Second Cancers Among 104760 Survivors of Cervical Cancer: Evaluation of Long-Term Risk

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Background Given the extended survival of patients diagnosed with cervical cancer, the large number of these women treated with radiotherapy, and the presence in this population of established cancer risk factors such as human papillomavirus (HPV) infection and cigarette smoking, it is important to clarify long-term trends in second cancer risk.

Methods Using data from 104760 one-year survivors of cervical cancer reported to 13 population-based cancer registries in Denmark, Finland, Norway, Sweden, and the United States, we calculated standardized incidence ratios (SIRs) for second cancers overall and cancers at particular sites among women with cervical cancer, including cervical cancer patients who were treated or not treated with radiation, over more than 40 years of follow-up. Cox regression models were used to assess the time-varying association of radiotherapy with risk of second cancers and to assess the interaction of radiation treatment with age at diagnosis. All statistical tests were two-sided.

Results Among 104760 one-year survivors of cervical cancer, the risk of all second cancers taken together was increased to a statistically significant extent (n = 12496; SIR = 1.30; 95% confidence interval [CI] = 1.28 to 1.33). Compared with the general population, in both radiotherapy (N = 52613) and no-radiotherapy groups (N = 27382), risks for HPV-related cancers (of the pharynx, genital sites, and rectum/anus) and smoking-related cancers (of the pharynx, trachea/bronchus/lung, pancreas, and urinary bladder) were elevated to a statistically significant extent. Cervical cancer patients treated with radiotherapy, but not those who did not receive radiotherapy, were at increased risk for all second cancers and cancers at heavily irradiated sites (colon, rectum/anus, urinary bladder, ovary, and genital sites) beyond 40 years of follow-up compared with women in the general population. The association of radiotherapy with second cancer risk was modified by age at cervical cancer diagnosis for rectum/anus, genital sites, and urinary bladder, with higher hazard ratios for second cancer at younger ages of cervical cancer. After adjustment for competing mortality, the 40-year cumulative risk of any second cancer was higher among women diagnosed with cervical cancer before age 50 (22.2%; 95% CI = 21.5% to 22.8%) than among women diagnosed after age 50 (16.4%; 95% CI = 16.1% to 16.9%).

Conclusion Cervical cancer patients treated with radiotherapy are at increased risk of second cancers at sites in close proximity to the cervix beyond 40 years of follow-up.

J Natl Cancer Inst 2007;99:1634–43

Cervical cancer is the second most common malignancy among women worldwide (1). Given the 67.2% 10-year relative survival rate for cervical cancer patients and the large number of women treated with radiotherapy (2), it is important to clarify long-term trends in second cancer risk. Furthermore, the presence of established cancer risk factors including human papillomavirus (HPV) infection (3) and cigarette smoking makes cervical cancer survivors a population at high risk for second primary cancers (4–7).

Few series have evaluated second cancer risk beyond 30 years of follow-up among cervical cancer patients (2,4,7,8), and the site-specific risk among 40-year survivors has not been previously quantified. Previous studies have shown that the increased second cancer risk among cervical cancer survivors persists beyond 30 years of follow-up and continues to increase with longer follow-up

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See "Funding" and "Notes" following "References."

DOI: 10.1093/jnci/djm201

(2,4,7,8). In this large population-based study, we report trends in long-term incidence of second cancers among 104 760 cervical cancer survivors, spanning more than 40 years of follow-up. A subset of patients with cervical cancer who were reported in the previous studies (2,4,7,8) have been included in the current report with extended follow-up. We assessed radiotherapy-related risk of second primary cancers among women who were initially treated with radiotherapy through both external comparisons with the general population and internal comparisons with cervical cancer patients who did not receive radiotherapy. We also assessed risk of second cancers that are known to be associated with HPV infection and tobacco use.

