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## Cervical cancer survivors at increased risk of subsequent tobacco-related malignancies, United States 1992–2008

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### Abstract

**Purpose**—Persistent smoking among cancer survivors may increase their risk of subsequent malignancies, including tobacco-related malignancies. Despite these risks, nearly 40 % of women diagnosed with cervical cancer continue to smoke after diagnosis. This study describes the relative risk of developing any subsequent and tobacco-related malignancy among cervical cancer survivors.

**Methods**—We examined data from the year 1992 to 2008 in 13 Surveillance, Epidemiology and End Results registries. We calculated the standardized incidence ratio (SIR) and 95 % confidence limits (CLs) for all subsequent and tobacco-related malignancies among cervical cancer survivors. Tobacco-related malignancies were defined according to the 2004 *Surgeon General's Report on the Health Consequences of Smoking*. For comparison with cervical cancer survivors, SIRs for subsequent malignancies were also calculated for female survivors of breast or colorectal cancers.

**Results**—The SIR of developing a subsequent tobacco-related malignancy was higher among cervical cancer survivors (SIR = 2.2, 95 % CL = 2.0–2.4). Female breast (SIR = 1.1, 95 % CL = 1.0–1.1) and colorectal cancer survivors (1.1, 1.1–1.2) also had an elevated risk. The increased risk of a subsequent tobacco-related malignancy among cervical cancer survivors was greatest in the first 5 years after the initial diagnosis and decreased as time since diagnosis elapsed.

**Conclusion**—Women with cervical cancer have a two-fold increased risk of subsequent tobacco-related malignancies, compared with breast and colorectal cancer survivors. In an effort to decrease their risk of subsequent tobacco-related malignancies, cancer survivors should be targeted for tobacco prevention and cessation services. Special attention should be given to cervical cancer survivors whose risk is almost twice that of breast or colorectal cancer survivors.

### Keywords

Second primary neoplasms; Uterine cervical neoplasms; Epidemiology; Tobacco

## Background

There are approximately 250,000 cervical cancer survivors in the United States [1, 2]. Previous studies suggest cervical cancer survivors have a greater risk of developing any subsequent malignancy, compared with other cancer survivors [3, 4]. The elevated risk of subsequent malignancies among cervical cancer survivors has been attributed to increased cancer vulnerability due to infection with Human Papillomavirus (HPV), adverse effects of cancer treatment, including radiation therapy; and risky health behaviors among survivors, including cigarette smoking [5].

Tobacco use poses a substantial health hazard to cancer survivors [6, 7], including an increased risk of subsequent malignancies [8]. The estimated smoking prevalence among cervical cancer survivors exceeds 40 % compared with 14 % among breast cancer survivors, 12 % among colorectal cancer survivors [9, 10], and 18 % among the general population of US women [11]. The comparably high smoking prevalence reported among cervical cancer survivors may increase their risk of subsequent malignancies, especially for cancers related to tobacco use [11].

In our study, we examined relative risk of subsequent tobacco-related malignancies and demographic characteristics among women who had been diagnosed with cervical, breast, or female colorectal cancers as their initial (index) cancer diagnosis. Of these three cancers, cervical cancer is the only one definitively caused by tobacco use, according to the 2004 *Surgeon General's Report on the Health Consequences of Smoking* [12]; however, breast and colorectal cancers have also been associated with tobacco use in some evaluations [13, 14]. Widely used screening tests are available for all three cancer sites [15]. We report the standardized incidence ratios (SIRs) for subsequent tobacco-related malignancies among cervical cancer survivors, as well as among breast and colorectal cancer survivors.

## Methods

We analyzed 1992–2008 cancer incidence data from 13 population-based cancer registries participating in the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) Program (Atlanta, Connecticut, Detroit, Hawaii, Iowa, New Mexico, San Francisco-Oakland, Los Angeles, San Jose-Monterey, Seattle-Puget Sound, Utah, Alaska Native Tumor Registry, and ten counties in rural Georgia). These registries cover 14 % of the US population. All cancer sites were categorized using the *International Classification of Diseases for Oncology, 3rd edition (ICD-0-3)*. Only women with malignant microscopically confirmed index tumors were included in the analysis. Index cervical (C53), breast (C50), and female colorectal cancer (C18-20), cancers were excluded if identified by death certificate or autopsy-only, as follow-up information would not be available for these cases.

