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ORIGINAL ARTICLE – CANCER RESEARCH

Risk of second primary cancers in individuals diagnosed with index smoking- and non-smoking- related cancers

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Abstract

Purpose As the number of cancer survivors in the United States increases, quantifying the risks and burden of second primary cancers (SPCs) among cancer survivors will help develop long-term prevention and surveillance strategies. We describe the risk of developing a SPC among survivors of 10 cancer sites with the highest survival rates in the United States.

Methods Adult patients diagnosed with an index smoking-related (urinary bladder, kidney and renal pelvis, uterine cervix, oral cavity and pharynx, and colon and rectum) and index non-smoking-related (prostate, thyroid, breast, corpus and uterus, and non-Hodgkin lymphoma) cancers were identified from Surveillance, Epidemiology, and End Results (2000–2015). SPC risks were quantified using standardized incidence ratios (SIRs) and excess absolute risks (EARs) per 10,000 person-years at risk (PYR).

Results A cohort of 2,903,241 patients was identified and 259,685 (8.9%) developed SPC (7.6% of women and 10.3% of men). All index cancer sites (except prostate) were associated with a significant increase in SPC risk for women and men. Patients diagnosed with smoking-related index cancers (SIR range 1.20–2.16 for women and 1.12–1.91 for men) had a higher increased risk of SPC than patients with non-smoking-related index cancers (SIR range 1.08–1.39 for women and 1.23–1.38 for men) relative to the general population.

Conclusion We found that 1-in-11 cancer survivors developed a SPC. Given the increasing number of cancer survivors and the importance of SPC as a cause of cancer death, there is a need for increased screening for and prevention of SPC.

Keywords Second primary cancer · Malignant neoplasm · Smoking-associated cancers · Cancer survivors · Surveillance Epidemiology and End Results (SEER) program

Introduction

In 2016, there were 15.5 million cancer survivors in the United States and this number will likely exceed 20 million by 2024 (American Cancer Society 2018). Because improvements in cancer treatment have greatly increased survival following a cancer diagnosis (Siegel et al. 2015), there is a

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growing community of cancer survivors with unique medical needs. Cancer survivors already face significant medical, psychosocial and economic challenges, including diagnosis of second primary cancer (SPC), which has been rising in incidence since the 1980s (Alfano and Rowland 2006; Crystal et al. 2009; Ye et al. 2016). SPC account for at least 16% of new cancer diagnoses (Travis 2006). Those diagnosed with SPC's have lower 5-year survival rates compared to primary malignancies (Keegan et al. 2017).

Tobacco use is a leading preventable cause of death in the United States. It is associated with cancers of the urinary bladder, kidney, renal pelvis, uterine cervix, oral cavity and pharynx, colon and rectum and accounts for one-third of cancer-related deaths (Hackshaw et al. 2004). Smoking adversely affects the effectiveness of cancer treatment, such as radiation treatment, and may lead to increased cancer pain (Daniel et al. 2009; Ditre et al. 2011). Although cancer diagnosis may be a life-changing event, a substantial number of patients continue to smoke post-diagnosis (Osazuwa-Peters et al. 2017; Westmaas et al. 2014).

While late toxic effects of chemotherapy and radiation therapy contribute to the increased prevalence of SPC in cancer survivors, other behavioral factors like smoking also contribute to increased risk of SPC (Boffetta and Kaldor 1994). Previous studies from around the world have documented varying degrees of increased risk of SPC in first primary smoking-related cancer survivors (head and neck, bladder cancer) compared to non-smoking-cancer survivors (melanoma, thyroid cancer, lymphoma, leukemia) (Curtis 2006; Feller et al. 2020; Jégu et al. 2014; Youlden and Baade 2011). Studies in the United States have shown that patients with smoking-related cancers, including head and neck, bladder, and lung cancer, are at increased risk of SPC (Adjei Boakye et al. 2018; Khanal et al. 2017; Son et al. 2013).

Although we know that patients with tobacco-related cancers are at a higher risk of SPC than the general population, studies examining the risk and burden of SPC in smoking-related cancers compared to non-smoking-related cancers in the United States are scarce. Knowledge of the risk of SPC among survivors of smoking-related and non-smoking-related cancers can have implications for the pattern and intensity of screening for SPC and the clinical management of survivors of such cancers. We examined ten cancers with the highest survival rates with the variable association to tobacco use and identified risks of SPC and the anatomic sites at increased risk of SPC. Given the increasing number of cancer survivors and the importance of the cause of cancer death, we expect our findings will improve secondary prevention and surveillance guidelines.

Methods

Data source and population

We analyzed 2000–2015 cancer incidence and survival data from 18 population-based cancer registries participating in the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) Program. SEER is a publicly available, nationally representative population-based cancer database which covers approximately 30% of the US population (Surveillance, Epidemiology, and End Results Program 2017) and contains more than 8 million cancer cases (Surveillance, Epidemiology, and End Results Program 2016). It is the premier source of cancer statistics in the United States, covering about 97% of all incident cancers in its registry areas (Zippin et al. 1995). All cancers, primary and subsequent, occurring among residents of geographic registries comprising SEER are reportable, and the program has near-universal follow-up (Harlan and Hankey 2003). Patients were excluded if their cancer was identified by death certificate or autopsy-only, as follow-up information would not be available for these cases. The National Cancer Institute does not require institutional review board approval for use of this de-identified data set.

We identified patients aged ≥ 20 years who were diagnosed with a first primary cancer from the 10 sites with highest survival rates (Jemal et al. 2017) and stratified as either smoking-related (urinary bladder, kidney and renal pelvis, uterine cervix, oral cavity and pharynx, and colon and rectum) or non-smoking related (prostate, thyroid, breast, corpus and uterus, and non-Hodgkin lymphoma) from SEER (2000–2015). Even though lung and pancreatic cancers are caused by smoking, we did not include them in our study because they had very low survival rates. Cancers were defined using the SEER site recode based on the International Classification of Diseases for Oncology third edition (Fritz et al. 2000) primary site and histology codes (eTable 1). Only patients with malignant microscopically confirmed index cancers were included in the analysis.

SPC definition

Definition of SPC was based on established SEER criteria and previous literature (Adjei Boakye et al. 2018, 2019a, b; Curtis et al. 2006; Johnson et al. 2007; Muir and Percy 1991). These rules define multiple primaries as two or more tumors arising in different sites, or at the same site with different histology. An SPC was defined as the first subsequent primary cancer occurring at least 2 months after first cancer diagnosis (Adjei Boakye et al.

2018, 2019a, b; Curtis et al. 2006; Johnson et al. 2007). The person-year at risk (PYR) for each patient began at 2 months of follow-up and ended at the date of SPC diagnosis, last known vital status, death, or the end of the study period of follow-up (December 2015), whichever came first. Extensions, recurrences, metastasis, third and subsequent cancers were not included. Because survivors with distant stage may not survive long enough to develop SPC, we excluded those patients in sensitivity analyses; but the results were similar to the main analyses (eTable 2).

