

Primary Cancers Before and After Prostate Cancer Diagnosis

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BACKGROUND: The occurrence of multiple cancers may indicate common etiology; and, although some studies have investigated the risk of second primary cancers after prostate cancer (PCa), there are no studies on cancers before PCa. **METHODS:** The PCBaSe Sweden database is based on the National Prostate Cancer Register (NPCR), which covers >96% of PCa cases. The authors estimated the prevalence and cumulative incidence of different cancers before and after PCa diagnosis in 72,613 men according to PCa treatment and disease stage in PCBaSe and their matched comparison cohort of men who were free of PCa. **RESULTS:** In total, 6829 men were diagnosed with another primary cancer before their PCa diagnosis, including 138 men at the time of PCa diagnosis and 5230 men were diagnosed after PCa diagnosis. Cancer of the bladder or colon and nonmelanoma of the skin were the 3 most frequently observed cancers before and after PCa diagnosis. At the time of PCa diagnosis, the prevalence of these 3 cancers was 1.94% for bladder cancer, 1.08% for colon cancer, and 1.08% for nonmelanoma skin cancer, compared with 1.30%, 0.96%, and 1.03%, respectively, for the matched comparison cohort. Five years after PCa diagnosis, the difference in incidence proportion between PCa men and their comparison cohort was 7‰ (95% CI, 5.6‰-8.5‰), 1.3‰ (0‰-2.6‰), and 1.6‰ (0.6‰-2.6‰) for these 3 cancers, respectively. From a uro-oncologic point of view, it is interesting to note that the prevalence of kidney cancer at the time of PCa diagnosis was 0.42% compared with 0.28% for the matched comparison cohort. **CONCLUSIONS:** Approximately 17% of all PCa occurred in combination with another primary cancer (before or after PCa diagnosis). Detection bias probably explains part of this observation, but further investigations are required to assess possible underlying mechanisms. *Cancer* 2012;118:6207-16. © 2012 American Cancer Society.

KEYWORDS: prostate cancer, second primary cancer, endocrine treatment, curative treatment, surveillance.

INTRODUCTION

Given the increase in cancer survival and enhanced longevity, more cancer survivors are exposed to the risk of a second primary cancer. Over the last decades, several studies have investigated the risk of second primary cancers after an index cancer.¹⁻¹⁰ In the case of prostate cancer (PCa), only a few studies have investigated the risk of second primary cancers; and, to our knowledge, none have specifically focused on PCa as a secondary cancer.¹¹⁻¹⁷ For secondary cancers after PCa, the Surveillance, Epidemiology, and End Results (SEER)-Medicare database indicated that men with PCa who underwent orchiectomy had an almost 40% increased risk of colorectal cancer.¹² Another study based on 489 men diagnosed with PCa reported an almost 2-fold risk of bladder cancer.¹⁵ Prostate cancer has been reported as a common second cancer after diagnosis of other urologic cancers.^{18,19} For instance, a Swiss study based on 297 men with newly diagnosed, nonmuscle-invasive bladder cancer indicated that PCa and lung cancer were more frequent than expected in the general population (standardized incidence ratio, 4.3 and 5.7, respectively).²⁰

To help assess the risk of PCa in cancer survivors as well as the risk of a secondary cancer in men with PCa, we evaluated the occurrence of cancers before and after a PCa diagnosis in a cohort of more than 70,000 men with PCa, including 6829 men who were diagnosed with another cancer before a PCa diagnosis and 5230 men who were diagnosed with another cancer after a PCa diagnosis.

MATERIALS AND METHODS

Study Population and Data Collection

The PCBaSe Sweden database is based on the National Prostate Cancer Register (NPCR) of Sweden, which started in 1996 and captures >96% of all newly diagnosed, biopsy-confirmed PCa compared with the Swedish Cancer Registry,²¹

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which has an under reporting rate for PCa of <3.7%.²² The NPCR includes date of diagnosis, age at diagnosis, tumor stage, tumor differentiation, serum level of prostate-specific antigen (PSA) at the time of diagnosis, and primary treatment received or planned up to 6 months after the date of diagnosis. A more detailed description of the NPCR has been published elsewhere.²³ By using the Swedish 10-digit personal identity number, PCBaSe was linked to other national registers, allowing for information to be obtained regarding demographics, comorbidities, socioeconomic status (SES), and causes of death.^{24,25} Diagnoses of cancers before and after PCa were taken from the National Cancer Registry using International Classification of Diseases, 7th revision (ICD-7) codes. Socioeconomic characteristics were assessed by record linkages to the 1960 to 1990 5-yearly census databases and were based on SES, which, in turn, is based on occupational group and stratifies men into the categories white-collar worker, blue-collar worker, not gainfully employed, and unknown.²⁵ Starting in 1997, the Cause of Death Register has collected date and underlying cause of death coded according to ICD-10.²⁴ Detailed information on the data content of PCBaSe is published elsewhere.²⁶

For our current analyses, the following information was obtained from PCBaSe: age, serum PSA levels, treatment information at the time of diagnosis, tumor grade and stage, SES, cancer diagnoses, and date of death. Tumor stage was defined based on the TNM classification and Gleason scores.²³

Other incident cancers, which were categorized according to the ICD-7, were grouped into cancer sites as set in the Eurostat European shortlist for cause of death.²⁷ We only studied those cancers that occurred regularly in combination with PCa by selecting those groups of cancer sites with a minimum of 200 events (before or after PCa diagnosis) among men in PCBaSe Sweden.

