Original Article

Risk of Second Primary Tumors in Men Diagnosed With Prostate Cancer

A Population-Based Cohort Study

Elizabeth J. Davis, MD[1,2]; Jennifer L. Beebe-Dimmer, MPH, PhD[3,4]; Cecilia L. Yee, MS[3,4]; and Kathleen A. Cooney, MD[1,2,5]

BACKGROUND: The survival of men diagnosed with prostate cancer has improved over time, and the current 10-year relative survival rate is 99.7%. The long survival of patients with this common cancer raises questions about the risk of a second primary cancer and the need for continued surveillance. **METHODS:** A population-based cohort of 441,504 men who were diagnosed with prostate cancer between 1992 and 2010 was identified from Surveillance, Epidemiology and End Results Program (SEER) data (SEER13). The standardized incidence ratio (SIR) was calculated as an estimate of the risk of a second primary malignancy based on the incidence in the general population. **RESULTS:** Prostate cancer survivors had a lower risk of being diagnosed with another cancer overall compared with the US population (SIR = 0.60; 95% confidence interval, 0.60-0.61). The risks of leukemia and cancers of the oral cavity and pharynx, esophagus, stomach, colon and rectum, liver, gallbladder, pancreas, lung and bronchus, and larynx were significantly lower. Conversely, these patients had a greater risk of bladder, kidney, and endocrine and soft tissue cancers. Men who received treatment with radiation therapy (external-beam radiation therapy) had long-term increases in their risk of bladder cancer (SIR = 1.42) and rectal cancer (SIR = 1.70) risk compared with who did not receive radiation ($SIR_{bladder} = 0.76$; $SIR_{rectal} = 0.74$). There were significant racial differences in the risk of being diagnosed with a second primary cancer, and the magnitude and direction of these risks depended on tumor type. **CONCLUSIONS:** Prostate cancer survivors remain at risk of subsequent malignancies, and race and treatment choice important determinants of long-term risk. ***Cancer*** **2014;120:2735-41.** *© 2014 American Cancer Society.*

KEYWORDS: prostate cancer, SEER, epidemiology, multiple primaries.

INTRODUCTION

Prostate cancer is the most commonly diagnosed noncutaneous malignancy among men in the United States.[1] Since the widespread adoption of screening with serum prostate-specific antigen (PSA), the majority of men are diagnosed with localized disease. Combined with improvements in clinical therapies, the survival of men diagnosed with prostate cancer has increased to the current estimates for 10-year and 15-year relative survival at 98% and 91%, respectively.[2] The long life expectancy of these patients exposes them to the possibility of developing second primary malignancies. Second-order or higher order malignancies affected 16% of cancer survivors as a whole in 2003.[3] Risk factors for second malignancies are multifactorial and can include treatment for the initial cancer, normal aging, lifestyle and environmental factors, and genetic susceptibility. From a clinical perspective, the identification of patients who are at increased risk of experiencing subsequent malignancies is important for optimizing treatment and may help identify those who would benefit from enhanced screening. With regard to genetic predisposition, cancers that occur together may help identify a more homogeneous phenotype for future gene discovery efforts.

MATERIALS AND METHODS

Data Source

The National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program database was used to identify the cohort of men for this study. The demographic and incidence data collected by the SEER registries generally are

Corresponding author: Kathleen A. Cooney, 7216 Cancer Center, 1500 E. Medical Center Drive, Ann Arbor, MI 48109-5948; Fax: (734) 936-7376; kcooney@umich.edu

[1]Department of Internal Medicine, University of Michigan Medical School, Ann Arbor, Michigan; [2]University of Michigan Comprehensive Cancer Center, Ann Arbor, Michigan; [3]Karmanos Cancer Institute, Division of Population Studies and Disparities Research, Detroit, Michigan; [4]Department of Oncology, Wayne State University, Detroit, Michigan; [5]Department of Urology, University of Michigan Medical School, Ann Arbor, Michigan

Additional supporting information may be found in the online version of this article.

We recognize the contribution of Dr. Claudia Salinas and the Epidemiology Research Core at Karmanos Cancer Institute toward this analysis and article.

DOI: 10.1002/cncr.28769, **Received:** January 6, 2014; **Revised:** April 9, 2014; **Accepted:** April 21, 2014, **Published online** May 19, 2014 in Wiley Online Library (wileyonlinelibrary.com)

considered to be representative of the US population as a whole.[4,5] The SEER13 registry data are used by the SEER*Stat software program (Surveillance Research Program, National Cancer Institute, Bethesda, Md) to estimate the incidence of secondary malignancies in the prostate cancer cases and includes individual-level data from 1992 to 2010 from 13 registries (Atlanta, Connecticut, Detroit, Hawaii, Iowa, New Mexico, San Francisco-Oakland, Seattle-Puget Sound, Utah, Los Angeles, San Jose-Monterey, Rural Georgia, and the Alaska Native Tumor Registry). The SEER13 data cover 13.4% of the total US population and 11.5%, and 11.3% of the total white and black US population, respectively.