Statistical analysis

The standard "person-year approach" to describe relative and absolute excess risk of developing SPC was used (Breslow and Day 1987; Curtis et al. 2006). This method "person-year approach" compares the number of observed SPCs (Observed) to the number of expected cancers (Expected) if patients with an index cancer had experienced the same cancer rates as the general population. The number of expected cancers in the general population was calculated for a cohort of individuals with identical age, sex, race, and time period to the SPC. The expected number of cancers was estimated by multiplying sex-, age-, race-, and calendar year-specific SEER cancer incidence rates (available at https://seer.cancer.gov) with the accumulated person-years at risk. The standardized incidence ratio (SIR) (Schoenberg and Myers 1977), adapted to cancer registry data (Begg et al. 1995), is a relative measure of the strength of the association between two cancers. SIR was defined as the ratio of observed to expected (Observed/Expected) SPCs. Confidence intervals for SIR were calculated with Byar's approximation to the Poisson distribution (Breslow and Day 1987). SIRs whose 95% confidence interval (CI) excluded the value of 1.0 suggested that the observed number of SPCs were significantly higher than the expected cancers (2-sided $P < 0.05$). The excess absolute risk (EAR) (Curtis et al. 2006) is an absolute measure of the burden of additional cancer occurrences in a given population. EAR was calculated as the excess (Observed–Expected) number of SPCs per 10,000 PYR. SIR and EAR values were calculated in SEER*Stat version 8.3.4 (Surveillance Research Program, National Cancer Institute). Other analyses were performed using SAS version 9.4 statistical software (SAS Institute, Cary, NC) and R version 3.2.2.

Results

Patient population

Of the 2,903,241 patients with a first primary cancer from the 10 sites, 259,685 (8.9% [10.3% for men and 7.6% for women]) developed a SPC (Table 1). Among patients with smoking-related cancers, 84,091 (10.3%) developed SPC compared to 163,073 (8.3%) patients with non-smoking related cancers. Median follow-up time for the entire cohort was 3.8 years, mean age was 63.1 years (SD = 13.6), 49.9% were male, 80.5% were whites, and 58.4% were married.

Risk of SPC

Among men, all index cancer sites except prostate were associated with a significant increase in SPC risk (SIR range for index smoking-related cancers: 1.12–1.91; and for index non-smoking-related cancers: 1.23–1.38), compared to the general population (Fig. 1a). SPC risk was highest among men diagnosed with index oral cavity and pharynx cancer (SIR = 1.91 [95% CI 1.87–1.95] and EAR = 133 per 10,000 PYR) and lowest among men diagnosed with index colon and rectum cancer (SIR = 1.12 [95% CI 1.11–1.14] and EAR = 23 per 10,000 PYR; Figs. 1a and 2a). The SIR of SPC among men with index smoking-related cancers was 1.47 (95% CI 1.46–1.48, corresponding to an EAR of 90 cases per 10,000 PYR). This was higher than men with index non-smoking-related cancers (SIR = 1.35; 95% CI 1.33–1.37, corresponding to EAR = 50 cases per 10,000 PYR) [Table 2 (SIR > 1 and EAR ≥ 0.5 per 10,000 PYR) and eTable3 (all sites with SIR > 1)].

Similarly, among women, all index cancer sites were associated with a significant increase in SPC risk (SIR range for index smoking-related cancers: 1.20 – 2.16; and for index non-smoking-related cancers: 1.08–1.39) relative to the general population (Fig. 1b). SPC risk was highest among women diagnosed with index oral cavity and pharynx cancer (SIR = 2.16 [95% CI 2.09–2.24] and EAR = 130 per 10,000 PYR) and lowest among women diagnosed with index corpus and uterus, NOS cancer (SIR = 1.08 [95% CI 1.06–1.10] and EAR = 9 per 10,000 PYR; Figs. 1b and 2b). The SIR of SPC among women with index smoking-related cancers was 1.47 (95% CI: 1.46–1.49, corresponding to an EAR of 60 cases per 10,000 PYR). This was higher than women with index non-smoking-related cancers (SIR = 1.17; 95% CI 1.16–1.18, corresponding to EAR = 19 cases per 10,000 PYR) [Table 2 (SIR > 1 and EAR ≥ 0.5 per 10,000 PYR) and eTable3 (all sites with SIR > 1)].

Anatomic sites at increased risk of SPC

Among men diagnosed with index smoking-related cancers, the highest SIR of SPC was observed for other smoking-related cancers: second cancers of the head and neck (gum and other mouth, floor of mouth, tongue, and hypopharynx), small intestine, thyroid, kidney and lung and bronchus (Table 2). The excess burden of disease, as measured by EAR in number of excess cases per 10,000 PYR, was highest

Table 1 Patient and tumor characteristics of the study cohort, overall and stratified by sex, SEER 2000–2015