We defined subsequent primary cancers, according to SEER general rules [16, 17], as cancers diagnosed at least 2 months after a primary cancer diagnosis, which did not include cancers indicated in the medical records as recurrent or metastases of a single primary. The subsequent primary cancers included those reported to the SEER incidence registry, and since we would not need follow-up data beyond the second cancer case, we included death

certificate and autopsy-only cases. More detailed information on identifying subsequent cancers can be found in the SEER Program code manual [16]. Tobacco-related malignancies (lung/bronchial, pharyngeal, laryngeal, esophageal, stomach, pancreatic, kidney/renal, urinary bladder, cervical, and acute myelogenous leukemia) are those in which “the evidence is sufficient to infer a causal relationship” with disease onset, according to the 2004 *Report of the Surgeon General on the Health Consequences of Smoking* [12].

We limited our analyses to SEER13 registries from 1992 and forward, because data on expanded race and ethnicity categories became available in SEER in 1992. Racial groups were defined as non-Hispanic (NH) white, NH black, NH Asian/Pacific Islander (API), NH American Indian/Alaska Native (AI/AN), and unknown race. Hispanic ethnicity was included; persons categorized as Hispanic ethnicity can be of any race.

### Statistical analysis

We calculated the SIR (ratio of observed [O]/expected [E]) and 95 % confidence limits (95 % CL) of all cancer sites (excluding basal cell and squamous cell skin cancers) and subsequent tobacco-related malignancies among women with an index cervical, breast, or colorectal cancer. The person-years (PY) at risk of each woman began at 2 months after the index cancer diagnosis and accrued until the date of last known vital status, date of death, or end of the study period, whichever occurred first. To estimate the expected numbers of subsequent cancer for each stratum, the PY (stratified according to patient age at initial diagnosis into 5-year age groups, race, and calendar year) accumulated by the index cases was multiplied by the strata-specific cancer incidence rates, using data extracted from the SEER 1992–2008 cancer registry incidence files. The observed and expected numbers of cancers were summed over the strata to obtain totals in each cancer site. The SIR (or O/E ratio) estimates the risk of developing a second cancer in women who survived primary previous cancer diagnosis of the cervix, breast, or female colorectal, compared with women in the general population. Statistical tests on the SIRs and the 95 % CLs derivations assumed Poisson distribution. We stratified the SIRs by race/ethnicity, site of index cancer, and latency period (2 months to <1 year, 1 to <5 years, 5 to <10 years, 10 to <15 years, 15 years or more) since the first cancer diagnosis. SEER\*Stat software, version 7.0.4, was used for data analyses.

### Results

Among women included in this study, cervical cancer was the least common first cancer diagnosis ( $n = 26,290$ ), compared with breast ( $n = 348,310$ ) or colorectal cancer ( $n = 109,032$ ) diagnoses (Table 1). Cervical cancer survivors were younger (mean age = 49.7), compared with breast (mean age = 60.8) or colorectal cancer survivors (mean age = 69.6). The majority of women included in this study were NH white; however, women of other races/ethnicities accounted for a larger proportion of cervical cancer survivors, compared with breast or colorectal cancer survivors.

Cervical cancer survivors had a higher risk (SIR = 1.4; 95 % CL = 1.3–1.5) for all subsequent malignancies, compared with breast (1.2, 1.2–1.2) or colorectal cancer survivors (1.2, 1.1–1.2) (Table 2). Cervical cancer survivors also had a higher risk (2.2, 2.0–2.4) for

developing subsequent tobacco-related malignancies, compared with breast (1.1, 1.0–1.1) or colorectal cancer survivors (1.1, 1.1–1.2); however cervical cancer survivors had the lowest risk of non-tobacco-related malignancies (1.1, 1.1–1.2), compared with breast (1.3, 1.3–1.3) or colorectal (1.2, 1.2–1.2) cancer survivors.