Patients and Methods

The cohort for this study was composed of women who were diagnosed with invasive cervical cancer, had survived at least 1 year, and were reported to one of 13 cancer registries (N = 104 760). The participating cancer registries included those of Denmark, Sweden, Norway, Finland, and nine areas of the United States covered by the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program (Connecticut, Hawaii, Iowa, New Mexico, and Utah and the metropolitan areas of San Francisco–Oakland, Detroit, Seattle–Puget Sound, and Atlanta). The calendar years of study and the number of study subjects with invasive cervical cancer from each registry who were included in analyses are shown in Table 1. Follow-up began 1 year after the diagnosis of invasive cervical cancer and ended on the date of second cancer diagnosis, death, or the end of study follow-up, whichever occurred first. Incident second primary cancers occurring at least 1 year after cervical cancer diagnosis were identified by linkage within the respective cancer registry files. Cancers subsequent to the second cancer were not included in the current analyses.

Information regarding initial treatment for cervical cancer in terms of broad categories (e.g., surgery and/or radiotherapy) was recorded in each cancer registry except that of Sweden. Approximately 63% (n = 52 613) of women with cervical cancer received radiotherapy initially, either alone or in combination with other treatments. Radiation treatments involved external beam radiotherapy, brachytherapy with an intracavity radiation source, or both (7). Treatment information was missing for all 22 878 patients from Sweden and for 137, 443, and 1306 patients from Denmark, Finland, and Norway, respectively. After exclusion of all women without treatment information (n = 24 765), we categorized women into two groups, those who received any radiotherapy (n = 52 613) and those who did not (n = 27 382).

Statistical Methods

External Comparisons. Expected numbers for second cancers were calculated by applying registry-, 5-year age group– and 5-year calendar year–, and (in the case of SEER registries) race-specific female general population rates to the appropriate person-time accrued by cervical cancer patients in the cohort. The SEER program registries were combined for this analysis. The standardized incidence ratio (SIR) was calculated as the ratio of observed (O) to expected (E) number of patients diagnosed with cancer, and 95% confidence intervals (CI) were calculated using the method described by Liddell (9,10). SIRs were calculated for all cervical cancer patients and for the patients who did or did not receive radiotherapy. SIRs and 95% confidence intervals were calculated for all second cancers together, all solid cancers, and cancers at specific sites. Because external general population rates were not available separately for cancers of the rectum and anus from the Scandinavian registries, we report SIRs separately for cancers of the rectum (rectum and rectosigmoid junction) and anus (anus, anal canal, and anorectum) from the SEER program only.

The radiation doses to target organs were not available from the cancer registries; however, we classified second cancer sites into three groups according to average dose ranges calculated in a previous case–control study (11). Heavily irradiated sites (>3 Gy) were the small intestine (average radiation dose: 10–20 Gy), colon (24 Gy), rectum/anus (30–60 Gy), urinary bladder (30–60 Gy), uterine corpus (165 Gy), ovary/fallopian tubes (32 Gy), other female genital sites (66 Gy), and bone and connective tissue (7–22 Gy). Moderately irradiated sites (1–3 Gy) were the stomach, liver, pancreas, gall bladder/ducts, and kidneys. Lightly irradiated sites (<1 Gy) were the lip, tongue, salivary glands, mouth, pharynx, esophagus, nose/nasal cavity/sinus, larynx, trachea/bronchus/lung, breast, eye, brain and central nervous system, and thyroid (11). Statistically significant differences in site-specific SIRs between the radiotherapy group and no-radiotherapy group were identified based on non-overlapping 95% confidence intervals.

We evaluated log-linear trends in SIRs over follow-up intervals (defined as 1–9 years, 10–19 years, 20–29 years, 30–39 years, and ≥40 years) by calculating a P_{trend} (10). Because the effects of radiotherapy on cancer incidence are not generally apparent until 10–15 years after therapy (12), we excluded the first follow-up interval

CONTEXT AND CAVEATS

Prior knowledge

Previous studies have indicated that the risk of second cancers is increased among cervical cancer survivors, but overall and site-specific risks among very long-term survivors were unclear.

Study design

The authors used cancer registry data to compare the incidence of cancer in cervical cancer survivors with that of the general population. Regression models were used to determine the association of potential risk factors among these survivors with the incidence of second cancers overall and of particular second cancers.

