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ORIGINAL REPORT

Second Cancers After Squamous Cell Carcinoma and Adenocarcinoma of the Cervix

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The Appendix is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).

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ABSTRACT

Purpose
Although cervical squamous cell carcinoma (SCC) and adenocarcinoma (AC) are both caused by human papillomavirus (HPV) infection, they differ in cofactors such as cigarette smoking. We assessed whether these cofactor differences translate into differences in second cancer risk.

Patients and Methods
We assessed second cancer risk among 85,109 cervical SCC and 10,280 AC survivors reported to population-based cancer registries in Denmark, Finland, Norway, Sweden, and the United States. Risks compared to the general population were assessed using standardized incidence ratios (SIR).

Results
Overall cancer risk was significantly increased among both cervical SCC survivors (n = 10,559 second cancers; SIR, 1.31; 95% CI, 1.29 to 1.34) and AC survivors (n = 920 second cancers; SIR, 1.29; 95% CI, 1.22 to 1.38). Risks of HPV-related and radiation-related cancers were increased to a similar extent among cervical SCC and AC survivors. Although significantly increased in both groups when compared with the general population, risk of smoking-related cancers was significantly higher among cervical SCC than AC survivors ($P = .015$; SIR for cervical SCC = 2.07 *v* AC = 1.78). This difference was limited to lung cancer (SIR for cervical SCC = 2.69 *v* AC = 2.18; $P = .026$). The increased lung cancer risk among cervical AC survivors was observed for both lung SCC and lung AC. SIRs for second cancers of the colon, soft tissue, melanoma, and non-Hodgkin's lymphoma were significantly higher among cervical AC than SCC survivors.

Conclusion
The second cancer profiles among cervical SCC and AC survivors mirror the similarities and differences in cofactors for these two histologies. Because smoking is not a cofactor for cervical AC, the increased lung cancer risk suggests a role for additional factors.

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INTRODUCTION

Cervical cancer is the second most common cancer among women, with an estimated worldwide burden of 493,000 new cases and 274,000 deaths each year.[1] Cervical cancer presents in two major histologic forms, namely, squamous cell carcinoma (SCC), which constitutes 80% to 85% of all cases, and adenocarcinoma (AC), which constitutes 15% to 20%.[2] Cervical SCC and AC are both caused by human papillomavirus (HPV) infection and share several risk factors, including high-risk sexual behavior.[3-7] However, the cofactor profiles of SCC and AC also show important differences.[3-7] The most prominent difference pertains to cigarette smoking, which is associated with increased risk of SCC, but not AC.[3-7] Although high parity is associated with increased risk of both histologic subtypes, the association is believed to be weaker for AC than SCC.[4,5,8] Obesity is associated with increased risk of AC, but not SCC,[9] and patients with cervical AC have been shown to be of relatively higher socioeconomic status (SES) than those with SCC, in some,[10] but not all studies.[11,12]

Previous studies have quantified the increased risk of second primary cancers among cervical cancer survivors.[13-17] This increased risk arises from several factors, including radiation treatment, HPV infection, cigarette smoking, and hormonal factors.[13-17] However, no study has assessed second cancer risk separately for cervical SCC and AC survivors. Because cofactors such as cigarette smoking, which contributes to second cancer risk, differ between SCC and AC, it is important to assess whether these cofactor differences translate

into differences in second cancer risk. In a previous analysis, we assessed long-term risk of second primary cancers among 104,760 cervical cancer survivors who were observed for more than 40 years.[13] In this study, we assessed second cancer risk separately for cervical SCC and AC survivors.

PATIENTS AND METHODS

The study cohort comprised women diagnosed with invasive cervical cancer reported to population-based cancer registries in Denmark (1943 to 1998), Finland (1953 to 2001), Norway (1953 to 1999), Sweden (1958 to 2001), and nine areas in the United States covered by the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program (1973 to 2002).[13] Follow-up for invasive second primary cancers began 1 year after cervical cancer diagnosis and ended at the earliest occurrence of second cancer diagnosis, death, or end of study period. Incident second primary cancers were identified by linkage within the respective cancer registry.[13]

Using histology codes noted in Appendix Table A1, we classified 104,760 cervical cancers into SCC (n = 85,109) and AC (n = 10,280). Women with other/unknown histologies (n = 9,371) were excluded. We were unable to separate adenosquamous histologies from ACs for the non-SEER registries; however, for SEER program registries, adenosquamous cases were included in the other/unknown histologies category and were thus excluded.