Given the suggested link between the prevalence of urologic cancers^{18,19} we also obtained detailed information about bladder and kidney cancer diagnoses from the National Bladder and Kidney Cancer Registers. For kidney cancer, we used information on disease stage (stages I-IV); and, for bladder cancer, we used information on tumor grade (grades 1-3).

Analysis

To compare the prevalence of other primary cancers between men with and without PCa, we randomly selected a comparison cohort of 3 men who were free of

PCa (at the time the index cancer was diagnosed) of the same age (± 1 year) from the same county for each patient with PCa registered in PCBaSe between January 1, 1997 and December 31, 2006. Thus, for each man with PCa, our study contained 3 matched men without PCa (defined as the *comparison cohort*). This comparison cohort allowed us to make absolute comparisons in terms of multiple primary cancers between men with and without PCa.

To quantify primary cancers before PCa diagnosis, we estimated the prevalence of these cancers at the time of PCa diagnosis (index case) in the cohort of men with PCa and at the corresponding time point in the matched comparison cohort. Estimates and confidence intervals (CIs) for proportions were calculated using normal approximation of the binomial distribution. Furthermore, we quantified the median lag time between diagnosis of these other primary cancers and PCa diagnosis. Primary cancers after a PCa diagnosis were quantified by estimating the cumulative incidence of these cancers²⁸ while censoring for the end of follow-up and considering death as a competing risk. Estimates and CIs for cumulative incidence were calculated using normal approximation of the estimated cumulative incidence.²⁸ This estimate is a proportion and is referred to here as the *incidence proportion*.²⁹ These incidence proportions are presented graphically for the PCa cohort and their comparison cohort according to treatment group (surveillance, curative treatment, and endocrine treatment) and PCa stage (distant metastases, regionally metastatic or high risk, and intermediate or low risk). In addition, the absolute difference in incidence proportions with 95% CIs between men with PCa and their comparison cohort was quantified at 1 year and at 5 years after PCa diagnosis.

Graphs also were repeated for all insulin-like growth factor-1 (IGF-1)-related cancers combined (colon, rectum, thyroid, and hematologic cancers³⁰) and for all urologic cancers combined (bladder, kidney, and penile cancers). For bladder and kidney cancers, we also report the distribution of grade and stage according to the time of PCa diagnosis. This information was obtained from the National Quality Register for Bladder Cancer (1997-2006) and Kidney Cancer (2003-2006).

Statistical analyses were performed with the Statistical Analysis Systems (SAS) (release 9.1.3; SAS Institute, Inc., Cary, NC) and R version 2.7.2 (R Foundation for Statistical Computing, Vienna, Austria). The Swedish Central Ethics Committee (Dnr O-14-2007) and the Ethics Committee at Umea University (Dnr 07-049M) approved this project.

Table 1. Baseline Characteristics of Men With Prostate Cancer and Their Comparison Cohort in The Swedish Prostate Cancer Database (PCBaSe)

Characteristic	No. of Patients (%)	
	Men with PCa, N = 72,613	Comparison Cohort, N = 217,839
Follow-up: Mean±SD, y	3.5 ± 2.5	3.8 ± 2.5
Age group, y		
<65	18,604 (25.6)	52,563 (24.1)
65-74	26,323 (36.3)	78,366 (36)
75-84	22,667 (31.2)	69,858 (32.1)
≥85	5019 (6.9)	17,052 (7.8)
Civil status		
Married	49,809 (68.6)	141,025 (64.7)
Divorced/widower/unmarried	22,796 (31.4)	76,807 (35.3)
Missing data	8 (0)	0 (0)
Socioeconomic status		
High	35,275 (48.6)	96,403 (44.3)
Low	36,389 (50.1)	115,749 (53.1)
Not gainfully employed/unclassified/missing	949 (1.3)	5687 (2.6)
PCa risk category³¹		
Distant metastases	12,750 (17.6)	
Regionally metastatic	6066 (8.4)	
High risk	15,636 (8.4)	
Intermediate risk	20,058 (27.6)	
Low risk	16,352 (22.5)	
Missing data	1751 (2.6)	
PCa treatment		
Surveillance	18,924 (26.1)	
Curative treatment	23,007 (31.7)	
Endocrine treatment	30,682 (42.3)	

Abbreviations: PCa, prostate cancer; SD, standard deviation.

RESULTS

The current study was based on 72,613 men who were diagnosed with PCa between 1996 and 2007, including 18,924 men who underwent surveillance, 23,007 men who received curative treatment, and 30,682 men who received endocrine treatment (Table 1). In total, 6829 primary cancers were diagnosed before PCa diagnosis, 138 were diagnosed at the time of PCa diagnosis, and 5230 were diagnosed after PCa diagnosis (Table 2).