Contribution

The risk of second cancers at sites that receive high doses of radiation during the treatment of cervical cancer increased with time, and the increase extended beyond 40 years after treatment.

Implications

The findings of this study may be useful in optimizing screening for second cancers among cervical cancer survivors.

Limitations

The multiple statistical comparisons conducted may have led to false-positive associations between the incidence of particular cancers and certain potential risk factors.

Table 1. Characteristics of 1-year survivors of cervical cancer reported to population-based cancer registries*

Cancer registry	No. of patients	Average age at diagnosis, y†	Person-years of follow-up	Average follow-up, y	No. of second primary cancers
All registries (1943–2001)‡	104760	50.1	1281401 (100.0)§	12.2	12496
Denmark (1943–1998)	30183	49.5	425632 (33.2)	14.1	4039
US SEER program(1973–2001)	27466	48.6	248016 (19.4)	9.0	2218
Sweden(1958–2001)	22878	50.6	303614 (23.7)	13.3	3238
Norway(1953–1999)	14227	50.1	181466 (14.2)	12.8	1774
Finland(1953–2001)	10006	53.9	122672 (9.5)	12.3	1227

* All women were diagnosed with cervical cancer as a first primary cancer and survived at least 1 year. SEER = Surveillance, Epidemiology, and End Results.

† Average age at diagnosis of first primary cervical cancer.

‡ Calendar years of diagnosis of cervical cancer.

§ Percentage of total follow-up contributed by registry.

(1–9 years) in the assessment of trends in SIRs. Excess absolute risk (EAR; excess cancer risk per 10000 person-years) was calculated as ([observed cancers minus expected cancers]/person-years) multiplied by 10000. Finally, we calculated cumulative risks for any second cancer (except cervical cancer) after accounting for competing mortality (specific for sex, registry, age, and calendar period) using the method described by Gooley et al. (13). Cumulative risks for women with cervical cancer stratified by age at cervical cancer diagnosis (<50 and ≥50 years) were calculated across follow-up times of 10, 20, 30, and 40 years and compared with cumulative risks for women in the general population; 95% confidence intervals for cumulative risks were calculated using counting process methods (14).

Internal Comparisons. Cervical cancer survivors who did not receive radiotherapy are more similar to survivors who received radiotherapy than are women in the general population in terms of unmeasured cervical cancer cofactors. Therefore, to further assess the effects of radiotherapy, we performed internal comparisons of risk between the radiotherapy and the no-radiotherapy group using Cox regression models. Internal comparisons were restricted to women with known treatment information (n = 79995). The proportionality assumption was checked by investigating several interactions. These internal comparisons focused specifically on the statistical interaction of radiotherapy with 1) follow-up time (for all second cancers, second cancers at heavily irradiated sites grouped together, and second cancers at individual sites close to the cervix, i.e., the rectum/anus, genital sites, urinary bladder, and colon) and 2) with age at cervical cancer diagnosis (for cancers at sites close to the cervix: rectum/anus, genital sites, urinary bladder, and colon). Because hysterectomies would have been performed on a large proportion of women with cervical cancer, we did not perform internal comparisons for cancers of uterine corpus and ovary/fallopian tubes.

The interaction of radiotherapy with follow-up time was assessed in two steps: First, we used an extended Cox regression model to estimate hazard ratios (HRs; any radiotherapy versus no-radiotherapy) specific for each follow-up interval (10–19, 20–29, 30–39, and ≥40 years). Second, we assessed log-linear trends in interval-specific hazard ratios by evaluating a model that incorporated a linear interaction between the treatment variable and follow-up interval. Follow-up time was used as the time scale for Cox regression analyses, and the first latency interval (1–9 years of follow-up) was excluded. These Cox regression models were adjusted simultaneously for registry, age at cervical cancer diagnosis (treated as a continuous variable centered at age 50), interaction of treatment with age at cervical cancer diagnosis, calendar year of cervical cancer diagnosis (treated as a continuous variable centered at year 1977), and interaction of treatment with calendar year of cervical cancer diagnosis.