	Frequency (Percentage)				
	All patients ($n=2,903,241$)	Men		Women	
		Index malignancy ($n=1,544,486$)	SPC ($n=161,507$)	Index malignancy ($n=1,565,621$)	SPC ($n=121,622$)
Second primary cancer					
No	2,643,556 (91.1)				
Yes	259,685 (8.9)				
Sex					
Women	1,456,069 (50.1)				
Men	1,447,172 (49.9)				
Age at diagnosis of index malignancy, years					
< 55	756,672 (26.1)	236,893 (18.3)	14,575 (9.8)	477,804 (35.5)	27,400 (24.8)
55–64	770,532 (26.5)	383,457 (29.5)	39,057 (26.2)	320,389 (23.8)	27,629 (25.0)
65 +	1,376,037 (47.4)	677,610 (52.2)	95,580 (64.1)	547,403 (40.7)	55,444 (50.2)
Race					
White	2,337,799 (80.5)	1,038,575 (80.0)	125,953 (84.4)	1,081,533 (80.4)	91,738 (83.0)
Black	326,339 (11.3)	156,664 (12.1)	16,204 (10.9)	142,109 (10.6)	11,382 (10.3)
Other[a]	239,103 (8.2)	102,741 (7.9)	7,055 (4.7)	121,954 (9.1)	7,353 (6.7)
Marital status at diagnosis of index malignancy					
Married	1,694,261 (58.4)	839,820 (64.7)	102,294 (68.5)	695,523 (51.7)	56,624 (51.3)
Divorced/separated/widowed	603,253 (20.8)	173,205 (13.3)	20,617 (13.8)	374,896 (27.9)	34,535 (31.3)
Never married	387,446 (13.3)	157,019 (12.1)	14,101 (9.5)	202,457 (15.1)	13,869 (12.6)
Unknown	218,281 (7.5)	127,916 (9.9)	12,200 (8.2)	72,720 (5.4)	5,445 (4.9)
Year of diagnosis of index malignancy					
2000–2004	876,706 (30.2)	375,139 (28.9)	69,651 (46.7)	379,447 (28.2)	52,469 (47.5)
2005–2009	927,190 (31.9)	419,851 (32.3)	52,860 (35.4)	415,947 (30.9)	38,532 (34.5)
2010 +	1,099,345 (37.9)	502,970 (38.8)	26,701 (17.9)	550,202 (40.9)	19,472 (17.6)
Grade of index malignancy					
Well	348,829 (12.0)	84,484 (6.5)	9,489 (6.4)	234,453 (17.4)	20,403 (18.5)
Moderate	1,117,923 (38.5)	547,155 (42.2)	66,974 (44.9)	463,010 (34.4)	40,784 (36.9)
Poor	753,315 (26.0)	383,723 (29.6)	39,993 (26.8)	305,645 (22.7)	23,954 (21.7)
Undifferentiated/unknown	683,174 (23.5)	282,598 (21.8)	32,756 (22.0)	342,488 (25.5)	25,332 (22.9)
Stage of index malignancy					
Localized	1,722,093 (59.3)	800,825 (61.7)	96,605 (64.7)	757,258 (56.3)	67,405 (61.0)
Regional	680,009 (23.4)	236,911 (18.3)	24,886 (16.7)	387,723 (28.8)	30,489 (27.6)
Distant	307,655 (10.6)	151,844 (11.7)	9,349 (6.3)	139,928 (10.4)	6,534 (5.9)
Unknown/unstaged	193,484 (6.7)	108,380 (8.4)	18,372 (12.3)	60,687 (4.5)	6,045 (5.5)
Index cancer site					
Prostate	782,520 (27.0)	710,654 (54.8)	71,866 (48.2)	NA	NA
Female Breast	724,149 (24.9)	NA	NA	667,424 (49.6)	56,725 (51.4)
Colon and rectum	435,574 (15.0)	202,616 (15.6)	21,375 (14.3)	195,758 (14.6)	15,825 (14.3)
Non-Hodgkin lymphoma	188,432 (6.5)	91,290 (7.0)	10,011 (6.7)	79,892 (5.9)	7,239 (6.6)
Urinary bladder	187,951 (6.5)	116,410 (9.0)	25,211 (16.9)	41,047 (3.1)	5,283 (48)
Corpus and uterus, NOS	149,717 (5.2)	NA	NA	139,586 (10.4)	10,131 (9.2)
Kidney and renal pelvis	141,154 (4.9)	78,224 (6.0)	9,461 (6.3	49,021 (3.6)	4,448 (4.0)
Thyroid	132,017 (4.6)	28,062 (2.2)	2,211 (1.5)	96,854 (7.2)	4,890 (4.4)
Oral cavity and pharynx	112,689 (3.9)	70, 704 (5.5)	9,077 (6.1)	29,464 (2.2)	3,444 (3.1)
Uterine cervix	49,038 (1.7)	NA	NA	46,550 (3.5)	2,488 (2.3)

SEER surveillance, epidemiology, and end results, *SPC* second primary cancer

[a]Includes American Indian/AK Native, Asian/Pacific Islander, Unknown

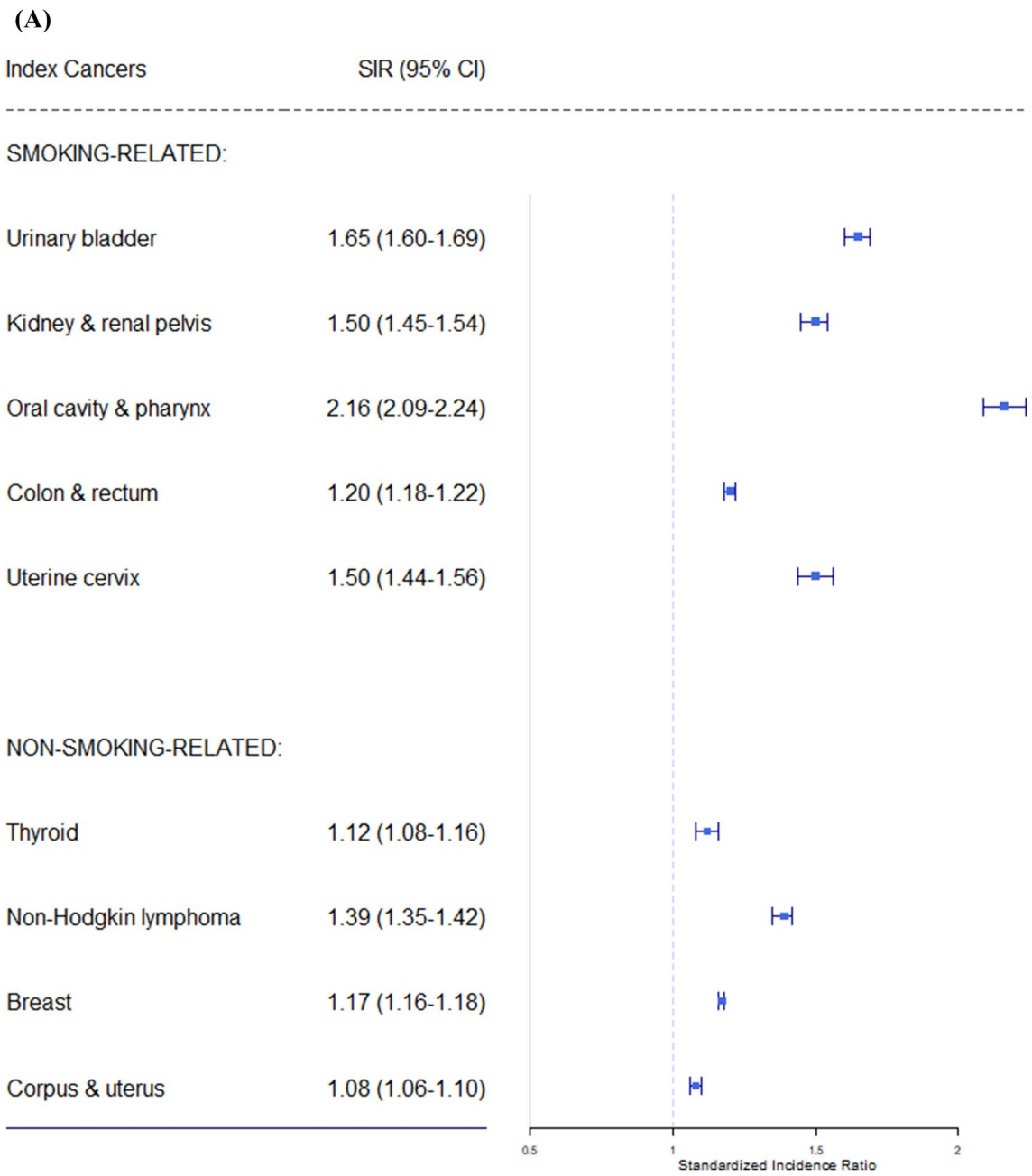

Fig. 1 Standardized incidence ratio (SIR) of second primary malignant neoplasm[#] among cancer survivors, by anatomic site of each index cancer: **a** men, and **b** women, SEER 2000–2015. [#]Excludes non-melanoma skin; *SEER* Surveillance, Epidemiology, and End Results