Separately for SCC and AC, we compared risk for each second cancer with that in the general population using the standardized incidence ratio (SIR), calculated as the ratio of observed and expected number of cancers. The expected number of cancers was calculated by applying female general population cancer incidence rates, specific to registry, age (in 5-year groups), calendar year (in 5-year groups), and race (only for SEER data), to person-years accrued by cervical cancer survivors. Exact Poisson 95% CIs were calculated for the SIR estimates.[18]

We grouped second cancer sites as smoking-related cancers (lip, tongue, mouth, pharynx, esophagus, larynx, trachea/bronchus/lung, pancreas, liver, stomach, kidney, and urinary bladder),[19] HPV-related cancers (tongue, mouth, pharynx, rectum/anus, and female genital sites including vagina and vulva),[1] and cancers at heavily irradiated sites (small intestine, colon, rectum/anus, urinary bladder, uterine corpus, ovary/fallopian tubes, female genital sites including vagina and vulva, bone, and soft tissue).[13] For each second cancer site, as well as for the grouped categories of smoking-related, HPV-related, and heavily irradiated second cancers, we compared SIRs between cervical SCC and AC survivors using Poisson regression. Thus, our analyses included three different comparisons: cervical SCC survivors versus women in the general population (SIR for SCC survivors), cervical AC survivors versus

Table 1. Characteristics of Women With Cervical Cancer Stratified by Histology

Characteristic	Condition			
	Squamous Cell Carcinoma of Cervix		Adenocarcinoma of Cervix	
	No.	%	No.	%
No. of patients	85,109		10,280	
No. of person-years	1,061,885		98,704	
Registry				
Denmark (1943-1998)	24,942	29.3	2,123	20.6
US SEER program (1973-2002)	20,534	24.1	3,389	33.0
Sweden (1958-2001)	19,717	23.2	2,467	24.0
Norway (1953-1999)	12,283	14.4	1,189	11.6
Finland (1953-2001)	7,633	9.0	1,112	10.8
Age at cervical cancer diagnosis, years				
< 40	22,215	26.1	2,798	27.2
40-49	21,758	25.6	2,745	26.7
50-59	17,984	21.1	2,002	19.5
60+	23,152	27.2	2,735	26.6
Calendar year of cervical cancer diagnosis				
< 1960	11,724	13.8	689	6.7
1960-1974	27,768	32.6	1,860	18.1
1975-1989	28,236	33.2	3,684	35.8
1990+	17,381	20.4	4,047	39.4
Stage of cervical cancer				
Local	28,356	33.3	4,153	40.4
Regional	9,392	11.0	1,105	10.7
Distant	2,265	2.7	386	3.8
Unknown	45,096	53.0	4,636	45.1
Initial treatment				
Any radiotherapy	43,683	51.3	4,226	41.1
No radiotherapy	20,239	23.8	3,389	32.9
Other/unknown	21,187	24.9	2,665	26.0
Race*				
White	15,421	75.1	2,783	82.1
Black	3,214	15.6	255	7.5
Other/unknown	1,899	9.3	351	10.4

Abbreviation: SEER, Surveillance, Epidemiology, and End Results.
*Data on race were available only from the US SEER program.

women in the general population (SIR for AC survivors), and comparisons of SIRs for cervical SCC survivors versus cervical AC survivors. All statistical tests were two sided and *P* values less than .05 were considered as statistically significant.