Study Population

The cohort was composed of 441,504 men who were diagnosed with a first primary, microscopically confirmed, malignant prostate cancer (*International Classification of Diseases for Oncology* third edition histology classification codes for carcinoma not otherwise specified [8010], nonsmall cell carcinoma [8046], adenocarcinoma not otherwise specified [8140], cribriform carcinoma [8201], adenocarcinoma with mixed subtypes [8255], mucinous adenocarcinoma [8480], mucin-producing adenocarcinoma [8481], and acinar cell carcinoma [8550]) who were reported to 1 of the 13 SEER registries between January 1, 1992 and December 31, 2010. We excluded cases that were reported only on death certificate or autopsy and those with unknown age at diagnosis. We restricted the cohort to men aged $\geq$20 years to ensure that men with early onset (aged $<$55 years at diagnosis) prostate cancer would be captured.

Statistical Analysis

Second primary malignancies required a minimum 2-month latency period after the primary diagnosis to exclude synchronous primary cancers. Multiple primary standardized incidence ratios (MP-SIRs) were calculated as a measure of the relative risk of a second primary malignancy using SEER*Stat software version 8.0.4. More detailed information on both SEER*Stat software and the method the software uses to derive the standard incidence ratios (SIRs) are available on the SEER registry website (available at: http://seer.cancer.gov/seerstat/; accessed March 14, 2014).[6] Specifically, the observed incidence of second malignancy among men previously diagnosed with prostate cancer was compared with the expected incidence based on the corresponding segment of the US general population (ie, similarly aged white men and black men in the SEER13 geographic areas). In addition, because the survival of patients initially diagnosed with distant stage disease would be considerably shorter than the survival of patients diagnosed with locoregional disease, we performed a separate analysis excluding the patients who had distant disease at time of diagnosis.

Analyses were stratified by age at prostate cancer diagnosis (early onset [ages 20-54 years] or late onset [aged $\geq$55 years]), race (white or black), latency period (2-11 months, 12-59 months, 60-120 months, or $>$120 months from the date of prostate cancer diagnosis), and calendar period of prostate cancer diagnosis (1992-2000 or 2001-2010). Results also were considered according to whether or not men received radiation therapy (external-beam radiation therapy [EBRT]) as their initial treatment for prostate cancer. In the SEER database, the first treatment received in the year after prostate cancer diagnosis is recorded as the primary treatment. For this particular analysis, only second primary tumors that were diagnosed $>$120 months after the original date of prostate cancer diagnosis were eligible. The risk of being diagnosed with a second cancer among patients with prostate cancer, as opposed to the general population, was compared between the aforementioned groups using either the chi-square goodness-of-fit test (or Fisher exact test) or an evaluation of the confidence intervals (CIs) between groups to determine any overlap. A 2-sided P value $<$ .05 was considered statistically significant.

RESULTS

We identified 441,504 men who were diagnosed with prostate cancer between January 1, 1992 and December 31, 2010 from the SEER13 geographic areas. Men were aged $\geq$20 years at the time of prostate cancer diagnosis, and the majority of cancers were diagnosed between ages 65 and 74 years. Of these, 44,310 men (10%) developed a second primary malignancy during the observation period (Table 1). Compared with cancer incidence in the general population, men with prostate cancer had a lower risk overall for a second primary malignancy (SIR = 0.60; 95% CI, 0.60-0.61), which was slightly lower for solid tumors (SIR = 0.57; 95% CI, 0.56-057) than for other invasive cancers. The reductions in risk were significant for leukemia and for cancers of the oral cavity and pharynx, esophagus, stomach, colon and rectum, liver, gallbladder, pancreas, lung and bronchus, and larynx. Conversely, there were significant increases in risk for cancers of soft tissue including heart, bladder, kidney, and endocrine system among men with prostate cancer compared with the general population. Because the data cover a wide period of time, during which diagnostic and

TABLE 1. Risk of a Second Malignancy in US Men Diagnosed With Prostate Cancer (1992-2010), by Tumor Site