Cox proportional hazards regression models were used to assess the interaction of treatment with age at cervical cancer diagnosis. In these models, an interaction term with age was included to estimate the hazard ratio for treatment (radiotherapy versus no-radiotherapy) for four groups of age at cervical cancer diagnosis (<40 years, 40–49 years, 50–59 years, and ≥60 years). The model included additional adjustment for registry, calendar year of cervical cancer diagnosis (treated as a continuous variable), and interaction of treatment with calendar year. Log-linear trends in radiotherapy-related hazard ratios across age categories were evaluated by incorporating an interaction term between treatment and age group.

Results

The cohort included 104760 one-year survivors of invasive cervical cancer who were followed-up for 1281401 person-years (average 12.2 years; range = 1–55 years) (Table 1). Among the registries, Denmark contributed the highest number of person-years, followed in order by Sweden, the United States (the registries in the SEER program), Norway, and Finland (Table 1). The follow-up period ≥40 years after cervical cancer diagnosis comprised contributions from Denmark (7011 person-years), Sweden (1194 person-years), Norway (929 person-years), and Finland (814 person-years). Cervical cancer was diagnosed at an average age of 50.1 years (standard deviation = 14.4 years), and the median calendar year of cervical cancer diagnosis was 1977 (range = 1943–2001).

Second Cancer Risk Compared With the External General Population

In all, 12496 incident second cancers were observed during follow-up (Table 2; SIR = 1.30, 95% CI = 1.28 to 1.33; EAR = 22.7 per 10000 person-years). Small but statistically significant differences were observed across registries in overall SIRs for a second cancer

Table 2. Observed numbers and SIRs of second cancers by treatment for cervical cancer*