Within each racial and ethnic population, cervical cancer survivors had the highest risk of a subsequent tobacco-related primary malignancy, compared with breast or colorectal cancer survivors (Table 3). NH white cervical cancer survivors had the highest risk of a subsequent tobacco-related malignancy (2.4, 2.1–2.7), followed by NH black (2.1, 1.6–2.6), Hispanic (2.1, 1.7–2.5), and NH API (1.8, 1.4–2.4) women (Table 3). By anatomic site, cervical cancer survivors had a higher risk of a subsequent malignancy at each tobacco-related cancer site (with the exception of acute myelogenous leukemia), compared with breast or colorectal cancer survivors (Table 4). This includes a significantly higher risk of cancers of the lung and bronchus (2.8, 2.5–3.1), urinary bladder (2.6, 2.0–3.4), esophagus (2.1, 1.0–3.9), and stomach (1.9, 1.3–2.7).

For 15 years after diagnosis, cervical cancer survivors had a higher risk of a subsequent tobacco-related malignancy compared with breast or colorectal cancer survivors (Fig. 1). After 15 years post cancer diagnosis, the risk of subsequent tobacco-related malignancies among cervical cancer survivors had decreased, reaching SIRs similar to those of breast and colorectal cancer survivors.

## Discussion

Using SEER registry data, we examined the SIR for developing subsequent malignancies among women initially diagnosed with cervical, breast, or colorectal cancer. While our findings confirm previous studies which indicated that cervical cancer survivors have an increased risk of developing subsequent malignancies; [3, 18] we also found that cervical cancer survivors have a significant, two-fold higher risk of subsequent tobacco-related malignancies in comparison with breast and colorectal cancer survivors. NH black, API, AI/AN, and Hispanic women each account for a larger proportion of cervical cancer survivors than breast or colorectal cancer survivors. Higher rates of cervical cancer among non-white women are well documented and are often attributed to differences in Pap testing, including treatment of pre-invasive disease and follow-up of abnormal test results [19–22]. We also found that women diagnosed with cervical cancer have the highest risk of developing a subsequent tobacco-related malignancy over a 15-year period immediately following diagnosis, which then decreases to risks similarly observed in other cancer survivors.

HPV infection is the primary cause of cervical cancer [23]. Along with cervical cancer, esophageal, head and neck, and oral cancer are also related to HPV infection [24] and tobacco use [12]. HPV infection has been shown to have a synergistic effect with cigarette smoking [25], and cervical cancer survivors have a higher smoking prevalence compared with other cancer survivors [9, 10]. It may be that HPV-induced susceptibility to cancer, in addition to a high smoking prevalence, contributes to the increased risk of subsequent tobacco-related malignancies among cervical cancer survivors.

HPV infection wanes due to clearance, resulting in a decreased subsequent cancer risk over an extended period of time [26, 27]. This may explain our finding that cervical cancer survivors are at the greatest risk of a subsequent malignancy for up to 15 years post cancer diagnosis. Additionally, positive changes in health behaviors, such as avoidance of tobacco and alcohol, over time and among older cancer survivors may also explain this finding [28]. Healthy lifestyle behaviors have been shown to improve survivorship among women previously diagnosed with cervical cancer [29, 30]. Cervical cancer is typically diagnosed in young women and the survival rates are high in the United States [31]; therefore, cervical cancer survivors face more years at risk of developing a new malignancy compared with other cancer survivors. However, some unhealthy behaviors which are associated with increased cancer risk have often been reported among this group. Cervical cancer survivors have been shown to smoke and consume more alcohol than other cancer survivors; [9, 10] each of these behaviors are linked to increased cancer risk among survivors [32], and may be related to the increased risk of subsequent malignancies, including subsequent tobacco-related malignancies observed in this report.

While we are unable to conduct a comprehensive analysis of socioeconomic status (SES) using SEER data variables in this study, the outcomes we report are likely influenced by differences in income and education. Cervical cancer survivors typically report lower SES [33, 34], which may result in less access to quality health care. Furthermore, a recent CDC study found smoking prevalence to be highest among poor and less educated populations [11]. These factors may be associated with our finding of an increased risk of subsequent tobacco-related malignancies among cervical cancer survivors.