for lung and bronchus (24.9), followed by urinary bladder (16.6), prostate (14.4), and colon and rectum (9.0). Among men diagnosed with index non-smoking-related cancers, the highest SIR and EAR were observed for second cancers of the non-Hodgkin lymphoma, acute myeloid leukemia, thyroid, Kaposi sarcoma and salivary gland.

Among women diagnosed with index smoking-related cancers, the highest SIR of SPC was observed for other smoking-related cancers: second cancers of the head and neck, vaginal, urinary bladder and lung and bronchus (Table 2). The excess burden of disease, as measured by EAR in the number of excess cases per 10,000 PYR, was highest for lung and bronchus (26.7), followed by colon and rectum (8.9), and urinary bladder (7.7). Among women diagnosed with index non-smoking-related cancers, the highest SIR and EAR were observed for second cancers of the

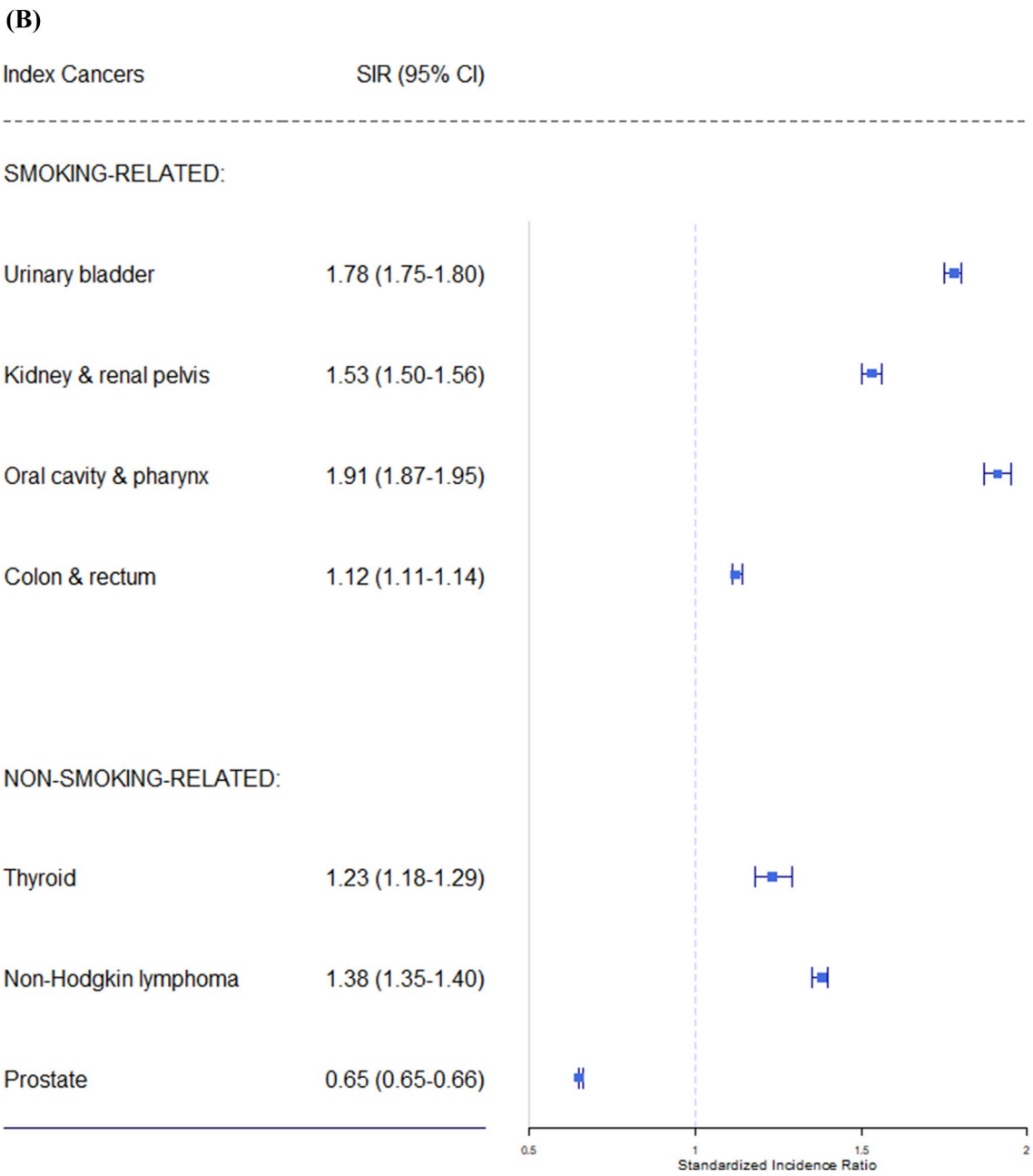

Fig. 1 (continued)

non-Hodgkin lymphoma, acute myeloid leukemia, thyroid, and breast.

Subsites at increased risk for SPC (SIR > 1 and EAR ≥ 0.5 per 10,000 PYR) by each index cancer for both genders are presented in Tables 3 and 4. For patients diagnosed with index smoking-related cancers, the second cancers they developed were mainly other smoking-related, especially for men. Detailed information on the location of common SPCs by each index cancer and stratified by sex is provided in eTables 4 and 5.