To further investigate lung cancer risk among cervical SCC and AC survivors, we calculated SIRs separately for second primary SCCs of the lung and second primary ACs of the lung. Expected numbers for each histologic subtype of lung cancer were calculated by applying female general population cancer incidence rates, specific to lung cancer histology, registry, age, calendar year, and race (only for SEER data), to person-years accrued by cervical SCC and AC survivors. These SIRs were calculated overall and after stratification by time since cervical cancer diagnosis (1 to 4, 5 to 9, 10 to 19, and ≥ 20 years).

RESULTS

Characteristics of cervical SCC and AC survivors are presented in Table 1. Age at cervical cancer diagnosis was similar for SCC and AC patients (mean age = 50.2 and 50.0 years, respectively). The proportion of cases of AC histology increased during the study period, with ACs constituting approximately 19% of cervical cancers in the most recent calendar period (1990 and beyond). SCC patients were treated by radiation more frequently than AC patients (51.3% *v* 41.1%). In the SEER registries, a higher proportion of AC patients than SCC patients were white (82.1% *v* 75.1%).

Compared with women in the general population, overall cancer risk was significantly increased among both cervical SCC survivors (Table 2; n = 10,559 second cancers during 1,061,885 person-years of follow-up; SIR, 1.31; 95% CI, 1.29 to 1.34) and cervical AC survivors (n = 920 second cancers during 98,704 person-years of follow-up; SIR, 1.29; 95% CI, 1.22 to 1.38). We also assessed overall second cancer risk separately across calendar period of cervical cancer diagnosis and for SEER and non-SEER registries (Table 2). For both cervical SCC and AC survivors, second cancer risk did not vary significantly by calendar period of cervical cancer diagnosis. In contrast, the overall risk of second cancers was significantly higher among survivors in the non-SEER registries than those in SEER registries (Table 2). Nonetheless, regardless of calendar period of cervical cancer diagnosis or registry, no significant differences were observed in overall second cancer risk between cervical SCC and AC survivors.

Among both SCC and AC survivors, SIRs for the grouped categories of smoking-related cancers, HPV-related cancers, and cancers at heavily-irradiated sites were significantly increased (Table 3). The most frequent second cancers among both SCC and AC survivors were those of the lung, breast, and colon (Table 3). Among cervical SCC survivors, SIRs for most second cancers were significantly increased. Highest SIRs following cervical SCC were observed for cancers of female genital sites (SIR, 5.00; including vagina, vulva, and other/unspecified genital sites), urinary bladder (SIR, 3.48), and lung (SIR, 2.69). Among cervical AC survivors, significantly increased SIRs were observed for second cancers of the colon, rectum/anus, pancreas, trachea/bronchus/lung, bone, soft tissue, female genital sites, urinary bladder, and non-Hodgkin's lymphoma (NHL). Highest SIRs following cervical AC were observed for cancers of the soft tissue (SIR, 4.70), bone (SIR, 4.66), and female genital sites (SIR, 3.87). Both cervical SCC and AC survivors were at significantly decreased risk of cancers of the breast and uterine corpus than women in the general population (Table 3).

We evaluated whether the SIRs for second cancers were significantly different between cervical SCC and AC survivors (*P* values in Table 3). No significant differences between SCC and AC survivors were observed in the SIRs for the grouped categories of HPV-related cancers or cancers at heavily irradiated sites. In contrast, the SIR for smoking-related second cancers (grouped together) was significantly higher among SCC than AC survivors (SIR, 2.07 *v* 1.78; $P = .015$). In particular, risk of second lung cancer was significantly higher among SCC survivors than AC survivors (SIR, 2.69 *v* 2.18; $P = .026$). SIRs for other smoking-related second cancers (lip, tongue, mouth, pharynx,

Table 2. Risk of Second Primary Cancers Among Cervical Squamous Cell Carcinoma and Adenocarcinoma Survivors Stratified by Calendar Year of Cervical Cancer Diagnosis and Registry