Our study has several strengths and limitations. The large data set allows for a detailed temporal quantification of risk of subsequent cancer, as well as comparisons by demographic characteristics. The SEER Program's high data standards and quality control help ensure the validity of the results in ascertaining and coding malignancies. An additional strength stems from population-based structure of SEER, which excludes potential selection or referral biases that may be present in studies using clinical or hospital-based cases. The data presented in our analyses may be underestimated, since they would not include subsequent cancer cases if cancer survivors left the SEER catchment area. In addition, subsequent cancer cases that were not microscopically confirmed or identified by death certificate/autopsy may not be included in these analyses, which would further underestimate our findings for subsequent malignancy risk. Also, the SEER population may not be generalizable of the US population, as SEER oversamples non-white and urban populations [33]. It is also possible that prior treatment, such as radiotherapy for the index cancer, might have led to the development of a subsequent malignancy [34]. We were unable to assess this effect and interpret it accordingly using the SEER data since treatment data are not available in the limited public-use data file. Our analyses do not include data on smoking prevalence; therefore, we are unable to determine which cancer survivors place themselves at risk of subsequent malignancies by continuing to smoke after the index cancer diagnosis. Finally, cancer registry data do not include information on risk factors for cancer including HPV infection, co-morbid conditions, and family history.

According to SEER cancer registry general rules; subsequent malignancies include all malignant, microscopically confirmed tumors diagnosed at least 2 months after the index malignancy, which were not considered recurrent or metastatic in the medical records [16]. While there are multiple treatment options for invasive cervical cancer (surgical resection, chemotherapy, radiation, etc.) [35], we have limited treatment information for these cases which would help exclude potential misclassifications. Therefore, we were unable to exclude based on the available information subsequent cervical cancer diagnoses among women whose index cancer diagnosis was also cervical cancer. These cases were therefore retained under the assumption that the numerous data quality checks applied to the SEER data has led to their accurate classification as new, primary malignancies.

Scientific advances in cervical cancer prevention, screening to achieve early detection, and treatment have largely decreased the cervical cancer burden in the United States, thus making cervical cancer a model for cancer prevention and control [36]. However, cervical cancer survivors may face an increased risk of a subsequent tobacco-related cancer diagnosis due to prior treatment [37], and their high prevalence of persistent smoking after a cancer diagnosis [9, 10]. According to our findings, cervical cancer survivors have a higher risk of a subsequent tobacco-related cancer diagnosis (including stomach, esophageal, lung and pancreatic cancer), when compared to the risk among other cancer survivors. While cervical cancer is typically associated with high survival rates, other tobacco-related cancer diagnoses can be far more deadly [38]. For example, the 5-year overall survival rate for cervical cancer is 68.6 %, much higher than the 5-year survival rates for stomach (26.3 %), esophageal (16.8 %), lung (15.6 %), and pancreatic (5.5 %) cancers [38]. Therefore, while an individual may survive the initial diagnosis of a cervical cancer, they may risk death from another potentially preventable tobacco-related malignancy.

According to the Institute of Medicine, an expansion of cancer survivorship support (including campaigns to raise awareness of cancer survivorship, surveillance for cancer survivors and prevention to avoid recurrent cancer diagnoses among survivors) is needed to ensure delivery of appropriate cancer care [29]. Health care providers are recommended to provide cancer survivors with a “Survivorship Care Plan,” which summarizes treatment and delivers follow-up directions [29, 30]. A survivorship care plan for cervical cancer survivors should also address the dangers of tobacco use and subsequent malignancy risk which appears immediately after diagnosis, and continues throughout the patient’s lifetime. In addition, the importance of modifying other health behaviors such as limiting alcohol consumption, eating a healthy diet, and engaging in regular physical activity should also be communicated to survivors, as these behaviors may result in decreased risk of recurrent or new cancers [29].