	All patients†			Any radiotherapy		No radiotherapy	
	(n = 104 760; py = 1 281 401)			(n = 52 613; py = 621 913)		(n = 27 382; py = 337 707)	
Site of second cancer	Observed	SIR (95% CI)	EAR‡	Observed	SIR (95% CI)	Observed	SIR (95% CI)
All cancers§	12 496	1.30 (1.28 to 1.33)	22.73	6796	1.34 (1.31 to 1.38)	2244	1.06 (1.02 to 1.11)
All solid cancers	11 720	1.31 (1.29 to 1.34)	21.88	6397	1.36 (1.33 to 1.39)	2102	1.06 (1.02 to 1.11)
Heavily irradiated sites‖	4603	1.51 (1.47 to 1.56)	12.21	2664	1.59 (1.54 to 1.66)	605	0.97 (0.90 to 1.06)
Small intestine	63	1.80 (1.39 to 2.31)	0.22	31	1.84 (1.25 to 2.62)	7	1.05 (0.42 to 2.18)
Colon	1168	1.22 (1.16 to 1.30)	1.69	670	1.22 (1.13 to 1.32)	178	0.93 (0.80 to 1.08)
Rectum/anus¶	817	1.84 (1.72 to 1.98)	2.93	482	1.90 (1.74 to 2.09)	108	1.28 (1.06 to 1.55)
Urinary bladder	949	3.44 (3.23 to 3.67)	5.25	536	3.51 (3.22 to 3.83)	109	1.93 (1.59 to 2.34)
Uterine corpus	484	0.74 (0.68 to 0.81)	−1.32	308	0.91 (0.81 to 1.02)	16	0.11 (0.06 to 0.18)
Ovary/fallopian tubes	462	0.88 (0.81 to 0.97)	−0.46	269	0.97 (0.86 to 1.10)	67	0.62 (0.48 to 0.79)
Other female genital#	497	4.81 (4.40 to 5.25)	3.07	278	4.73 (4.19 to 5.32)	102	5.00 (4.08 to 6.08)
Bone	32	2.70 (1.85 to 3.82)	0.16	19	3.00 (1.81 to 4.70)	3	1.18 (0.24 to 3.46)
Soft tissue	114	2.53 (2.10 to 3.05)	0.54	59	2.84 (2.16 to 3.67)	10	1.13 (0.54 to 2.09)
Moderately irradiated sites**	1543	1.29 (1.24 to 1.37)	2.78	897	1.30 (1.22 to 1.39)	223	1.15 (1.01 to 1.32)
Stomach	492	1.30 (1.19 to 1.43)	0.90	317	1.31 (1.17 to 1.47)	48	0.96 (0.72 to 1.29)
Liver	84	1.10 (0.88 to 1.36)	0.06	45	1.10 (0.81 to 1.48)	18	1.31 (0.78 to 2.08)
Pancreas	447	1.37 (1.25 to 1.50)	0.94	256	1.35 (1.19 to 1.53)	75	1.26 (1.00 to 1.59)
Gall bladder/ducts	178	1.14 (0.98 to 1.32)	0.17	97	1.19 (0.97 to 1.46)	21	0.94 (0.59 to 1.45)
Kidney	342	1.35 (1.22 to 1.51)	0.70	182	1.34 (1.15 to 1.55)	61	1.26 (0.97 to 1.63)
Lightly irradiated sites††	4674	1.17 (1.14 to 1.21)	5.48	2439	1.21 (1.16 to 1.26)	1136	1.11 (1.05 to 1.18)
Lip	31	1.66 (1.13 to 2.36)	0.10	23	2.17 (1.38 to 3.27)	5	1.61 (0.52 to 3.76)
Tongue	32	1.18 (0.81 to 1.67)	0.04	20	1.36 (0.84 to 2.12)	4	0.61 (0.16 to 1.57)
Salivary gland	15	0.68 (0.38 to 1.13)	−0.05	6	0.51 (0.19 to 1.13)	2	0.43 (0.05 to 1.57)
Mouth	66	1.48 (1.15 to 1.89)	0.17	32	1.30 (0.90 to 1.85)	21	1.98 (1.23 to 3.04)
Pharynx	52	1.83 (1.37 to 2.41)	0.18	23	1.57 (1.00 to 2.37)	15	2.28 (1.28 to 3.78)
Esophagus	101	1.42 (1.16 to 1.73)	0.24	68	1.55 (1.21 to 1.97)	12	0.90 (0.47 to 1.58)
Nasal cavity/sinus	20	1.21 (0.74 to 1.88)	0.03	11	1.15 (0.57 to 2.06)	5	1.46 (0.47 to 3.43)
Larynx	56	2.02 (1.53 to 2.63)	0.22	30	1.92 (1.30 to 2.75)	17	1.99 (1.16 to 3.19)
Trachea/bronchus/lung	1912	2.57 (2.47 to 2.70)	9.14	1119	2.74 (2.58 to 2.91)	422	1.93 (1.76 to 2.13)
Pleura	11	1.23 (0.61 to 2.21)	0.02	3	0.59 (0.12 to 1.73)	5	3.02 (0.98 to 7.07)
Breast	2011	0.77 (0.74 to 0.81)	−4.49	905	0.71 (0.67 to 0.76)	562	0.85 (0.79 to 0.93)
Eye	29	1.21 (0.81 to 1.74)	0.04	19	1.46 (0.88 to 2.29)	3	0.64 (0.13 to 1.87)
Brain/central nervous system	234	0.93 (0.82 to 1.06)	−0.13	116	0.94 (0.78 to 1.14)	45	0.86 (0.63 to 1.16)
Thyroid	102	0.96 (0.79 to 1.17)	−0.03	62	1.26 (0.97 to 1.62)	18	0.60 (0.36 to 0.95)
Other sites							
Melanoma	199	0.74 (0.65 to 0.86)	−0.53	84	0.68 (0.55 to 0.85)	51	0.70 (0.53 to 0.93)
Non-Hodgkin lymphoma	333	1.27 (1.14 to 1.42)	0.56	157	1.20 (1.02 to 1.40)	68	1.11 (0.86 to 1.41)
Hodgkin lymphoma	31	0.97 (0.66 to 1.38)	−0.01	17	1.04 (0.61 to 1.67)	9	1.20 (0.55 to 2.29)
Multiple myeloma	120	0.89 (0.74 to 1.07)	−0.11	71	0.95 (0.75 to 1.21)	16	0.63 (0.36 to 1.04)
Chronic lymphocytic leukemia	77	0.87 (0.69 to 1.10)	−0.08	44	0.87 (0.63 to 1.17)	16	0.91 (0.52 to 1.49)
Chronic myelocytic leukemia	31	0.94 (0.64 to 1.34)	−0.01	14	0.74 (0.41 to 1.25)	8	1.23 (0.53 to 2.44)
Acute lymphoblastic leukemia	5	0.63 (0.21 to 1.49)	−0.02	1	0.26 (0.00 to 1.46)	2	1.09 (0.12 to 3.95)
Acute non-lymphocytic leukemia	122	1.72 (1.43 to 2.06)	0.40	65	1.68 (1.30 to 2.15)	18	1.12 (0.67 to 1.78)

