagnosis of any (other than prostate cancer) second primary cancer, or end of follow-up (1st January 2009), whichever came first. For patients with prostate cancer as a second primary cancer, time at risk is defined as the time between their first and second primary cancer diagnosis.

[b] Restricted to patients with 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 (without bladder cancer).

Source: Netherlands Cancer Registry.