Parameter	Squamous Cell Carcinoma of Cervix		Adenocarcinoma of Cervix		*P* for Squamous Cell Carcinoma *v* Adenocarcinoma*
	SIR	95% CI	SIR	95% CI	
No. of patients	85,109		10,280		
No. of person-years	1,061,885		98,704		
All second cancers except cervix	1.31	1.29 to 1.34	1.29	1.22 to 1.38	.592
Year of cervical cancer diagnosis					
< 1960	1.28	1.23 to 1.34	1.42	1.19 to 1.70	.244
1960-1974	1.31	1.28 to 1.35	1.27	1.13 to 1.43	.560
1975-1989	1.32	1.28 to 1.37	1.29	1.16 to 1.43	.594
1990+	1.40	1.30 to 1.51	1.26	1.06 to 1.50	.283
P for trend		.141†		.361†	
Registry					
SEER	1.20	1.15 to 1.26	1.16	1.02 to 1.33	.526
Non-SEER	1.34	1.31 to 1.37	1.34	1.25 to 1.45	.934
P		< .001‡		.035‡	

Abbreviations: SIR, standardized incidence ratio; SEER, Surveillance, Epidemiology, and End Results.
*P values comparing SIR for cervical squamous cell carcinoma *v* cervical adenocarcinoma survivors were calculated using Poisson regression.
†P values for trend in SIRs across calendar periods of cervical cancer diagnosis were calculated using Poisson regression.
‡P values comparing SIR for SEER versus non-SEER registries were calculated using Poisson regression.

Table 3. Risk of Second Primary Cancers Among Cervical Cancer Survivors Stratified By Histology of Cervical Cancer

Second Cancer Site	Squamous Cell Carcinoma of Cervix			Adenocarcinoma of Cervix			*P* for Squamous Cell Carcinoma *v* Adenocarcinoma*
	No. of Observed Second Cancers	SIR	95% CI	No. of Observed Second Cancers	SIR	95% CI	
No. of patients		85,109			10,280		
No. of person-years		1,061,885			98,704		
Smoking-related cancers†	3,923	2.07	2.01 to 2.14	287	1.78	1.58 to 2.00	.015
HPV-related cancers‡	1,248	2.30	2.18 to 2.43	91	2.01	1.63 to 2.48	.238
Heavily irradiated sites§	3,858	1.50	1.46 to 1.56	349	1.63	1.46 to 1.81	.242
Lip	26	1.66	1.09 to 2.44	3	2.23	0.45 to 6.59	.584
Tongue	28	1.25	0.83 to 1.81	0	0.00	0.00 to 1.74	—
Mouth	60	1.61	1.24 to 2.08	3	0.91	0.18 to 2.67	.333
Pharynx	49	2.06	1.53 to 2.73	0	0.00	0.00 to 1.77	—
Esophagus	89	1.50	1.21 to 1.86	4	0.82	0.22 to 2.12	.239
Stomach	422	1.32	1.21 to 1.46	28	1.16	0.78 to 1.69	.527
Small intestine	54	1.82	1.37 to 2.39	3	1.17	0.24 to 3.44	.454
Colon	963	1.20	1.13 to 1.28	102	1.54	1.26 to 1.88	.017
Rectum/anus	677	1.81	1.68 to 1.96	60	1.97	1.51 to 2.54	.523
Liver	73	1.13	0.89 to 1.43	3	0.56	0.11 to 1.67	.241
Pancreas	381	1.38	1.25 to 1.53	34	1.53	1.06 to 2.14	.551
Larynx	48	2.10	1.55 to 2.79	1	0.49	0.01 to 2.73	.149
Trachea/bronchus/lung	1,649	2.69	2.57 to 2.83	126	2.18	1.82 to 2.61	.026
Bone	26	2.63	1.72 to 3.87	4	4.66	1.27 to 12.05	.289
Soft tissue	89	2.36	1.90 to 2.91	16	4.70	2.69 to 7.64	.011
Breast	1,643	0.76	0.73 to 0.80	177	0.85	0.74 to 1.00	.142
Female genital‖	434	5.00	4.55 to 5.50	28	3.87	2.57 to 5.60	.194
Uterine corpus	421	0.77	0.70 to 0.85	32	0.66	0.46 to 0.94	.271
Ovary/fallopian tubes	383	0.87	0.79 to 0.97	42	1.15	0.83 to 1.56	.165
Kidney	287	1.34	1.20 to 1.51	23	1.32	0.84 to 1.98	.928
Urinary bladder	811	3.48	3.25 to 3.74	62	3.23	2.48 to 4.15	.568
Melanoma	156	0.70	0.60 to 0.82	30	1.37	0.93 to 1.96	.001
Non-Hodgkin's lymphoma	272	1.25	1.11 to 1.41	38	1.84	1.30 to 2.53	.025

Abbreviation: SIR, standardized incidence ratio.