For primary cancers that had occurred at other sites with a minimum of 200 events (Table 2), we estimated the prevalence and median lag time at the time of PCa diagnosis (Table 3). Bladder cancer, colon cancer, and malignant melanoma of the skin were the most prevalent primary cancers at time of PCa diagnosis. Both for men with PCa and for the comparison cohort, the highest prevalence was observed for bladder cancer, with a higher prevalence for men with PCa (1.94% vs 1.30%). The median lag time between the primary bladder cancer diagnosis to the date of PCa diagnosis was 1.8 years, and it was 7.1 years to the index date for men in the comparison

cohort. Among men with a PCa diagnosis, the prevalence of the following other primary cancers also was greater than that in the comparison cohort: colon cancer, kidney cancer, nonmelanoma of the skin, brain cancer, and non-Hodgkin lymphoma. The prevalence of cancers of the rectum and respiratory system and leukemia was greater for men in the comparison cohort than for the men with PCa (Table 3).

In the next step, we calculated and graphically illustrated the incidence proportions of these primary cancers after a PCa diagnosis or after the index date for men in the comparison cohort (Figs. 1, 2). The difference in incidence proportions between men with PCa and men in the comparison cohort at 1 year and 5 years after PCa diagnosis also is detailed in Table 4. Again, colon and bladder cancer as well as melanoma of the skin stood out with statistically significant differences in proportions between men with and without PCa (range, 2.0-8.1) (Table 4). The difference for colon cancer was only statistically significant at 1 year after PCa diagnosis. Also, for kidney cancer, this difference in incidence proportion was

Table 2. The Number of Primary Cancers Diagnosed Before, At, and After Prostate Cancer Diagnosis

ICD-7 Code	Site	No. of Primary Cancers (%)		
		Before PCa Diagnosis, N = 6829	At the Time of PCa Diagnosis, N = 138	After PCa Diagnosis, N = 5230
140-149	Lip, oral cavity, pharynx	229 (3.4)	0 (0)	94 (1.8)
150	Esophagus	17 (0.2)	0 (0)	68 (1.3)
151	Stomach	137 (2)	0 (0)	189 (3.6)
153	Colon	784 (11.5)	3 (2.2)	581 (11.1)
154	Rectum, anus	365 (5.3)	9 (6.5)	355 (6.8)
155.0	Liver, intrahepatic bile ducts	10 (0.1)	0 (0)	55 (1.1)
155.1-155.3	Gallbladder, biliary tract	17 (0.2)	0 (0)	13 (0.2)
157	Pancreas	13 (0.2)	2 (1.4)	113 (2.2)
161,162	Larynx, trachea/bronchus/lung	247 (3.6)	1 (0.7)	522 (10)
178	Testis	109 (1.6)	0 (0)	7 (0.1)
180.0, 180.9	Kidney, renal cell	305 (4.5)	1 (0.7)	186 (3.6)
181	Bladder	1307 (19.1)	100 (72.5)	639 (12.2)
190	Melanoma of skin	643 (9.4)	0 (0)	240 (4.6)
191	Nonmelanoma of skin	780 (11.4)	2 (1.4)	599 (11.5)
193	Brain, nervous tissue	186 (2.7)	1 (0.7)	82 (1.6)
194	Thyroid gland	75 (1.1)	0 (0)	18 (0.3)
200-209	Lymph/hematopoietic tissue	560 (8.2)	7 (5.1)	530 (10.1)
200, 202	Non-Hodgkin lymphoma	289 (4.2)	2 (1.4)	233 (4.5)
204-207	Leukemia	129 (1.9)	3 (2.2)	158 (3)
201	Hodgkin lymphoma	38 (0.6)	0 (0)	10 (0.2)
203	Multiple myeloma	54 (0.8)	2 (1.4)	103 (2)
—	Other cancers	535 (7.8)	5 (3.6)	435 (8.3)

Abbreviations: ICD-7, International Classification of Diseases, 7th revision; PCa, prostate cancer.

Table 3. Prevalence of Other Primary Cancers at the Time of Prostate Cancer Diagnosis and Lag Time Between First Primary Cancer Diagnosis and Prostate Cancer Diagnosis or Index Date

ICD-7 Code	Site	Men With PCa		Comparison Cohort	
		Prevalence, %	Median Lag Time (1st-3rd Quartile), y	Prevalence, %	Median Lag Time (1st-3rd Quartile), y
140-149	Lip, oral cavity, pharynx	0.32	8.1 (3.6-16.6)	0.34	9.0 (3.6-18.1)
151	Stomach	0.19	8.7 (3.6-15.8)	0.19	7.3 (2.6-15.2)
153	Colon	1.08	6.1 (2.2-11.4)	0.96	5.5 (2.2-11.2)
154	Rectum, anus	0.52	5.6 (1.3-10.6)	0.67	5.9 (2.6-11.6)
161,162	Larynx, trachea/bronchus/lung	0.34	3.9 (1.1-10.8)	0.39	5.7 (1.7-13.7)
180.0-180.9	Kidney, renal cell	0.42	7.7 (2.2-14.7)	0.28	7.3 (3.0-15.2)
181	Bladder	1.94	1.8 (0.2-8.3)	1.30	7.1 (3.0-13.0)
190	Melanoma of skin	0.89	9.2 (3.7-16.6)	0.70	8.5 (3.7-16.1)
191	Nonmelanoma of skin	1.08	5.1 (2.0-10.3)	1.03	5.0 (2.1-10.0)
193	Brain, nervous tissue	0.26	10.3 (4.5-21.7)	0.22	10.2 (4.9-19.0)
200-209	Lymph/hematopoietic tissue	0.78	6.0 (2.2-12.9)	0.78	5.2 (2.2-11.0)
200, 202	Non-Hodgkin lymphoma	0.40	6.3 (2.5-13.4)	0.37	5.8 (2.4-11.7)
204-207	Leukemia	0.18	4.3 (2.0-8.9)	0.21	4.6 (1.8-8.7)
—	Other cancers	0.74	8.1 (3.0-17.6)	0.66	9.4 (3.5-18.2)

Abbreviations: ICD-7, International Classification of Diseases, 7th revision; PCa, prostate cancer.

statistically significant at both 1 year and 5 years after PCa diagnosis (2% [95% CI, 1.4%-2.6%] and 1.9% [95% CI, 1.2%-2.7%], respectively) (Table 4).