* py = person-years; SIR = standardized incidence ratio; EAR = excess absolute risk.

† Includes 24 765 patients for whom treatment information was not available (one from the SEER program, 137 from Denmark, 443 from Finland, and all patients [22 878] from Sweden).

‡ EAR was calculated as ([O − E]/person years) × 10 000.

§ Cancers of unspecified origin (n = 514) are included in the overall number of second cancers.

‖ Heavily irradiated sites (>3 Gy average radiation dose) (11). Category includes 17 cancers of other urinary sites.

¶ Includes cancers of the rectal junction.

Includes cancers of the vagina, vulva, and other unspecified genital sites.

** Moderately irradiated sites (1–3 Gy average radiation dose) (11).

†† Lightly irradiated sites (<1 Gy average radiation dose) (11). Category includes two cancers of other respiratory sites.

($P_{heterogeneity}$<.001; SIRs for Norway = 1.44, Sweden = 1.41, Finland = 1.40, Denmark = 1.21, and SEER program = 1.18). We also observed statistically significant heterogeneity in overall SIRs across registries for second cancers at heavily irradiated sites ($P_{heterogeneity}$<.001; SIRs for Norway = 1.70, Sweden = 1.76, Finland = 1.77, Denmark = 1.32, and SEER program = 1.32) and lightly irradiated sites ($P_{heterogeneity}$ = .015; SIRs for Norway = 1.29, Sweden = 1.14, Finland = 1.30, Denmark = 1.14, and SEER program = 1.14). No heterogeneity was observed for second cancers at moderately irradiated sites ($P_{heterogeneity}$ = .137).

Among all cervical cancer patients, the incidence of second cancers at several sites was elevated to a statistically significant extent and SIRs ranged from 1.22 to 4.81. The largest SIRs were observed for cancers of other female genital sites (vagina, vulva, and unspecified genital sites other than cervix; SIR = 4.81), urinary bladder (SIR = 3.44), and bone (SIR = 2.70). The largest excess absolute risks were observed for cancers of the trachea/bronchus/lung (EAR = 9.14 per 10 000 person-years), urinary bladder (EAR = 5.25 per 10 000 person-years), and female genital sites (EAR = 3.07 per 10 000 person-years).