**P* values comparing SIR for cervical squamous cell carcinoma versus cervical adenocarcinoma survivors were calculated using Poisson regression.

†Smoking-related cancers include cancers of the lip, tongue, mouth, pharynx, esophagus, larynx, trachea/bronchus/lung, pancreas, liver, stomach, kidney, and urinary bladder (19).

‡HPV-related cancers include cancers of the tongue, mouth, pharynx, rectum/anus, and female genital sites including vagina and vulva (1).

§Cancers at heavily-irradiated sites include cancers of the small intestine, colon, rectum/anus, urinary bladder, uterine corpus, ovary/fallopian tubes, female genital sites including vagina and vulva, bone, and soft tissue (13).

‖Female genital cancers include cancers of the vagina, vulva, and other/unspecified genital sites.

esophagus, larynx, pancreas, liver, stomach, kidney, and urinary bladder) were not significantly different between SCC and AC survivors. In addition, SIRs for colon cancer, soft tissue cancers, melanoma, and NHL were significantly higher among AC than SCC survivors (all $P < .05$).

Risk of second lung cancers was significantly increased among cervical SCC and AC survivors in both the SEER and non-SEER registries (SIRs for SCC = 2.53 and 2.76 and AC = 1.82 and 2.44, respectively). To further evaluate the increased lung cancer risk, we conducted analyses for the major histologic subtypes of lung cancer (Table 4). The 1,775 second primary lung cancers included 666 lung SCCs, 333 lung ACs, and 776 lung cancers of other/unknown histologies. Among cervical SCC survivors, risks of SCC lung cancer (SIR, 5.45) and AC lung cancer (SIR, 1.58) were both significantly elevated. The SIR for SCC lung cancer was exceptionally high during the initial years after cervical cancer diagnosis (SIR during 1 to 4 years, 10.86) and decreased thereafter. The increased risks for lung SCC and lung AC among cervical SCC survivors were evident beyond 20 years after cervical cancer diagnosis. Cervical AC survivors were also at significantly increased risk of both lung SCC and lung AC, and this increased risk was evident up to 20 years after cervical cancer diagnosis. Among both cervical SCC and AC survivors, SIRs for lung SCC were higher than SIRs for lung AC. In addition, the SIR for second lung SCC was higher among cervical SCC than AC survivors, whereas the SIR for second lung AC was higher among cervical AC than SCC survivors.

DISCUSSION

Our study is the first, to our knowledge, to assess second cancer risk separately for cervical SCC and AC survivors. The profiles of second cancers among cervical SCC and AC survivors largely mirror the similarities and differences in cofactors for these two histologic subtypes.[3-7] We found that compared with women in the general population, both cervical SCC and AC survivors were at a similar increased risk of all second cancers considered together, HPV-related cancers, and cancers at heavily irradiated sites. In contrast, although

Table 4. Risk of Second Lung Cancers Stratified by Histology of Cervical Cancer and Lung Cancer

Parameter	SCC of Cervix						AC of Cervix					
	SCC of Lung			AC of Lung			SCC of Lung			AC of Lung		
	Obs	SIR	95% CI	Obs	SIR	95% CI	Obs	SIR	95% CI	Obs	SIR	95% CI
Overall	635	5.45	5.04 to 5.90	296	1.58	1.41 to 1.78	31	3.04	2.07 to 4.32	37	1.96	1.38 to 2.71
Results according to time after cervical cancer diagnosis, years												
1-4	202	10.86	9.42 to 12.47	55	1.79	1.35 to 2.33	11	4.86	2.43 to 8.71	8	1.83	0.79 to 3.61
5-9	202	9.88	8.57 to 11.35	63	1.86	1.43 to 2.38	11	5.13	2.56 to 9.20	10	2.36	1.13 to 4.36
10-19	134	3.57	2.99 to 4.23	91	1.48	1.20 to 1.82	8	2.44	1.05 to 4.82	14	2.26	1.24 to 3.81
20+	97	2.43	1.98 to 2.98	87	1.42	1.14 to 1.76	1	0.39	0.01 to 2.23	5	1.23	0.40 to 2.89