The graphic representation of incidence proportions according to group (Fig. 1) indicate that patients with PCa who received endocrine treatment or underwent surveillance had a greater incidence proportion of other pri-

mary cancers than the comparison cohort. In contrast, for most primary cancers, the lowest incidence proportions were observed for men with PCa who received curative treatment. However, for bladder and kidney cancers and for melanoma of the skin and brain tumors, this group also experienced higher incidence proportions than their comparison group. When assessing the incidence

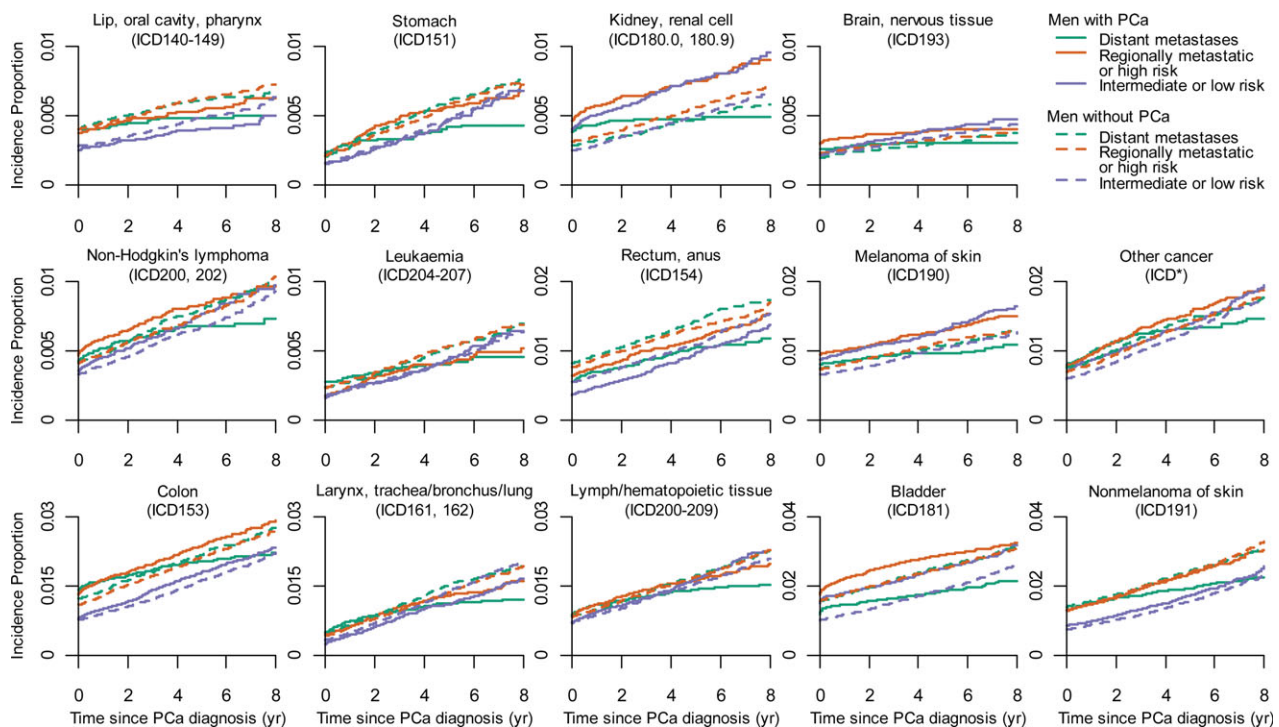


Figure 1. The incidence proportion of other primary cancers after a diagnosis of prostate carcinoma (PCa) is illustrated according to PCa treatment. International Classification of Diseases (ICD) codes for each disease site are indicated above each chart.