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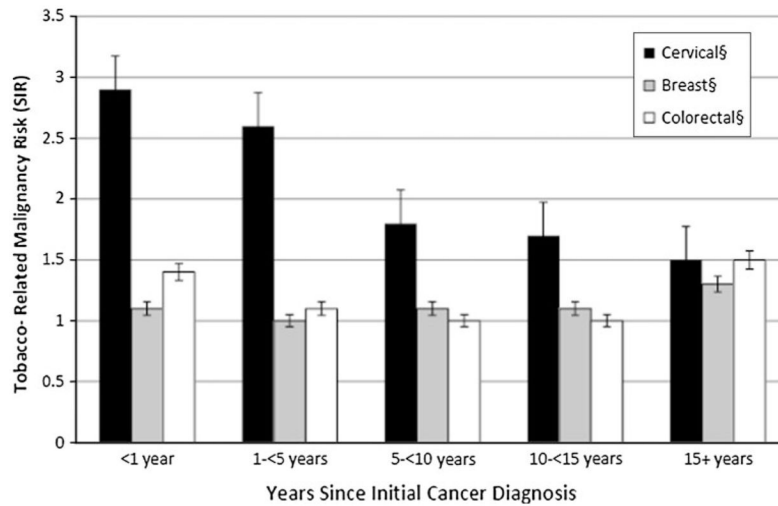
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**Fig. 1.**

Subsequent tobacco-related malignancy risk by time since index cancer diagnosis. Data are based on the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) Program from Jan. 1992 to Dec. 2008. SEER data used in this study were collected from 13 registries, covering 14 % of the US population. All cases were malignant, microscopically confirmed tumors, diagnosed at least 2 months after the index malignancy, and were not considered recurrent or metastatic in the medical records. Tobacco-related cancers (lung/bronchial, pharyngeal, esophageal, stomach, pancreatic, kidney/renal, urinary bladder, cervical and acute myelogenous leukemia) are defined according to the 2004 Report of the Surgeon General on The Health Consequences of Smoking. Standardized incidence ratio [SIR] (or the Observed/Expected ratio) is the number of new cases for each specific cancer, divided by the expected cancer-specific rate for the general population. § Index cancer cases include cervical, breast, and female colorectal cancer survivors

Demographic characteristics among cervical, breast and colorectal cancer survivors, females, SEER 1992–2008.

**Table 1**

Characteristic	Index cancer		
	Cervical <sup>a</sup> n = 26,290	Breast <sup>a</sup> n = 348,310	Colorectal <sup>a</sup> n = 109,032
	N	(%)	N (%)
<i>Age (years)</i>			
Mean age	49.7	60.8	69.6
< 30	1,824	6.9	2,088 0.6
30–49	13,329	50.7	87,678 25.2
50–69	7,884	30.0	158,285 45.4
70–79	2,148	8.2	64,341 18.5
80+	1,105	4.2	35,918 10.3
<i>Race/ethnicity</i>			
NH white	13,211	50.3	254,444 73.1
NH black	3,224	12.3	31,343 9.0
NH API	3,010	11.4	29,157 8.4
NH AI/AN	189	0.7	1,404 0.4
NH other/unknown	214	0.8	1,749 0.5
Hispanic	6,442	24.5	30,213 8.7

Analyses were conducted using SEER\*Stat software, version 7.0.4

Data are from the National Cancer Institute’s Surveillance, Epidemiology and End Results (SEER) Program from Jan. 1992–Dec. 2008. SEER data used in this study were collected from 13 registries, covering 14 % of the US population

NH non-hispanic

<sup>a</sup>Cervical, breast, and colorectal cancers are the index cancer diagnosis among female cancer survivors. Index cancers were microscopically confirmed tumors

**Table 2**  
Subsequent and tobacco-related malignancies among cervical, breast, and colorectal cancer survivors

Subsequent malignancies	Index cancer											
	Cervical <sup>a</sup>				Breast <sup>a</sup>				Colorectal <sup>a</sup>			
	n	SIR	LCL-UCL	n	SIR	LCL-UCL	n	SIR	LCL-UCL	n	SIR	LCL-UCL
All sites <sup>b</sup>	1,431	1.4*	1.3–1.5	31,826	1.2*	1.2–1.2	8,859	1.2*	1.1–1.2			
All sites (excluding basal and squamous cell skin cancers)	1,428	1.4*	1.3–1.5	31,686	1.2*	1.2–1.2	8,817	1.2*	1.1–1.2			
Tobacco-related cancers	560	2.2*	2.0–2.4	7,714	1.1*	1.0–1.1	2,527	1.1*	1.1–1.2			
Non-Tobacco-related cancers	871	1.1*	1.1–1.2	24,112	1.3*	1.3–1.3	6,332	1.2*	1.2–1.2			