Discussion

Cancer survivors are at long-term increased risk for SPCs compared to the general population as a result of genetic predisposition, chemoradiotherapy, human papillomavirus (HPV), environment, and lifestyle choices. In this population-based cohort study, we report risk of SPC among survivors of the top 10 cancers with the highest survival rates in the United States. We found that approximately 9% of survivors in our study were diagnosed with SPC (10.3% in patients with smoking-related and 8.3% in

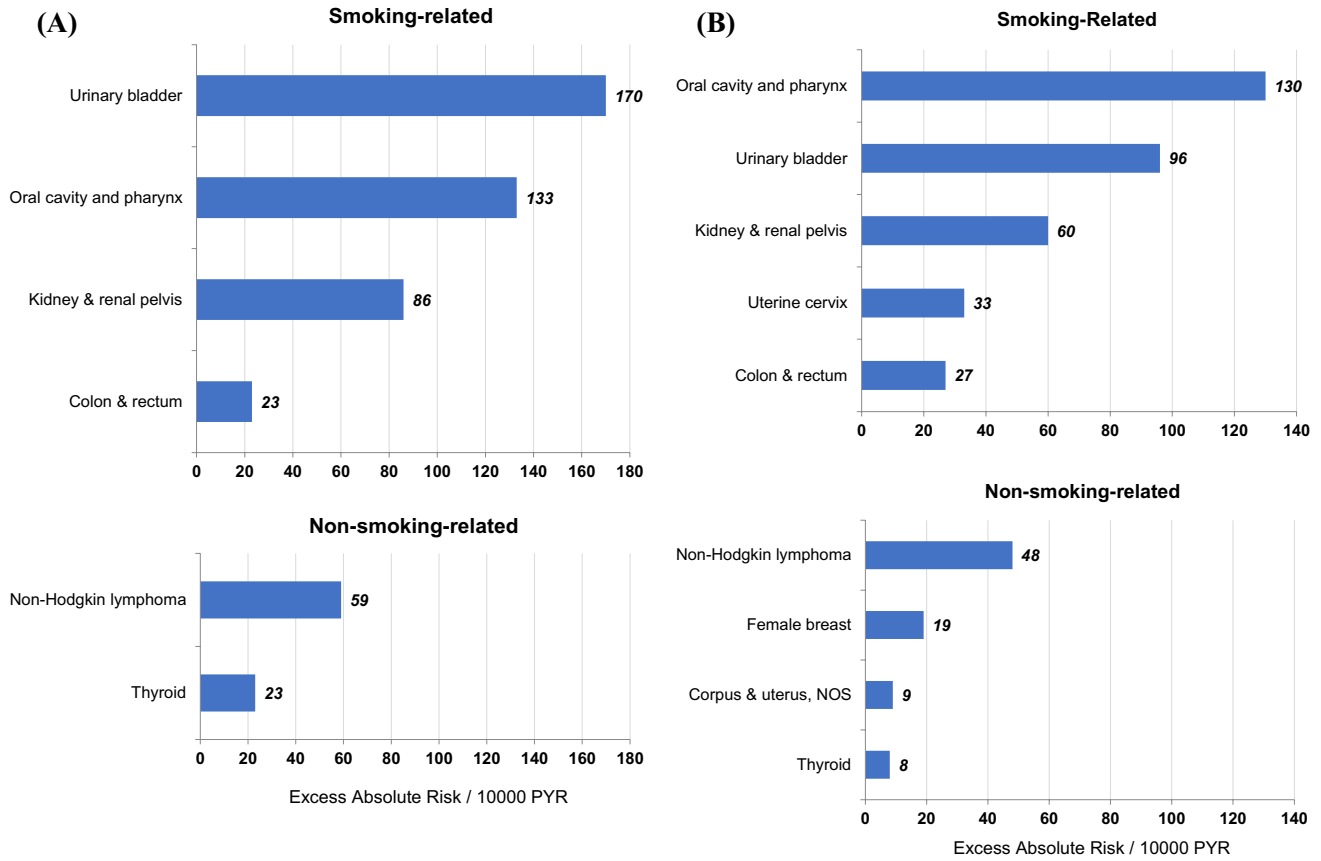

Fig. 2 Title: Excess absolute risk (EAR) of second primary cancer[#] among cancer survivors, by anatomic site of each index cancer*: **a** men, and **b** women, SEER 2000–2015. Excess absolute risk is per 10,000 person-year at risk; [#]Excludes Non-Melanoma Skin; *Prostate cancer is not displayed because it did not have a significant SPC risk *SEER* surveillance, epidemiology, and end results

non-smoking-related index cancers). Patients diagnosed with both index smoking-related and non-smoking-related cancers, except for prostate, had increased risk of SPC. Our finding is consistent with studies performed in France, Australia, Japan and Switzerland showing an increased risk of SPC for primary cancer survivors (Feller et al. 2020; Jégu et al. 2014; Tabuchi et al. 2012; Youlden and Baade 2011).

Similar to previous research, we did not see an increased risk of SPC among patients diagnosed with index prostate cancers overall (Davis et al. 2014; Siegel et al. 2015). The secondary cancers that patients diagnosed with index prostate cancers in our study developed were kidney and bladder, which have been documented to have association with radiation exposure from treatment and increased regional screening (Davis et al. 2014). While studies in the US have not documented an increased risk of SPC from prostate cancer, research in Sweden from 2001 to 2010 did show an increased overall risk for SPC (Chattopadhyay et al. 2018). In their study, Chattopadhyay et al. reported that prostate cancer survivors were at greater risk for colon, skin, bladder, thyroid, lung cancer and non-Hodgkin lymphoma secondary cancers (Chattopadhyay et al. 2018). In the United States, prostate cancer is the most common cancer in men (excluding skin cancer), with incidence skyrocketing since regular screening for prostate-specific antigen (PSA) starting in the 1990′s (Siegel et al. 2015). The reason prostate cancer is not associated with an increased overall risk of SPC in the US remains elusive, though it is possible that patients with subclinical low-grade prostate cancer diagnosed by PSA testing are not conferred a higher risk of SPC compared to those who have a more malignant course of the disease. The average age of diagnosis for prostate cancer is over 65, where men may also have competing cause of mortality including cardiovascular disease and respiratory illness, leaving a shorter time frame to develop SPC (Siegel et al. 2015). Future research examining SPC risk in prostate cancer should stratify by PSA diagnosed prostate cancer and by clinical stage.

To our knowledge, this is the first time the risk of SPC has been stratified by smoking relatedness across multiple index cancer sites in the United States. As expected, most of the second cancers that patients with index smoking-related cancers developed were also smoking-related, especially along the aerodigestive tract. Other studies examining SPCs have

Table 2 Anatomic sites at elevated risks of SPC according to the site of index cancer, SEER 2000–2015