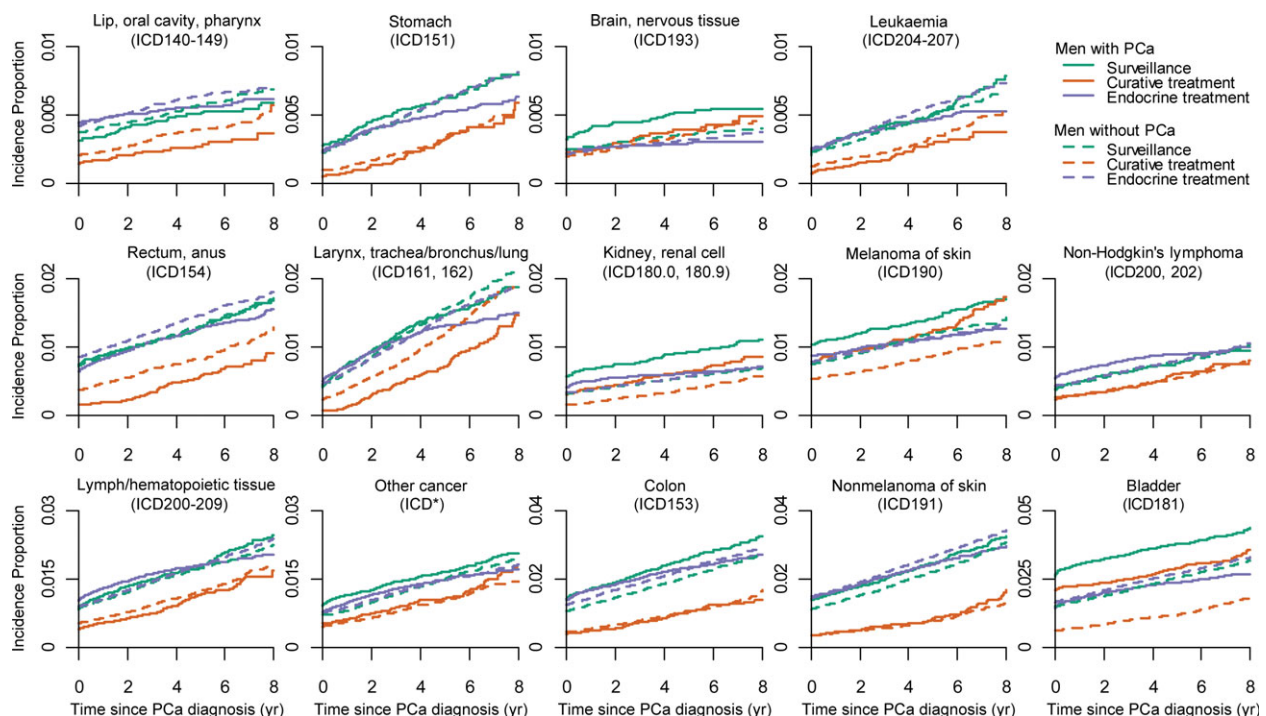
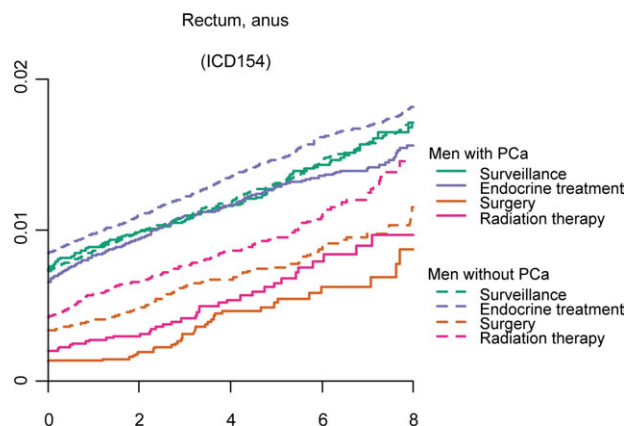


Figure 2. The incidence proportion of other primary cancers after a diagnosis of prostate carcinoma (PCa) is illustrated according to PCa stage. International Classification of Diseases (ICD) codes for each disease site are indicated above each chart.

Table 4. Incidence Proportion of Other Primary Cancers at 1 Year and 5 Years After Prostate Cancer Diagnosis for Men With Prostate Cancer and Their Comparison Cohort

ICD-7 Code	Site	One Year After PCa Diagnosis			Five Years After PCa Diagnosis		
		Proportion (95% CI), %		Difference, % (95% CI)	Proportion (95% CI), %		Difference, % (95% CI)
		Men With PCa	Cohort		Men With PCa	Cohort	
140-149	Lip, oral cavity, pharynx	3.5 (3.3, 3.9)	3.8 (3.5, 4.1)	-0.3 (-0.8, 0.2)	4.6 (4, 5.1)	5.5 (5.1, 5.8)	-0.9 (-1.5, -0.3)
151	Stomach	2.5 (2.1, 2.8)	2.5 (2.3, 2.7)	0 (-0.4, 0.4)	4.9 (4.3, 5.5)	5.4 (5, 5.7)	-0.5 (-1.2, 0.2)
153	Colon	13.2 (12.4, 14)	11.2 (10.8, 11.7)	2 (1.0, 2.9)	20.1 (19, 21.2)	18.8 (18.2, 19.5)	1.3 (0, 2.6)
154	Rectum, anus	6.4 (5.8, 7)	7.8 (7.5, 8.2)	-1.4 (-2.1, -0.7)	10.7 (9.8, 11.5)	12.3 (11.8, 12.8)	-1.6 (-2.6, -0.6)
161-162	Larynx, trachea/bronchus/lung	5.3 (4.8, 5.9)	5.6 (5.3, 5.9)	-0.3 (-0.9, 0.4)	11.7 (10.8, 12.6)	14 (13.4, 14.6)	-2.3 (-3.4, -1.2)
180.0-180.9	Kidney, renal cell	5.2 (4.6, 5.7)	3.1 (2.9, 3.4)	2 (1.4, 2.6)	7.1 (6.4, 7.7)	5.2 (4.8, 5.5)	1.9 (1.2, 2.7)
181	Bladder	22.7 (21.6, 23.8)	14.6 (14.1, 15.1)	8.1 (6.9, 9.3)	29.1 (27.8, 30.4)	22.1 (21.4, 22.8)	7 (5.6, 8.5)
190	Melanoma of skin	9.6 (8.9, 10.4)	7.6 (7.3, 8)	2 (1.2, 2.8)	12.3 (11.5, 13.2)	10.7 (10.2, 11.2)	1.6 (0.6, 2.6)
191	Nonmelanoma of skin	12.5 (11.7, 13.3)	11.9 (11.4, 12.4)	0.6 (-0.3, 1.6)	19.7 (18.6, 20.9)	19.8 (19.2, 20.5)	-0.1 (-1.4, 1.2)
193	Brain-nervous tissue	2.9 (2.5, 3.3)	2.4 (2.2, 2.6)	0.5 (0.1, 0.9)	3.8 (3.3, 4.3)	3.4 (3.1, 3.7)	0.4 (-0.1, 1)
200-209	Lymph/hematopoietic tissue	10.2 (9.5, 10.9)	9.3 (8.9, 9.7)	0.9 (0.1, 1.8)	15.9 (14.9, 16.9)	16.2 (15.6, 16.8)	-0.3 (-1.5, 0.9)
200-202	Non-Hodgkin lymphoma	5.1 (4.6, 5.6)	4.3 (4.1, 4.6)	0.8 (0.2, 1.3)	8.5 (7.6, 9.3)	7.6 (7.2, 8)	0.8 (-0.1, 1.8)
204-207	Leukemia	2.5 (2.1, 2.8)	2.5 (2.3, 2.7)	0 (-0.5, 0.4)	4.2 (3.7, 4.7)	4.8 (4.5, 5.2)	-0.7 (-1.3, 0)
—	Other cancers	9.1 (8.4, 9.8)	7.6 (7.3, 8)	1.5 (0.7, 2.3)	14.1 (13.2, 15.1)	13.5 (12.9, 14)	0.7 (-0.4, 1.8)