Tobacco-related cancers (lung/bronchial, pharyngeal, esophageal, stomach, pancreatic, kidney/renal, urinary bladder, cervical, and acute myelogenous leukemia) are defined according to the 2004 *Report of the Surgeon General on the Health Consequences of Smoking*

SIR standardized incident ratio, LCL lower confidence limit, UCL upper confidence limit

\* Denotes SIR differs significantly from 1 ( $p < 0.05$ )

<sup>a</sup> Index cancer cases include cervical, breast, and female colorectal cancer survivors

<sup>b</sup> All sites includes basal and squamous cell skin cancers

Racial and ethnic demographics among cervical, breast and colorectal cancer survivors subsequently diagnosed with a tobacco-related malignancy

**Table 3**

Subsequent malignancies	Cervical <sup>a</sup>			Breast <sup>a</sup>			Colorectal <sup>a</sup>		
	N	SIR	LCL-UCL	N	SIR	LCL-UCL	N	SIR	LCL-UCL
NH white	317	2.4*	2.1–2.7	6,143	1.0*	1.0–1.1	1,917	1.1*	1.1–1.2
NH black	75	2.1*	1.6–2.6	688	1.2*	1.1–1.3	264	1.2*	1.1–1.4
NH API	53	1.8*	1.4–2.4	438	1.2*	1.1–1.3	207	1.4*	1.2–1.6
NH AI/AN	–	–	–	19	1.3	0.8–2.1	6	1.5	0.5–3.2
NH other	–	–	–	–	–	–	–	–	–
Hispanic	112	2.1*	1.7–2.5	424	0.9*	0.8–1.0	133	0.9	0.8–1.1

Tobacco-related cancers (lung/bronchial, pharyngeal, esophageal, stomach, pancreatic, kidney/renal, urinary bladder, cervical and acute myelogenous leukemia) are defined according to the 2004 *Report of the Surgeon General on the Health Consequences of Smoking*

NH non-Hispanic

Data for NH AI/AN and NH other/unknown are suppressed due to <6 cases

\* Denotes SIR differs significantly from 1 ( $p < 0.05$ )

<sup>a</sup> Index cancer cases include cervical, breast, and female colorectal cancer survivors

**Table 4**

Subsequent tobacco-related malignancies by site

Cancer site	Cervical <sup>d</sup>			Breast <sup>d</sup>			Colorectal <sup>d</sup>		
	N	O/E	LCL-UCL	N	O/E	LCL-UCL	N	O/E	LCL-UCL
Oral cavity and pharynx	24	1.5	1.0-2.3	453	1.1*	1.0-1.2	104	0.9	0.7-1.1
Esophagus	10	2.1*	1.0-3.9	156	1.0	0.9-1.2	52	1.0	0.8-1.4
Stomach	29	1.9*	1.3-2.7	442	1.1	1.0-1.2	180	1.2*	1.1-1.4
Pancreas	29	1.2	0.8-1.7	794	1.0	0.9-1.1	263	1.0	0.8-1.1
Larynx	7	2.1	0.9-4.4	65	0.8*	0.6-1.0	20	0.9	0.6-1.4
Lung and bronchus	332	2.8*	2.5-3.1	3,840	1.0*	1.0-1.1	1,267	1.1*	1.1-1.2
Cervix uteri	34	1.5*	1.1-2.2	177	0.6*	0.5-0.7	82	1.2	0.9-1.5
Urinary bladder	54	2.6*	2.0-3.4	701	1.0	0.9-1.1	275	1.2*	1.0-1.3
Kidney and renal pelvis	29	1.3	0.9-1.9	695	1.2*	1.1-1.3	224	1.3*	1.2-1.5
Acute myeloid leukemia	12	1.8	0.9-3.2	391	2.1*	1.9-2.4	60	1.0	0.8-1.3

Tobacco-related cancers (lung/bronchial, pharyngeal, esophageal, stomach, pancreatic, kidney/renal, urinary bladder, cervical, and acute myelogenous leukemia) are defined according to the 2004 Report of the Surgeon General on The Health Consequences of Smoking

\* Denotes SIR differs significantly from 1 ( $p < 0.05$ )

<sup>d</sup> Index cancer cases include cervical, breast, and female colorectal cancer survivors