Second Tumor Site[a]	Obs[b]	Exp[c]	SIR (95% CI)[d]
All sites	44,310	73,262	**0.60 (0.60-0.61)**
All solid tumors	36,852	65,185	**0.57 (0.56-0.57)**
Oral cavity and pharynx	1251	1647	**0.76 (0.72-0.80)**
Esophagus	842	1040	**0.81 (0.76-0.87)**
Stomach	1392	1609	**0.87 (0.82-0.91)**
Small intestine	315	297	1.06 (0.95-1.18)
Colon excluding rectum	5113	5709	**0.90 (0.87-0.92)**
Rectum and rectosigmoid junction	1967	2088	**0.94 (0.90-0.98)**
Liver	637	1040	**0.61 (0.57-0.66)**
Gallbladder	104	128	**0.81 (0.66-0.99)**
Pancreas	1781	1913	**0.93 (0.89-0.98)**
Lung and bronchus	8615	11,158	**0.77 (0.76-0.79)**
Soft tissue including heart	407	357	**1.14 (1.03-1.26)**
Melanoma of the skin	2681	2710	0.99 (0.95-1.03)
Male breast	142	161	0.88 (0.74-1.04)
Urinary bladder	5885	5620	**1.05 (1.02-1.07)**
Kidney	2213	1980	**1.12 (1.07-1.17)**
Brain	631	614	1.03 (0.95-1.11)
Endocrine system	440	393	**1.12 (1.02-1.23)**
Thyroid	372	337	1.10 (1.00-1.22)
Lymphoma	2935	2985	0.98 (0.95-1.02)
Hodgkin lymphoma	118	140	0.85 (0.70-1.01)
NHL	2817	2846	0.99 (0.95-1.03)
Myeloma	1078	1091	0.99 (0.93-1.05)
Leukemia	1906	2098	**0.91 (0.87-0.95)**
Larynx	651	806	**0.81 (0.75-0.87)**

Abbreviations: CI, confidence interval; Exp, expected; NHL, non-Hodgkin lymphoma; Obs, observed; SIR, standard incidence ratio.
[a] Boldface indicates tumor sites for which the SIR was significantly different.
[b] Second primary malignancies diagnosed within 2 months of the initial prostate cancer diagnosis were not included.
[c] Expected malignancies were estimated from the incidence rate at the tumor sites in the general US population.
[d] Unadjusted SIRs were based on 2,889,094 person-years at risk (n = 441,504).

treatment methods may have changed, we considered whether there were differences by calendar period of the data (1992-2000 vs 2001-2010). The only important differences observed by calendar period were for kidney cancer in prostate cancer patients, for which the risk increased in the recent era ($SIR_{1992\text{-}2000} = 1.01$ [95% CI, 0.95-1.06] vs $SIR_{2001\text{-}2010} = 1.32$ [95% CI, 1.24-1.41]). Repeat analyses removing those men who had prostate cancer initially diagnosed as distant stage disease did not materially change the risk estimates (data not shown).

Latency

In the 2 to 11 months after prostate cancer diagnosis, there was an increased risk of urinary bladder, kidney, thyroid, and endocrine system cancers and of lymphoma (including both Hodgkin and non-Hodgkin lymphoma). At >120 months from diagnosis, the risk was decreased for all of these malignancies among all patients (see online Supporting Information)

Age at Prostate Cancer Diagnosis

We considered whether the age of prostate cancer diagnosis (ie, early onset vs late onset) modified the risk of second primary malignancies. Men with early onset prostate cancer had a modestly higher risk of both bladder cancer (SIR = 1.29; 95% CI, 1.10-1.51) and thyroid cancer (SIR = 1.63; 95% CI, 1.19-2.18) compared with men in the general population and in contrast to men who were diagnosed at older ages (bladder cancer, SIR = 1.04 [95% CI, 1.01-.07]; thyroid cancer, SIR = 1.02 [95% CI, 0.90-1.15]).

Race

There were significant differences in the relative risk estimates between blacks and whites for several cancer sites (Table 2). The risks of a secondary diagnosis of stomach, colon, bladder, and kidney cancers and of leukemia—particularly chronic lymphocytic leukemia—all were higher in black men who had prostate cancer compared with white men who had prostate cancer. Likewise, the reduction in risk was significantly less in black patients compared with white patients for cancers of the lung and bronchus. It is noteworthy that there was a reversal in the direction of the SIRs for chronic lymphocytic leukemia and colon cancer, in which black men with prostate cancer had significant increase in the risk for both cancers (SIR = 1.27 and SIR = 1.10, respectively) compared with the general population, whereas white men with prostate cancer had a significantly reduced risk (SIR = 0.87 and SIR = 0.88, respectively). There were no cancers for which the relative risk estimates among white men with prostate cancer were higher than those for black men with prostate cancer.