Site of index cancer	Site of SPC	Observed SPC	SIR 95% CI	EAR per 10,000 PYR
Men				
Index smoking-related cancers				
	All sites excluding non-melanoma skin	64,824	1.47 (1.46, 1.49)	88.62
	Prostate	16,936	1.38 (1.36, 1.40)	19.87
	Urinary bladder	7863	2.20 (2.15, 2.24)	18.19
	Lung and bronchus	10,306	1.54 (1.51, 1.57)	15.29
	Colon and rectum	6638	1.56 (1.52, 1.60)	10.12
	Kidney and renal pelvis	3599	2.20 (2.13, 2.27)	8.34
	Tongue	1021	2.77 (2.61, 2.95)	2.77
	Thyroid	737	2.21 (2.06, 2.38)	1.72
	Esophagus	1066	1.59 (1.50, 1.69)	1.68
	Ureter	471	5.75 (5.24, 6.3)	1.65
	Small intestine	507	2.46 (2.25, 2.68)	1.28
	Pharynx	426	2.25 (2.04, 2.48)	1.01
	Larynx	671	1.36 (1.26, 1.47)	0.76
	Pancreas	1433	1.12 (1.06, 1.18)	0.65
	Floor of mouth	210	3.39 (2.95, 3.88)	0.63
	Liver	1015	1.17 (1.10, 1.24)	0.62
	Tonsil	344	1.72 (1.54, 1.91)	0.61
	Hypopharynx	230	2.53 (2.21, 2.87)	0.59
	Stomach	1012	1.16 (1.09, 1.23)	0.59
Index non-smoking-related cancers[a]				
	All sites excluding non-melanoma skin	12,699	1.35 (1.33, 1.37)	50.29
	Non-hodgkin lymphoma	1688	4.07 (3.87, 4.26)	19.46
	Acute myeloid leukemia	410	4.93 (4.46, 5.43)	5.00
	Lung and bronchus	1607	1.16 (1.11, 1.22)	3.46
	Kidney and renal pelvis	584	1.59 (1.46, 1.72)	3.30
	Thyroid	302	3.50 (3.12, 3.92)	3.30
	Prostate	2755	1.05 (1.01, 1.09)	1.87
	Stomach	238	1.31 (1.15, 1.48)	0.86
	Kaposi sarcoma	59	6.25 (4.75, 8.06)	0.76
	Salivary gland	72	2.37 (1.85, 2.98)	0.64
	Liver	238	1.19 (1.04, 1.35)	0.57
Women				
Index smoking-related cancers				
	All sites excluding non-melanoma skin	31,380	1.39 (1.38, 1.41)	48.36
	Colon and rectum	4467	1.77 (1.72, 1.82)	10.65
	Lung and bronchus	5249	1.52 (1.48, 1.57)	9.89
	Urinary bladder	2254	3.46 (3.31, 3.6)	8.78
	Kidney and renal pelvis	1466	2.51 (2.38, 2.64)	4.83
	Thyroid	940	1.95 (1.82, 2.07)	2.50
	Tongue	441	4.50 (4.09, 4.94)	1.88
	Corpus uteri	1434	1.18 (1.12, 1.24)	1.17
	Small intestine	318	2.89 (2.58, 3.23)	1.14
	Vagina	187	4.17 (3.6, 4.82)	0.78
	Ureter	162	5.36 (4.57, 6.25)	0.72
	Stomach	466	1.36 (1.24, 1.49)	0.67
	Floor of mouth	133	6.76 (5.66, 8.01)	0.62

Table 2 (continued)

Site of index cancer	Site of SPC	Observed SPC	SIR 95% CI	EAR per 10,000 PYR
	Cervix uteri	320	1.47 (1.32, 1.64)	0.56
Index non-smoking-related cancers				
	All sites excluding non-melanoma skin	78,643	1.17 (1.16, 1.18)	18.97
	Female breast	26,090	1.33 (1.32, 1.35)	10.68
	Thyroid	2852	1.62 (1.56, 1.68)	1.78
	Non-Hodgkin lymphoma	3825	1.35 (1.31, 1.39)	1.63
	Acute myeloid leukemia	1277	2.46 (2.33, 2.60)	1.25
	Kidney and renal pelvis	2306	1.30 (1.25, 1.36)	0.88
	Ovary	2271	1.17 (1.12, 1.22)	0.54
	Colon and rectum	7065	1.05 (1.02, 1.07)	0.51
	Lung and bronchus	10,153	1.03 (1.01, 1.05)	0.51

Only SPCs with statistically significant risk and EAR ≥ 0.5 are shown

SPC second primary cancer, *SEER* surveillance, epidemiology, and end results, *SIR* Standardized incidence ratio, *EAR* excess absolute risk, *PYR* person-year at risk; *CI* confidence interval

[a]Excludes prostate since it didn't have an increased risk of developing SPC

also shown that survivors of head and neck cancer (HNC) and cervical cancer are at higher risk for secondary HNC as well as aerodigestive tract malignant neoplasms (Adjei Boakye et al. 2018; Gan et al. 2013; Teng et al. 2015). Research in France, Switzerland and Australia has shown similarly higher increased risk for SPC with smoking-related primary cancers (Feller et al. 2020; Jégu et al. 2014; Youlden and Baade 2011).

Current care in cancer survivorship often focuses on modifiable risk factors such as tobacco use to improve long-term quality of life and reduce SPC risk (Kaul et al. 2017). Despite the known risks of tobacco use and recommendations encouraging smoking abstinence (National Comprehensive Cancer Network 2017), many cancer patients continue to smoke after diagnosis (Osazuwa-Peters et al. 2017; Westmaas et al. 2014). Multiple clinical studies have indicated that with an integrated approach and dedicated clinical efforts towards tobacco cessation, cancer survivors are more successful at quitting tobacco use (de Moor et al. 2008; Ostroff et al. 2014). In light of current research in the field demonstrating the short-term and long-term harmful effects of tobacco, healthcare providers, should actively discuss smoking cessation programs with their patients if they have a history of smoking. In addition, studies have reported that HPV has an association with risk of SPCs among survivors of HPV-associated cancers (Suk et al. 2018; Wang et al. 2020). Previous research suggests a joint effect of tobacco carcinogens leading to DNA damage and decreased immune clearance of HPV causing malignancy (Poppe et al. 1996; Prokopczyk et al. 1997). New guidelines in the United States by the Centers for Disease Control Advisory Committee on Immunization Practices now suggest catch-up vaccination for persons up to age 45 as the vaccine still demonstrates efficacy in protecting people from further HPV infection.

In our study, men diagnosed with non-smoking-related cancers were at increased risk for non-Hodgkin lymphoma, acute myeloid leukemia, Kaposi sarcoma and salivary gland cancer, while women were at increased risk for non-Hodgkin lymphoma, acute myeloid leukemia, thyroid, and breast. Our data parallels previous research on SPC which showed cancer survivors were at increased risk for breast, non-Hodgkin lymphoma, leukemia and thyroid cancer (Donin et al. 2016; Mariotto et al. 2007). Cancer survivors may be at greater risk for acute myeloid leukemia, non-Hodgkin lymphoma, and breast cancers as a result of cancer treatment (Iglesias et al. 2017; Kim et al. 2013; Knight et al. 2009; Mattsson et al. 1997; Tubiana 2009). While cancer treatment has previously been associated in the literature with some SPCs we observed in our results, Kaposi sarcoma is not commonly known to be associated with chemoradiotherapy. Since we did not exclude human immunodeficiency virus (HIV) patients in our study, we cannot ignore that HIV status alone may have contributed to the increased risk of secondary Kaposi sarcoma in men diagnosed with index non-smoking-related cancers. However, it is also possible that cancer survivors are at higher risk for long term immunosuppression secondary to therapy, contributing to the higher risk for Kaposi sarcoma (Jakob et al. 2011). Further investigation is needed to confirm this association. Additional examination is also warranted to evaluate the risk of SPCs after various treatment modalities.