Abbreviations: SCC, squamous cell carcinoma; AC, adenocarcinoma; Obs, observed number of cases; SIR, standardized incidence ratio.

significantly increased in both groups when compared with the general population, risk of smoking-related second cancers (particularly lung cancer) was significantly higher among cervical SCC than AC survivors. Cervical SCC and AC survivors also differed in their risk of second cancers of the colon and soft tissue, melanoma, and NHL, with higher risks observed among AC survivors.

Consistent with HPV being a necessary cause of both cervical SCC and AC and with a large proportion of cervical cancer patients receiving radiotherapy, we found that the risks of HPV-related and radiation-related second cancers were similar between cervical SCC and AC survivors. SCC and AC survivors were also similar in their risks for hormone-related second cancers, with significantly decreased risks of cancers of the breast and uterine corpus when compared with women in the general population. These deficits for breast and uterine corpus cancers could be related to treatments for cervical cancer, including hysterectomy and radiation treatment (resulting in ovarian ablation), which reduce subsequent risk of these cancers.[17,20]

An increased risk of lung cancer among cervical cancer survivors has been demonstrated previously.[13-17] However, prior studies did not distinguish cervical cancers by histology, and largely attributed the increased risk to cigarette smoking.[13-17] Of note, previous case-control studies and pooled analyses have shown that cigarette smoking is a risk factor for cervical SCC, whereas smoking does not increase risk of cervical AC.[3-7] The results of these studies imply that smoking is more common among SCC patients than women in the general population, while the prevalence of smoking among AC patients is similar to that in the general population. Consistent with this formulation, we found that SCC survivors, when compared with women in the general population, were at a significantly increased risk of most smoking-related second cancers. Likewise, the risks of smoking-related second cancers (grouped together) as well as for second lung cancers were significantly higher among cervical SCC than AC survivors (Table 3).

Contrary to expectation, however, we found that AC survivors were also at significantly increased risk of smoking-related second cancers, particularly lung cancer, compared with women in the general population. Given that smoking is not believed to be a cofactor for cervical AC,[3-7] this increased lung cancer risk among cervical AC survivors suggests a role for factors other than cigarette smoking. One such factor may be HPV infection, which has been implicated in lung cancer etiology.[21,22] Several previous case-series have detected HPV DNA in lung SCC and lung AC tumor tissues.[21,22] However, results have been inconsistent across studies, with HPV DNA detection rates in case-series ranging from 0% to 100%.[21] A few studies have also reported detection of integrated HPV genomes as well as expression of HPV E6 and E7 oncogenes in lung tumors,[23-25] which are characteristic features of cancers caused by HPV.[26]

An etiologic role for HPV infection in lung cancer may be plausible. Recurrent respiratory papillomatosis (RRP), which is caused by HPV, provides an interesting disease model. [26-28] RRP is characterized by laryngeal papillomas, but can also manifest with tracheal and bronchial papillomas.[26-28] Transmission of HPV to the respiratory tract is believed to occur at birth among childhood RRP cases and through oral sex for RRP cases that occur among young adults.[27,28] RRP lesions are generally benign, but malignant transformation of papillomas is known to occur.[26-28] Likewise, oral/respiratory infection acquired through high-risk sexual behavior, and subsequent malignant transformation, may explain, at least in part, the increased risk of lung cancer after cervical AC that we observed. Alternative explanations for the increased lung cancer risk among cervical AC survivors may include factors such as low SES and high parity, which have been associated with lung cancer risk in the general population.[29,30]