Abbreviations: CI, confidence interval; ICD-7, International Classification of Diseases, 7th revision; PCa, prostate cancer.

**Figure 3.** Incidence proportion of rectum cancer after a diagnosis of prostate carcinoma (PCa) is illustrated according to PCa stage. ICD154 indicates International Classification of Diseases code 154.

proportion of primary cancers according to PCa stage, almost all men with PCa had a greater incidence proportion than their comparison group (Fig. 2). Among men with PCa, those with intermediate-risk or low-risk cancer had the lowest incidence proportion, followed by those with distant metastases and regionally metastatic or high-risk cancer. This pattern was not observed for melanoma or for cancers of the bladder, lymph/hematopoietic system, or brain. Given the reported modestly increased risk of rectal cancer in men who have received external-beam therapy for PCa,³² we illustrated the incidence proportion for rectal cancer by treatment in which curative treatment was split between surgery and radiation therapy. No difference in pattern was observed for either curative treatment (Fig. 3). Finally, Figures 4 and 5 illustrate the patterns of incidence proportions for all urologic and IGF-I related cancers, respectively. However, the distribution of bladder and kidney cancers by stage/grade before PCa diagnosis was not very different before or after PCa diagnosis (Table 5).

DISCUSSION

To our knowledge, this is the first large observational study to assess primary cancers before and after PCa diagnosis using detailed information on PCa tumor stage and treatment at the time of diagnosis. Approximately 17% of all PCa occurred in combination with another primary cancer that was diagnosed either before or after the PCa diagnosis. When comparing men who had PCa men their matched comparison cohort, more primary cancers were observed both before and after PCa diagnosis. This was especially true for bladder cancer, colon cancer, renal cell cancer, and melanoma of the skin. The highest incidence

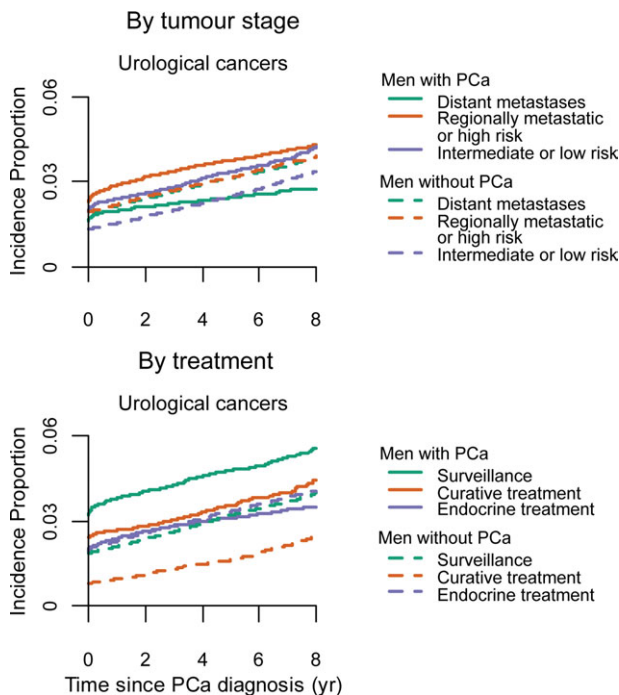


Figure 4. The incidence proportion of urologic cancers after a diagnosis of prostate carcinoma (PCa) is illustrated according to PCa treatment.

proportion was observed among men with PCa who received endocrine treatment or underwent surveillance, whereas those men with PCa who received treatment with curative intent were diagnosed less often with other primary cancers.