In our study, we compared the risk of developing an SPC to the general population. We acknowledge though that cancer survivors may have at baseline a genetic predisposition

Table 3 Anatomic sites at increased risk of SPC[#] according to the site of index cancer, Men, SEER 2000–2015

Site of index cancer	Site of SPC	Observed SPC	SIR 95% CI	EAR per 10,000 PYR
Smoking-related				
Colorectal				
	Small intestine	335	3.76 (3.37, 4.18)	2.45
	Lung and bronchus	3143	1.08 (1.04, 1.12)	2.30
	Kidney and renal pelvis	852	1.22 (1.14, 1.30)	1.53
	Thyroid	267	1.91 (1.69, 2.15)	1.27
	Esophagus	343	1.20 (1.07, 1.33)	0.56
Oral cavity and pharynx				
	Lung and bronchus	2216	3.29 (3.16, 3.43)	47.61
	Esophagus	349	4.75 (4.27, 5.28)	8.50
	Larynx	214	3.82 (3.32, 4.36)	4.87
	Thyroid	151	3.36 (2.84, 3.94)	3.27
	Colon and rectum	506	1.15 (1.05, 1.25)	1.99
	Liver	164	1.51 (1.29, 1.76)	1.70
	Kidney and renal pelvis	233	1.23 (1.08, 1.40)	1.34
	Non-Hodgkin lymphoma	243	1.21 (1.06, 1.37)	1.28
	Acute myeloid leukemia	69	1.77 (1.38, 2.24)	0.93
	Pancreas	161	1.23 (1.05, 1.43)	0.92
	Stomach	115	1.30 (1.08, 1.57)	0.83
	Soft tissue including heart	52	1.85 (1.38, 2.43)	0.74
Kidney and renal pelvis				
	Prostate	2549	1.43 (1.37, 1.48)	20.02
	Urinary bladder	1164	2.54 (2.39, 2.69)	18.55
	Thyroid	193	3.62 (3.12, 4.16)	3.67
	Lung and bronchus	1028	1.13 (1.06, 1.20)	3.17
	Liver	214	1.61 (1.40, 1.84)	2.13
	Non-Hodgkin lymphoma	307	1.17 (1.04, 1.31)	1.18
	Pancreas	209	1.20 (1.04, 1.37)	0.90
Urinary bladder				
	Prostate	7929	2.12 (2.07, 2.17)	64.81
	Lung and bronchus	3919	1.77 (1.71, 1.83)	26.36
	Kidney and renal pelvis	1091	2.15 (2.03, 2.29)	9.05
	Pancreas	493	1.17 (1.07, 1.28)	1.10
	Liver	308	1.25 (1.11, 1.39)	0.95
	Esophagus	270	1.25 (1.11, 1.41)	0.84
	Stomach	331	1.18 (1.06, 1.31)	0.78
	Larynx	189	1.25 (1.08, 1.44)	0.58
	Small intestine	97	1.50 (1.21, 1.82)	0.50
Non-smoking-related				
Prostate				
	Urinary bladder	9417	1.09 (1.07, 1.11)	1.55
	Kidney and renal pelvis	4596	1.14 (1.11, 1.17)	1.15
Thyroid				
	Prostate	553	1.33 (1.22, 1.44)	9.67
	Kidney and renal pelvis	115	2.09 (1.72, 2.51)	4.26
	Non-Hodgkin lymphoma	92	1.45 (1.17, 1.78)	2.02
	Melanoma of the skin	96	1.28 (1.03, 1.56)	1.47
	Soft tissue including heart	23	2.56 (1.63, 3.85)	1.00
	Acute myeloid leukemia	22	1.88 (1.18, 2.85)	0.73

Table 3 (continued)

Site of index cancer	Site of SPC	Observed SPC	SIR 95% CI	EAR per 10,000 PYR
Non-Hodgkin lymphoma				
	Acute myeloid leukemia	376	5.85 (5.28, 6.47)	6.81
	Lung and bronchus	1315	1.23 (1.16, 1.29)	5.31
	Thyroid	203	3.30 (2.86, 3.78)	3.09
	Hodgkin lymphoma	153	8.08 (6.85, 9.46)	2.93
	Kidney and renal pelvis	392	1.42 (1.28, 1.57)	2.52
	Melanoma of the skin	504	1.26 (1.15, 1.37)	2.25
	Stomach	191	1.37 (1.18, 1.57)	1.12
	Liver	198	1.34 (1.16, 1.53)	1.09
	Kaposi sarcoma	56	8.26 (6.24, 10.72)	1.08
	Salivary gland	56	2.38 (1.80, 3.09)	0.71

Only SPCs with statistically significant risk and EAR ≥ 0.5 are shown

SPC second primary cancer, *SEER* surveillance, epidemiology, and end results, *SIR* Standardized incidence ratio, *EAR* excess absolute risk, *PYR* person-year at risk; *CI* confidence interval

that increases their risk for primary and secondary neoplasms. In the last two decades, human understanding of genetics has evolved at an unprecedented rate. In 2004, 291 cancer genes were reported with over 20% of genes were germline mutations (Futreal et al. 2004). Recent genome-wide studies have found genetic associations that predispose subgroups of cancer survivors to various secondary malignancies (Knight et al. 2009; Morton et al. 2018). We should emphasize that because the SEER database does not include specific information on genetics, we can only speculate on the connection between the risk of SPC and genetics in our cohort. As research continues to expand our understanding of the contributions of genetics for SPCs, we expect more personalized cancer survivorship care, including surveillance.

Limitations and strengths

The findings presented should be interpreted in the context of study limitations. First is our inability to assess lifestyle factors such as tobacco or alcohol use, diet and HPV through the SEER database. It is likely that the subsite-specific differences in SPC risk are attributable to differences in these lifestyle factors. Second, SPCs may be underestimated since SPCs diagnosed among patients who migrate out of their SEER registry area are not reportable. This would affect the estimation of absolute risk, but probably not relative risk if migration among patients in the numerator and the denominator is similar. Third, although histological diagnosis of cancer and medical coding have improved, there is a chance SPCs could be a recurrence or metastasis or vice versa which could lead to overestimation of SPCs. The fourth limitation is the 2-month delay used to define SPC. To address our use of a 2-month delay to define a SPC, we conducted a sensitivity analysis using a longer time interval of 6 months and received similar results. Our decision to choose a 2-month delay is based on established conventions analyzing SPC (Adjei Boakye et al. 2018; Adjei Boakye et al. 2019a; Adjei Boakye et al. 2019b; Curtis et al. 2006; Johnson et al. 2007). Despite our limitations, SPC risks were based on a large SEER reference cohort, maximizing the internal validity and applicability of our results. In addition, the SEER registry data usually have high completeness, high-quality control, with nearly complete follow-up, and are representative of the entire patient population.