Initial Therapy for Prostate Cancer

Finally, we considered the influence of radiation therapy for prostate cancer on the subsequent risk of developing new malignancies (Table 3). For this analysis, we only considered new primary cancers that arose ≥10 years after prostate cancer treatment. In the cohort of 106,879 patients who were still under observation at that time, the SIRs were compared between the 66.7% of patients who did not receive radiation as their initial therapy for prostate cancer and the 23.9% who had a record of receiving EBRT. The remaining patients received radioactive seed implants (4.5%) or unspecified/combined radiotherapies (4.9%). Compared with men who did not receive

TABLE 2. Risk of Second Malignancy in US Men Diagnosed With Prostate Cancer, by Race

Second Tumor Site[a]	White, n = 345,585			Black, n = 57,362		
	Obs[b]	Exp[c]	SIR (95% CI)[d]	Obs[b]	Exp[c]	SIR (95% CI)[d]
All sites	36,138	59094	0.61 (0.61-0.62)	5764	9431	0.61 (0.60-0.63)
All solid tumors	29,874	52316	0.57 (0.56-0.58)	4922	8637	0.57 (0.55-0.59)
Oral cavity and pharynx	1039	1353	0.77 (0.72-0.82)	155	194	0.8 (0.68-0.93)
Esophagus	691	845	0.82 (0.76-0.88)	116	133	0.87 (0.72-1.04)
Stomach	**926**	**1139**	**0.81 (0.76-0.87)**	**275**	**254**	**1.08 (0.96-1.22)**
Small intestine	225	227	0.99 (0.87-1.13)	67	53	1.26 (0.98-1.61)
Colon excluding rectum	**3988**	**4538**	**0.88 (0.85-0.91)**	**835**	**757**	**1.1 (1.03-1.18)**
Rectum and rectosigmoid junction	1591	1686	0.94 (0.9-0.99)	246	229	1.07 (0.94-1.22)
Liver	424	716	0.59 (0.54-0.65)	127	165	0.77 (0.64-0.91)
Gallbladder	74	97	0.76 (0.6-0.95)	21	15	1.36 (0.84-2.07)
Pancreas	1375	1509	0.91 (0.86-0.96)	272	260	1.05 (0.93,1.18)
Lung and bronchus	**6635**	**8775**	**0.76 (0.74-0.77)**	**1483**	**1609**	**0.92 (0.88-0.97)**
Soft tissue including heart	342	303	1.13 (1.01-1.25)	44	29	1.52 (1.11-2.04)
Melanoma of the skin	2641	2611	1.01 (0.97-1.05)	17	17	1.00 (0.58-1.6)
Male breast	115	130	0.88 (0.73-1.06)	21	23	0.92 (0.57-1.41)
Urinary bladder	**5194**	**4972**	**1.04 (1.02-1.07)**	**430**	**334**	**1.29 (1.17-1.41)**
Kidney	**1707**	**1589**	**1.07 (1.02-1.13)**	**401**	**279**	**1.43 (1.30-1.58)**
Brain	554	543	1.02 (0.94-1.11)	50	39	1.29 (0.96-1.7)
Endocrine system	360	324	1.11 (1.00-1.23)	45	37	1.22 (0.89-1.64)
Thyroid	315	283	1.11 (0.99-1.24)	29	28	1.04 (0.69-1.49)
Lymphoma	2552	2572	0.99 (0.95-1.03)	225	208	1.08 (0.95-1.23)
Hodgkin lymphoma	105	120	0.87 (0.71-1.06)	10	12	0.85 (0.41-1.56)
NHL	2447	2452	1.00 (0.96-1.04)	215	196	1.10 (0.95-1.25)
Myeloma	793	815	0.97 (0.91-1.04)	245	215	1.14 (1.00-1.29)
Leukemia	**1609**	**1808**	**0.89 (0.85-0.93)**	**213**	**174**	**1.22 (1.06-1.4)**
CLL	**724**	**835**	**0.87 (0.80-0.93)**	**96**	**76**	**1.27 (1.03-1.55)**
AML	**472**	**481**	**0.98 (0.89-1.07)**	**69**	**49**	**1.41 (1.10-1.27)**
Larynx	490	622	0.79 (0.72-0.86)	142	144	0.99 (0.83-1.17)

Abbreviations: ALL, acute myeloid leukemia; CI, confidence interval; CLL, chronic lymphocytic leukemia; Exp, expected; NHL, non-Hodgkin lymphoma; Obs, observed; SIR, standard incidence ratio.