From a public health point of view, it is interesting to study the pattern of primary cancers in men with PCa, because age is strongly associated with the risk of PCa; longevity is increasing; and, worldwide, PCa is diagnosed in more than 670,000 men each year.^{33,34} A study based on incidence data for all malignant cancers diagnosed between 1989 and 2006 indicated that 7% of all men with PCa in 2007 developed multiple malignancies.³⁵ The 3 most common cancer diagnoses after PCa were urinary cancers (27%), colorectal cancers (20%), and non-melanoma skin cancers (19%).³⁵ Prostate cancer also was among the most commonly diagnosed second primary cancer after cancers of the urinary system (30%), colorectum (15%), male genitals (30%), soft tissues (14%), non-melanoma skin cancers (13%), melanoma skin cancers (10%), and non-Hodgkin lymphomas (10%).³⁵ Thus, our estimate of 17% appears to be in line with what has been reported previously. However, it is interesting to

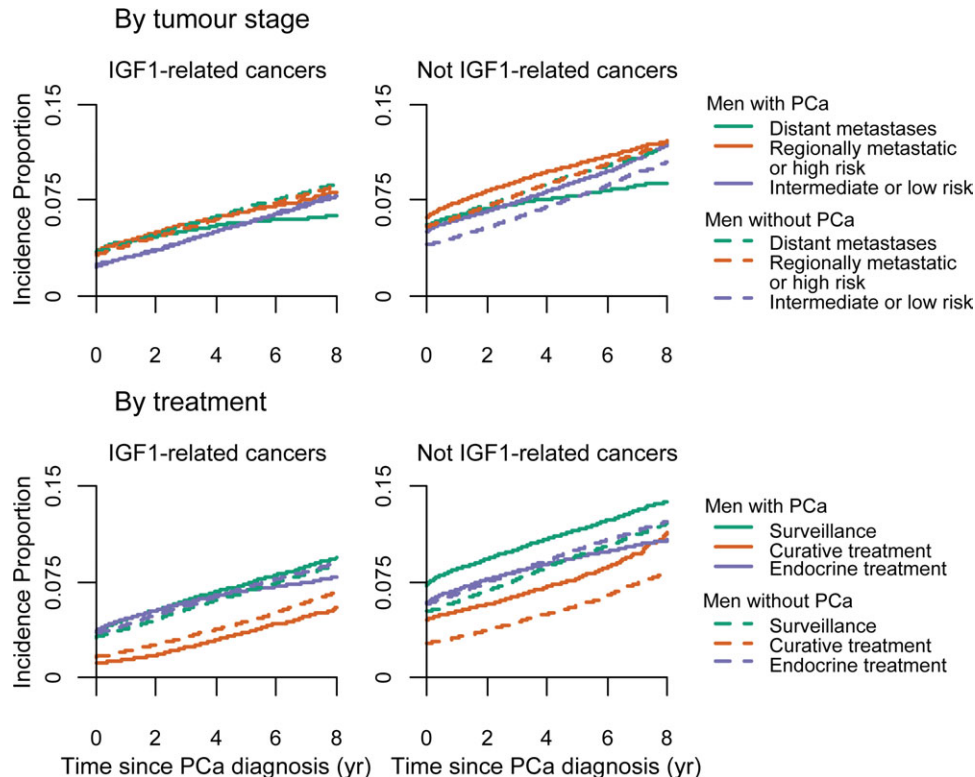


Figure 5. The incidence proportion of insulin-like growth factor 1 (IGF-1)-related cancers after a diagnosis of prostate carcinoma (PCa) is illustrated diagnosis according to PCa treatment.

Table 5. Distribution of Bladder and Kidney Cancer by Time of Prostate Cancer Diagnosis and Grade or Stage of Cancer

	No. of Patients (%)			
	Before PCa Diagnosis		After PCa Diagnosis	
	Men With PCa	Men Without PCa ^a	Men With PCa	Men Without PCa ^a
Bladder cancer grade^b				
1	95 (25)	100 (21)	474 (30)	484 (20)
2	171 (44)	151 (32)	617 (39)	857 (35)
3	113 (29)	190 (40)	425 (2)	1021 (41)
Kidney cancer stage^c				
I	3 (43)	30 (54)	22 (52)	81 (38)
II	1 (14)	6 (11)	6 (14)	24 (11)
III	1 (14)	8 (14)	7 (17)	51 (24)
IV	2 (29)	11 (20)	7 (17)	55 (26)

Abbreviation: PCa, prostate cancer.

^aGrade indicates the tumor grade of differentiation on diagnostic biopsy according to the World Health Organization classification: grade 1, highly differentiated; grade 2, intermediately differentiated; and grade 3, poorly differentiated, as recorded in the Bladder Cancer Register of Sweden between 1996 and 2006 (available at: <http://www.vinkancer.se/sv/registerrapporter/Blascancer>) [accessed March 15, 2012].

^bStage: I: T1, N0, M0; Stage II: T2, N0, M0; Stage III: T3, N0, M0 or T1, T2, T3, N1, M0; Stage IV: T4, any N, M0, Any T, N2, M0, Any T, Any N, M1, as registered in the Kidney cancer register of Sweden between 2003 and 2006 (available at: <http://www.vinkancer.se/sv/registerrapporter/Njurcancer>) [accessed March 15, 2012].