Conclusion

SPCs in cancer survivors pose a significant risk to the quality of life and obstacle to prognosis. In this population-based cohort study, one-in-11 cancer survivors developed a SPC. All index cancer sites (except prostate) had an increased risk of developing SPC. Patients diagnosed with index smoking-related cancers developed SPCs that were also smoking-related. As the population of cancer survivors continues to grow, vigilant monitoring and screening tailored to survivors of both smoking-related and non-smoking-related cancers are crucial to decrease the mortality, morbidity, and improve their quality of life among these survivors. Given the complexity of cancer etiology and cancer care, more research is needed to determine the factors that put these survivors at such high risks for certain SPCs.

Table 4 Anatomic sites at increased risks of SPC according to the site of index cancer, Women, SEER 2000–2015

Site of index cancer	Site of SPC	Observed SPC	SIR 95% CI	EAR per 10,000 PYR
Smoking-related				
Colorectal				
	Lung and bronchus	2318	1.13 (1.09, 1.18)	2.77
	Corpus uteri	913	1.34 (1.25, 1.43)	2.38
	Small intestine	245	3.79 (3.33, 4.30)	1.87
	Thyroid	419	1.72 (1.56, 1.89)	1.81
	Kidney and renal pelvis	465	1.37 (1.25, 1.50)	1.29
	Stomach	289	1.37 (1.22, 1.54)	0.81
Oral cavity and pharynx				
	Lung and bronchus	750	3.20 (2.97, 3.43)	36.39
	Esophagus	93	11.20 (9.04, 13.72)	5.98
	Thyroid	103	2.61 (2.13, 3.16)	4.48
	Larynx	44	9.20 (6.69, 12.36)	2.77
	Urinary bladder	66	1.55 (1.20, 1.97)	1.64
	Non-hodgkin lymphoma	89	1.31 (1.05, 1.61)	1.47
	Stomach	38	1.71 (1.21, 2.35)	1.12
	Bones and joints	17	11.05 (6.43, 17.69)	1.09
	Liver	30	1.99 (1.35, 2.85)	1.06
	Vulva	22	2.15 (1.35, 3.25)	0.83
Kidney and Renal Pelvis				
	Urinary bladder	470	5.83 (5.32, 6.39)	15.85
	Thyroid	240	3.45 (3.02, 3.91)	6.93
	Lung and bronchus	582	1.29 (3.18, 1.40)	5.28
	Pancreas	135	1.36 (1.14, 1.60)	1.44
	Non-hodgkin lymphoma	158	1.24 (1.06, 1.45)	1.26
	Brain	47	1.67 (1.23, 2.22)	0.77
	Small intestine	29	1.97 (1.32, 2.83)	0.58
Urinary Bladder				
	Lung and bronchus	1122	2.18 (2.05, 2.31)	28.07
	Kidney and renal pelvis	295	3.58 (3.18, 4.01)	9.84
	Vagina	21	3.29 (2.04, 5.03)	0.68
Cervical				
	Lung and bronchus	477	2.49 (2.27, 2.73)	11.25
	Vagina	122	41.46 (34.43, 49.50)	4.69
	Urinary bladder	101	3.23 (2.63, 3.93)	2.75
	Colon and rectum	199	1.36 (1.17, 1.56)	2.05
	Thyroid	116	1.53 (1.26, 1.83)	1.58
	Vulva	45	4.82 (3.52, 6.45)	1.40
	Kidney and renal pelvis	77	1.79 (1.42, 2.24)	1.34
	Ovary	76	1.52 (1.20, 1.91)	1.03
	Acute myeloid leukemia	33	2.88 (1.98, 4.04)	0.85
	Soft tissue including heart	28	2.83 (1.88, 4.09)	0.71
	Stomach	35	1.65 (1.15, 2.30)	0.54
Non-smoking-related				
Breast				
	Thyroid	1871	1.52 (1.45, 1.59)	1.50
	Acute myeloid leukemia	860	2.30 (2.14, 2.45)	1.14
	Corpus uteri	3373	1.15 (1.12, 1.19)	1.06
	Lung and bronchus	7417	1.04 (1.01, 1.06)	0.64

Table 4 (continued)

Site of index cancer	Site of SPC	Observed SPC	SIR 95% CI	EAR per 10,000 PYR
	Melanoma of the skin	1,916	1.13 (1.08, 1.18)	0.51
Endometria (corpus and uterus)				
	Colon and rectum	1266	1.37 (1.30, 1.56)	4.36
	Female breast	3016	1.10 (1.06, 1.14)	3.46
	Thyroid	383	1.64 (1.48, 1.82)	1.89
	Vagina	160	9.11 (7.75, 10.63)	1.8
	Ovary	412	1.52 (1.38, 1.68)	1.79
	Kidney and renal pelvis	383	1.53 (1.38, 1.69)	1.68
	Urinary bladder	303	1.24 (1.11, 1.39)	0.75
	Acute myeloid leukemia	124	1.73 (1.44, 2.06)	0.66
	Soft tissue including heart	99	2.02 (1.64, 2.46)	0.63
Thyroid				
	Female breast	1246	1.12 (1.06, 1.19)	2.78
	Kidney and renal pelvis	161	2.04 (1.74, 2.38)	1.65
	Non-hodgkin lymphoma	162	1.25 (1.07, 1.46)	0.66
	Salivary gland	37	4.86 (3.42, 6.69)	0.59
	Melanoma of the skin	167	1.20 (1.03, 1.40)	0.56
Non-Hodgkin lymphoma				
	Lung and bronchus	1039	1.29 (1.22, 1.38)	5.62
	Acute myeloid leukemia	234	5.51 (4.83, 6.26)	4.56
	Thyroid	301	2.63 (2.35, 2.95)	4.44
	Hodgkin lymphoma	104	8.78 (7.18, 10.64)	2.19
	Kidney and renal pelvis	223	1.65 (1.44, 1.88)	2.09
	Melanoma of the skin	230	1.27 (1.11, 1.45)	1.16
	Stomach	108	1.47 (1.21, 1.78)	0.83
	Urinary bladder	176	1.18 (1.01, 1.37)	0.65

Only SPCs with statistically significant risk and EAR $\geq$ 0.5 are shown

SPC second primary cancer, *SEER* surveillance, epidemiology, and end results, *SIR* Standardized incidence ratio, *EAR* excess absolute risk, *PYR* person-year at risk; *CI* confidence interval

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