[a] Boldface indicates those tumor sites with statistically significant group differences.

[b] Second primary malignancies diagnosed within 2 months of the initial prostate cancer diagnosis were not included.

[c] Expected malignancies were estimated from the incidence rate at the tumor sites in the general US population.

[d] Unadjusted standardized incidence ratio (SIR) based on 2,308,454 (White) and 351,384 (Black) person-years at risk, respectively.

radiation, men who received EBRT were significantly more likely than the general population to be diagnosed with rectal cancer ($SIR_{radiation} = 1.70$ vs $SIR_{noradiation} = 0.74$; $P < .0001$) and bladder cancer ($SIR_{radiation} = 1.42$ vs $SIR_{noradiation} = 0.76$; $P < .0001$). Both groups were at reduced risk of second primary malignancy and second solid tumors overall, but the magnitude of the reduction was less among men who received radiation (eg, for solid tumors, SIR = 0.72 [95% CI, 0.69-.76] among those who received EBRT compared with SIR = 0.51 [95% CI, 0.49-0.52] for those who were not exposed to radiation).

DISCUSSION

Overall, we observed that prostate cancer survivors had a 40% lower risk of developing a second primary cancer compared with the general US male population. Specifically, they had a lower risk of developing leukemia and cancers of the oral cavity and pharynx, esophagus, stomach, colon and rectum, liver, gallbladder, pancreas, lung and bronchus, and larynx. In contrast, men with prostate cancer had a higher risk of developing bladder, kidney, soft tissue, and endocrine cancers. The reduction in overall cancer risk in these patients is consistent with previous studies.[7-11] Although the reasons for the reduction in risk are not entirely clear, they may relate in part to the age of patients at the time of diagnosis of prostate cancer. Currently the mean age at diagnosis is 67 years[1]; however, the age at diagnosis has declined over the past few decades primarily because of PSA screening and earlier detection of preclinical cancers. Nevertheless, older men who have prostate cancer, particularly men with competing risks for death, may not have the same opportunity for a second diagnosis as all US men. Conversely, the increased risk of certain cancers may be explained by enhanced surveillance and screening after a prostate cancer diagnosis, leading to detection of latent malignancies.[10] This idea is supported by the existence of a strong temporal effect on kidney

TABLE 3. Risk of Second Malignancy in US Men Diagnosed With Prostate Cancer, by Primary Prostate Cancer Treatment

Second Tumor Site[a]	No Radiation, n = 71,242			EBRT, n = 25,569			
	Obs[b]	Exp[c]	SIR (95% CI)[d]	Obs[b]	Exp[c]	SIR (95% CI)[d]	*P*[e]
All sites	**4017**	**7353**	**0.55 (0.53-0.56)**	**1880**	**2494**	**0.75 (0.72-0.79)**	**< .0001**
All solid tumors	**3272**	**6452**	**0.51 (0.49-0.52)**	**1566**	**2166**	**0.72 (0.69-0.76)**	**< .0001**
Oral cavity and pharynx	98	152	0.64 (0.52-0.79)	39	49	0.79 (0.56-1.08)	.58
Esophagus	79	107	0.74 (0.58-0.92)	31	36	0.86 (0.59-1.23)	.67
Stomach	135	164	0.83 (0.69-0.98)	54	62	0.87 (0.65-1.14)	.50
Small intestine	38	33	1.15 (0.82-1.58)	16	12	1.38 (0.79-2.25)	.59
Colon excluding rectum	**415**	**576**	**0.72 (0.65-0.79)**	**198**	**213**	**0.93 (0.80-1.07)**	**.009**
Rectum and rectosigmoid junction	**142**	**192**	**0.74 (0.62-0.87)**	**112**	**66**	**1.7 (1.40-2.04)**	**< .0001**
Liver	47	105	0.45 (0.33-0.60)	17	35	0.49 (0.28-0.78)	.98
Gallbladder	16	15	1.07 (0.61-1.74)	2	6	0.35 (0.04-1.28)	.18
Pancreas	172	216	0.8 (0.68-0.93)	77	78	0.98 (0.78-1.23)	.11
Lung and bronchus	**770**	**1138**	**0.68 (0.63-0.73)**	**344**	**393**	**0.88 (0.79-0.97)**	**.0007**
Soft tissue including heart	42	42	1.01 (0.73-1.36)	21	15	1.42 (0.88-2.16)	.21
Melanoma of the skin	282	330	0.86 (0.76-0.96)	94	111	0.85 (0.69-1.04)	.53
Male breast	14	18	0.78 (0.43-1.31)	6	6	0.94 (0.34-2.05)	.8
Urinary bladder	**506**	**662**	**0.76 (0.70-0.83)**	**343**	**241**	**1.42 (1.28,1.58)**	**< .0001**
Kidney	220	209	1.05 (0.92-1.20)	72	67	1.07 (0.84-1.35)	.50
Brain	51	62	0.82 (0.61-1.08)	18	20	0.88 (0.52-1.40)	.95
Endocrine system	36	41	0.88 (0.62-1.22)	12	12	0.99 (0.51-1.72)	.82
Thyroid	30	35	0.86 (0.58-1.22)	10	10	0.97 (0.47-1.79)	.84
Lymphoma	280	334	0.84 (0.74-0.94)	122	116	1.05 (0.87-1.25)	.07
Hodgkin lymphoma	7	14	0.49 (0.20-1.01)	5	5	1.07 (0.35-2.51)	.32
NHL	273	320	0.85 (0.760.96)	117	112	1.05 (0.87-1.25)	.11
Myeloma	128	120	1.07 (0.89-1.27)	47	43	1.09 (0.80-1.45)	.89
Leukemia	220	238	0.92 (0.80-1.05)	77	87	0.88 (0.70-1.10)	.85
CLL	102	111	0.92 (0.75-1.12)	35	40	0.88 (0.61-1.22)	.82
AML	68	65	1.04 (0.81-1.32)	20	24	0.83 (0.51-1.29)	.43
Larynx	53	74	0.72 (0.54-0.94)	28	24	1.18 (0.78-1.70)	.10