We considered the possibility that pulmonary metastases, misclassified as primary lung cancers, contributed to the increased risk of lung cancer among cervical cancer survivors. The lung is a common site for distant metastases among cervical cancer patients.[31-33] Furthermore, the rate of pulmonary metastases may be higher after cervical AC than cervical SCC.[31,33] Indeed, our observations that among cervix SCC survivors, lung SCC risk was exceptionally high in the initial years after cervical cancer, and there was histologic clustering of cervical cancer and lung cancer (ie, risk of lung SCC was higher after cervical SCC than cervical AC, risk of lung AC was higher after cervical AC than after cervical SCC), both suggest that misclassified metastases could have contributed to part of the increased lung cancer risk among cervical cancer survivors. Nevertheless, the increased risk for lung SCC after cervical AC up to 20 years after diagnosis of cervical cancer argues against misclassified metastases as the entire explanation for the increased lung cancer risk among cervical AC survivors.

The highest SIR after cervical SCC was observed for second cancers of female genital sites (including vagina/vulva), whereas highest risk after cervical AC was observed for soft tissue cancers. While the risk of female genital second cancers was similar between cervical SCC and AC survivors, the SIR for soft tissue cancers was significantly higher among cervical AC than SCC survivors. The elevated risk of second cancers at female genital sites among cervical SCC survivors

may have arisen from increased exposure to HPV infections and/or high-dose radiation.[13,34] However, the reasons for significantly higher risk of soft tissue cancers among cervical AC than SCC survivors are currently unclear. In addition, SIRs for colon cancer, melanoma, and NHL were significantly higher among cervical AC than SCC survivors. These differences between cervical SCC and AC survivors could be related to the relatively higher SES of cervical AC compared with SCC patients. In the general population, colon cancer, melanoma, and NHL are more common among higher SES individuals.[35] Although both cervical SCC and AC are associated with low SES,[12] cervical AC patients have been shown to be of relatively higher SES than SCC patients.[10] One reason for this SES difference may be that Pap smear screening for cervical cancer is more efficient in diagnosing precursors of cervical SCC than of cervical AC.[4,5] Thus, in countries with organized cervical cancer screening programs, women diagnosed with invasive cervical SCC tend to be from lower SES groups who are less likely to participate in screening programs.[5]

We acknowledge several limitations of our study. We did not have information on cofactors for cervical SCC and AC, such as history of smoking, parity, or SES. In contrast to the decreasing incidence of cervical SCC, the incidence of cervical AC has increased during the past few decades in developed countries.[2,36] Therefore, although SIRs incorporate an adjustment for calendar year, it is possible that direct comparisons of SIRs between cervical SCC and AC may still be confounded by temporal shifts in the general population cancer patterns. In addition, some of the results we observed may have arisen from misclassification of cervical cancer histology. For the non-SEER registries, we could not exclude cervical adenosquamous cancers, which constitute 20% to 30% of ACs. Nonetheless, it is unclear whether etiologic cofactors differ for AC and adenosquamous cancers,[4] and we found that the second cancer profiles in the SEER data were similar irrespective of the inclusion of adenosquamous cancers with ACs (data not shown). We note that increased second cancer risk among cervical cancer survivors, irrespective of histology, may arise from increased medical surveillance among cancer survivors than among women in the general population.[37] Finally, it is possible that SIRs for some rare cancers among AC survivors may not have achieved statistical significance owing to low power.

In conclusion, we characterized second cancer risk among cervical AC survivors and compared the patterns of second cancers with cervical SCC survivors. Our results indicate that previously reported similarities and differences in cofactors between cervical SCC and AC translate into similarities and differences in second cancer risk profiles. Notably, although increased in both groups, risks of smoking-related second cancers were significantly higher among cervical SCC than AC survivors. Given that lung cancers constitute a high proportion of all second cancers (approximately 15%) among cervical cancer survivors, further studies are needed to clarify the potential etiologic role of HPV. Our results underscore the importance of cervical cancer cofactors in increasing second cancer risk among survivors.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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