^cData reflect the disease stage before or after the date of diagnosis for the index case.

note that, for cancer overall, a Dutch study reported that approximately 7% of all cancer survivors in 2007 had multiple malignancies, suggesting that multiple malignancies are more common among men with PCa.³⁵

There are several hypotheses about the occurrence of PCa in combination with other primary cancers. First, an increase in primary cancers after PCa diagnosis can probably be explained by an increase in diagnostic activity. In a study based on 5 cancer registries in Belgium, the Netherlands, and the United Kingdom, an almost 2-fold increased risk of a second neoplasm was reported for men with PCa.¹⁵ Another study based on the Swedish Multi-generation Register indicted a 3-fold increased risk of bladder cancer after PCa diagnosis. Although detection bias is likely to increase the risk of primary cancer after PCa diagnosis, this also may explain the occurrence of PCa as a second primary cancer. Our study corroborated these findings and specifically demonstrated an increase in cancers of the colon, kidney, bladder, lymph/hematopoietic tissue, and brain tissue as well as melanoma of the skin and non-Hodgkin lymphoma after PCa diagnosis among men with PCa compared with their comparison cohort. For cancers of the bladder and kidney, we observed an increased occurrence both before and after PCa diagnosis, which, not surprisingly, suggests that detection bias is strongest for urologic cancers. This also can be observed in Figure 4, which illustrates the incidence proportion of all urologic cancers combined. Nevertheless, it is interesting to note that there is no obvious difference in tumor stage or grade of bladder or

kidney cancer before or after PCa diagnosis, despite the higher number of urologic cancers after PCa diagnosis.

We observed no obvious difference in grade or stage distribution before or after PCa diagnosis. The small increases in poorly differentiated tumors and higher disease stage may have been caused by increasing age, because they also were observed in the comparison cohort, suggesting that there is no “unnecessary” screening for bladder or kidney cancer in men with PCa.

Apart from detection bias, PCa treatment may explain the increase in primary cancers after PCa diagnosis. In the SEER-Medicare database, as mentioned above, long-term androgen-deprivation therapy for PCa was associated with an increased risk of colorectal cancer.¹² Our Figure 2 illustrates the finding that the highest incidence proportion of colon cancer after PCa diagnosis was observed among men with PCa who underwent surveillance or received endocrine treatment. However, it also is noteworthy that the prevalence of colon cancer already was higher for men with PCa versus the comparison cohort before PCa diagnosis, suggesting that treatment cannot be the only contributor to the higher risk of colon cancer. Some long-term follow-up studies have reported a modestly increased risk of rectal cancer in men who have received external-beam radiation therapy for PCa, but the observation time in the current study probably is too short to reflect such an association.^{32,36} In addition, detection or surveillance bias may be more apparent for patients who undergo surveillance or receive endocrine treatment than for men

who receive curative treatment, because these patients may be followed less closely after awhile.

Another explanation for an increased risk of other primary cancers before and after PCa diagnosis is probably the similarity in etiologic factors. Although observational studies cannot address underlying biologic mechanisms, we tried to assess how the prevalence of hormone-related cancers, more specifically, IGF-1, is linked to PCa diagnosis (Fig. 5). Currently, the evidence for an increased risk of PCa among men with high levels of androgens is contradictory.³⁷⁻³⁹ There is more consistent evidence of an association between IGF-1 and the risk of PCa as well as colon cancer.^{40,41} In the current study, we observed that men with PCa who received endocrine treatment and those who underwent surveillance were at greater risk of developing IGF-1—related cancers than men in the comparison cohort (Fig. 4). In relation to endocrine treatment, it is also interesting to note the possible increased risk of breast cancer; however, this was not studied here because of the small number of patients.⁴²

Overall, our results indicate that men with PCa who received curative treatment had a much lower prevalence of other primary cancers compared with men in the comparison cohort. This probably reflects a treatment-selection mechanism. During the time of our study in Sweden, men who received curative treatment had lower all-cause mortality than the general Swedish male population, and many men were recommended for surveillance because they were not healthy enough to undergo radical treatment.⁴³ When we examined incidence proportions according to PCa stage, the general pattern indicates that men with PCa who had low-risk or intermediate-risk tumors had a lower prevalence of other primary cancers than their comparison cohort, which likely reflects a diagnostic bias. For instance, healthier individuals may be more likely to undergo screening.

The database we used contains more than 72,000 men with PCa and provides complete follow-up for each patient and linkage to other registers. Moreover, a matched comparison cohort of men free of PCa was available to compare the occurrence of other primary cancers between men with and without PCa. Although the cancer registry has very high completeness to collect information about cancer diagnosis before and after PCa diagnosis,²² the current study design has some limitations. Because PCa diagnosis was our starting point, data before PCa diagnosis were collected retrospectively.

In conclusion, approximately 17% of all PCa developed in combination with another primary cancer (before or after the PCa diagnosis). Cancer of the bladder, kidney,

and colon as well as nonmelanoma of the skin were the most frequently observed other primary cancers. These findings indicate that men with PCa are and need to be closely monitored for other cancer risks, especially of urologic cancers. Detection bias is likely to explain part of this observation, but further investigations are required to assess possible underlying etiologic mechanisms, such as IGF-I metabolism.

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CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

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