Abbreviations: ALL, acute myeloid leukemia; CI, confidence interval; CLL, chronic lymphocytic leukemia; EBRT, external-beam radiation therapy; Exp, expected; NHL, non-Hodgkin lymphoma; Obs, observed; SIR, standard incidence ratio.

[a] Boldface indicates those tumor sites with statistically significant group differences.

[b] Second primary malignancies diagnosed within 10 years of the initial prostate cancer diagnosis were not included.

[c] Expected malignancies were estimated from the incidence rate at the tumor sites in the general US population.

[d] Unadjusted SIRs were based on 259,054 (no radiation) and 83,793 (EBRT) person-years at risk.

[e] *P* values were calculated from chi-square goodness of fit tests or Fisher exact tests (Hodgkin lymphoma, gallbladder, male breast) by comparing the cumulative incidence for each specific second primary between patients with prostate cancer patients who received EBRT or no radiation (observed/n).

cancer risk, with a sharp increase in risk restricted to the year immediately after the initial prostate cancer diagnosis (see online Supporting Information).

Exposure to ionizing radiation is a known risk factor for cancer. Our current findings suggest that patients with prostate cancer who receive radiation therapy are at an increased risk of being diagnosed with certain cancers, particularly cancers of the bladder and rectum. The observation of an increase in risk among patients >10 years after their initial prostate cancer diagnosis highlights the need for continued surveillance of these patients. The occurrence of hematuria and hematochezia should be promptly evaluated. Our investigation is largely in agreement with earlier studies, which examined the risk of second primaries associated with receipt of radiation therapy; however, the current study examines the risk of all invasive cancers with a longer follow-up period and examines a greater number of biologically plausible latency intervals. Moon et al observed an increased risk of bladder cancer after EBRT versus brachytherapy.[12] Those authors also observed an increased risk of melanoma and cancers of the rectum, cecum, transverse colon, brain, stomach, and lung and bronchus among men who received EBRT compared with those who did not receive radiation, but they did not observe an increased risk of second malignancy among those who received radioactive implants or isotopes. That study had a 5-year exclusion time and a 10.6-year follow-up period. Brenner et al observed that, compared with surgery, radiotherapy was associated with a small increase in the risk of solid tumors.[13] The most significant increases in risk were for bladder cancer, rectal cancer, and lung cancer, and sarcomas. The exclusion period in that study was 2 months, and patients were followed for 4 years on average. However, Abdel-Wahab et al compared EBRT with brachytherapy and noted no significant increase in the risk of second primaries among

patients who received radiation.[14] Smaller studies have reported on the connection between radiation therapy and the risk of a second primary cancer with mixed results.[15-21] Neugut et al[22] used SEER data to investigate the risk of secondary malignancy after a prostate cancer diagnosis and observed an increased risk of bladder cancer and chronic lymphocytic leukemia, but not of rectal cancer or acute nonlymphocytic leukemia, among men who received radiation. It is noteworthy that the risk of bladder cancer increased with greater time from treatment, ranging from a relative risk (RR) of 1.0 (95% CI, 0.8-1.2) from 6 months to 5 years after treatment, to an RR of 1.3 (95% CI, 1.0-1.7) from 5 to 8 years after treatment, and to an RR of 1.5 (95% CI, 1.0-2.0) >8 years after treatment, similar to our current results. Similarly, Baxter et al[23] studied the effect of radiation on the risk of developing colorectal cancer at 3 different sites: rectum, rectosigmoid/sigmoid/cecum, and the rest of the colon. Similar to the current findings, those authors noted a significantly increased risk of rectal cancer among men who received radiation, with a hazard ratio of 1.7 (95% CI, 1.4-2.2), compared with men who did not receive radiation. There was no increased risk of cancer in the rest of the colon. Those authors excluded patients who had been diagnosed within 5 years of their initial prostate cancer diagnosis, and the patients were under observation for approximately 9 years.

There are many different management options for patients with localized prostate cancer, including radical prostatectomy, radiation therapy (EBRT and/or brachytherapy), and active surveillance. The selection of an approach is based on the physician's assessment of cancer risk and life expectancy as well as patient preferences. Our findings of increased risks of secondary bladder and rectal cancers among men who receive radiation for the management of localized prostate cancer may have an impact on the discussions between providers and their patients. It should be noted, however, that the absolute risk for both of these cancers in this setting is small.

Although we observed that prostate cancer survivors were at a reduced risk for a second primary, black men with prostate cancer tended to have greater risk compared with white men. For example, black men with prostate cancer did not exhibit the same magnitude of risk reduction for lung cancer observed for white men with prostate cancer. For malignancies with higher incidence among men with prostate cancer, the risk among black prostate cancer survivors was even higher, (eg, bladder and kidney). Racial disparities in prostate cancer risk and mortality are established.[24,25] However, to our knowledge, racial differences in the risk of second malignancy have not been reported previously. The etiology of the racial disparity observed in our study is not evident and may reflect differences in genetic susceptibility or environmental exposures, treatment received, or some combination of these factors. Further investigation will be required to understand this additional source of disparity for black men diagnosed with prostate cancer.

Strengths of this study include the use of a large, population-based design, which allows the results to be generalized across the United States. SEER data benefit from well defined data collection and extensive quality standards designed to assure that all eligible cases are captured[5] and that under-ascertainment of second primaries will be low. Potential limitations include the lack of detailed information available on treatment for prostate cancer other than the initial therapy received in the first year after diagnosis and on lifestyle factors and comorbidities other than cancer. In this study, misclassification of the treatment received probably would have been nondifferential and, thus, would have led to an underestimate of the actual risk of second primary malignancies associated with radiation therapy. Finally, the number of statistical tests performed to estimate the risk of a second primary by tumor type does increase the likelihood of observing a significant finding by chance alone, suggesting that these results should be interpreted with some caution.

In summary, the results from this study suggest that, although the risk of developing a secondary primary cancer among men with prostate cancer is lower than that in the general population, prostate cancer survivors remain at risk of certain malignancies, particularly for cancers that are likely to be influenced by radiation treatment for prostate cancer. Significant racial disparities also were detected, suggesting that black men with prostate cancer are more likely to experience second malignancies than their white counterparts. These findings have direct clinical implications and suggest a need for continued cancer surveillance among prostate cancer survivors.

FUNDING SUPPORT

This study was supported by a National Cancer Institute Specialized Programs of Research Excellence (SPORE) in Prostate Cancer grant (P50 CA69568) and NIH HHS Contract HHSN261201300011I (SEER). The Epidemiology Research Core is supported, in part, by NIH Center grant P30 CA022453 to the Karmanos Cancer Institute at Wayne State University.

CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

REFERENCES

1. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2012. *CA Cancer J Clin*. 2012;62:10-29.
2. American Cancer Society. Cancer Facts & Figures 2012. Atlanta, GA: American Cancer Society; 2011.
3. Ries LAG, Melbert D, Krapcho M, et al, eds. SEER Cancer Statistics Review, 1975-2004. Bethesda, MD: National Cancer Institute; 2007. Available at: http://seer.cancer.gov/csr/1975_2004/, based on November 2006 SEER data submission, posted to the SEER web site, 2007.
4. Hankey BF, Ries LA, Edwards BK. The Surveillance, Epidemiology, and End Results Program: a national resource. *Cancer Epidemiol Biomarkers Prev*. 1999;8:1117-1121.
5. Scosyrev E, Messing J, Noyes K, Veazie P, Messing E. Surveillance, Epidemiology, and End Results (SEER) Program and population-based research in urologic oncology: an overview. *Urol Oncol*. 2012; 30:126-132.
6. Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov/seerstat). SEER*Stat Database version 8.0.4: Incidence-SEER 13 registries research data, November 2012 submission (1992-2010) <Katrina/Rita Population Adjustment>-Linked To County Attributes-Total US, 1969-2011 Counties. Bethesda, MD: National Cancer Institute, DCCPS, Surveillance Research Program, Surveillance Systems Branch, 2013. Released April 2013, based on the November 2012 submission.
7. Kleinerman RA, Liebermann JV, Li FP. Second cancer following cancer of the male genital system in Connecticut, 1935-1982. *J Natl Cancer Inst Monogr*. 1985;68:139-147.
8. Osterlind A, Rorth M, Prener A. Second cancer following cancer of the male genital system in Denmark, 1943-1980. *J Natl Cancer Inst Monogr*. 1985;68:341-347.
9. Teppo L, Pukkala E, Saxen E. Multiple cancer—an epidemiologic exercise in Finland. *J Natl Cancer Inst*. 1985;75:207-217.
10. Liskow AS, Neugut AI, Benson M, Olsson CA, Birkhoff J, Chang CH. Multiple primary neoplasms in association with prostate cancer in black and white patients. *Cancer*. 1987;59:380-384.
11. McCredie M, Macfarlane GJ, Stewart J, Coates M. Second primary cancers following cancers of the kidney and prostate in New South Wales (Australia), 1972-1991. *Cancer Causes Control*. 1996;7:337-344.
12. Moon K, Stukenborg GJ, Keim J, Theodorescu D. Cancer incidence after localized therapy for prostate cancer. *Cancer*. 2006;107:991-998.
13. Brenner DJ, Curtis RE, Hall EJ, Ron E. Second malignancies in prostate carcinoma patients after radiotherapy compared with surgery. *Cancer*. 2000;88:398-406.
14. Abdel-Wahab M, Reis IM, Hamilton K. Second primary cancer after radiotherapy for prostate cancer—a SEER analysis of brachytherapy versus external beam radiotherapy. *Int J Rad Oncol Biol Phys*. 2008; 72:58-68.
15. Pawlish KS, Schottenfeld D, Severson R, Montie JE. Risk of multiple primary cancers in prostate cancer patients in the Detroit metropolitan area: a retrospective cohort study. *Prostate*. 1997;33:75-86.
16. Pickles T, Phillips N. The risk of second malignancy in men with prostate cancer treated with or without radiation in British Columbia, 1984-2000. *Radiother Oncol*. 2002;65:145-151.
17. Chrouser K, Leibovich B, Bergstralh E, Zincke H, Blute M. Bladder cancer risk following primary and adjuvant external beam radiation for prostate cancer. *J Urol*. 2005;174:107-110.
18. Liauw SL, Sylvester JE, Morris CG, Blasko JC, Grimm PD. Second malignancies after prostate brachytherapy: incidence of bladder and colorectal cancers in patients with 15 years of potential follow-up. *Int J Radiat Oncol Biol Phys*. 2006;66:6696-6673.
19. Boorjian S, Cowan JE, Konety BR, et al. Bladder cancer incidence and risk factors in men with prostate cancer: results from Cancer of the Prostate Strategic Urologic Research Endeavor. *J Urol*. 2007;177: 883-887.
20. Movsas B, Hanlon AL, Pinover W, Hanks GE. Is there an increased risk of second primaries following prostate irradiation? *Int J Radiat Oncol Biol Phys*. 1998;41:251-255.
21. Margel D, Baniel J, Wasserberg N, Bar-Chana M, Yossepowitch O. Radiation therapy for prostate cancer increases the risk of subsequent rectal cancer. *Ann Surg*. 2011;254:947-950.
22. Neugut AI, Ahsan H, Robinson E, Ennis RD. Bladder carcinoma and other second malignancies after radiotherapy for prostate carcinoma. *Cancer*. 1997;79:1600-1604.
23. Baxter NN, Tepper JE, Durham SB, Rothenberger DA, Virnig BA. Increased risk of rectal cancer after prostate radiation: a population-based study. *Gastroenterology*. 2005;128:819-824.
24. Chornokur G, Dalton K, Borysova ME, Kumar NB. Disparities at presentation, diagnosis, treatment, and survival in African American men, affected by prostate cancer. *Prostate*. 2011;71:985-997.
25. Bock CH, Powell I, Kittles RA, Hsing AW, Carpten J. Racial disparities in prostate cancer incidence, biochemical recurrence, and mortality [serial online]. *Prostate Cancer*. 2011;2011:716178.