Among cervical cancer patients who received radiotherapy, SIRs were elevated to a statistically significant extent for cancers at heavily (SIR = 1.59; 95% CI = 1.54 to 1.66), moderately (SIR = 1.30; 95% CI = 1.22 to 1.39), and lightly (SIR = 1.21; 95% CI = 1.16 to 1.26) irradiated sites (Table 2). In contrast, no substantial increase in the incidence of second cancers at heavily irradiated sites was observed among women who did not receive radiotherapy (SIR = 0.97), although SIRs for cancers at moderately and lightly irradiated sites (SIRs = 1.15 and 1.11, respectively) were increased to a small but statistically significant extent among women who did not receive radiotherapy. SIRs for HPV-related cancers (pharynx, genital sites, and rectum/anus) and smoking-related cancers (pharynx, larynx, trachea/bronchus/lung, pancreas, and urinary bladder) were statistically significantly increased in both treatment groups. Statistically significant deficits of breast cancer (SIRs = 0.71 and 0.85 in radiotherapy and no-radiotherapy groups) and melanoma were also observed in both treatment groups. Notable differences in SIRs between the radiotherapy and the no-radiotherapy groups were observed for certain cancers, with SIRs being statistically significantly higher in the radiotherapy group than in the no-radiotherapy group for cancers of soft tissue, stomach, colon, rectum/anus, urinary bladder, and trachea/bronchus/lung (Table 2). For hematologic sites, elevated SIRs were observed for non-Hodgkin lymphoma and acute non-lymphocytic leukemia in the radiotherapy group. No statistically significant increase was observed in either treatment group for Hodgkin lymphoma, chronic lymphocytic leukemia, chronic myelocytic leukemia, or acute lymphoblastic leukemia.

When cancers of the rectum and anus were evaluated separately in SEER (N = 27 466), statistically significant increases in overall SIRs were observed for cancers of both the rectum (SIR = 1.43; 95% CI = 1.14 to 1.76) and the anus (SIR = 3.12; 95% CI = 1.88 to 4.88). SIRs for rectum were statistically significantly increased only among women who received any radiotherapy (SIR = 1.61; 95% CI = 1.21 to 2.09 for radiotherapy versus SIR = 1.18; 95% CI = 0.80 to 1.69 for no radiotherapy). SIRs for anal cancer were statistically significantly increased in both radiotherapy and no-radiotherapy groups (SIR = 2.52; 95% CI = 1.08 to 4.96 and SIR = 3.79; 95% CI = 1.89 to 6.78, respectively).

Analysis of interval-specific SIRs and P_{trends} in SIRs across follow-up intervals (excluding the first 10 years of follow-up) among women initially treated with radiotherapy (Table 3) shows that overall risk for second cancers increased to a statistically significant extent with follow-up time from 1.27 in the interval of 10–19 years after treatment to 1.83 among 40-year survivors (P_{trend}<.001). SIRs for cancers of heavily irradiated sites considered together and for colon, rectum/anus, urinary bladder, ovary/fallopian tubes, and female genital sites considered separately were statistically significantly elevated beyond 40 years of follow-up, ranging from two-fold for colon cancer to ninefold for cancers of the vagina, vulva, and unspecified genital sites. Statistically significant increasing trends in SIRs over follow-up time were observed specifically for cancers of rectum/anus, bladder, ovary, and female genital sites. SIRs for second cancers at lightly irradiated sites, specifically for trachea/bronchus/lung, decreased to a statistically significant extent from 10 years to ≥40 years of follow-up. No statistically significant trends in SIRs across latency intervals were observed for second cancers of small intestine, colon, bone, soft tissue, and moderately irradiated sites. SIR for acute non-lymphocytic leukemia was statistically significantly increased only in the first 10 years of follow-up, whereas SIRs for chronic lymphocytic leukemia were not statistically significantly increased in any follow-up interval.

Among women who did not receive radiotherapy, statistically significantly elevated SIRs in the period beyond 40 years of follow-up were observed only for cancers of the urinary bladder, for which SIRs increased over follow-up intervals (SIR for 1–9 years = 1.99, 10–19 years = 1.53, 20–29 years = 1.53, 30–39 years = 3.32, and ≥40 years = 6.60; P_{trend}<.05). SIRs for all second cancers were elevated to a statistically significant extent during the first 10 years of follow-up (SIR = 1.13). SIRs for lung cancer were statistically significantly elevated through 40 years of follow-up, and SIRs for female genital sites were elevated through 30 years of follow-up (data not shown).

We analyzed cumulative risks of any cancer stratified by age for women with cervical cancer and for women in the external general population (Fig. 1). Among women who were less than 50 years of age at cervical cancer diagnosis, cumulative risks of any cancer were statistically significantly higher among cervical cancer survivors (cumulative risk at 10 years of follow-up = 3%, 20 years = 7%, 30 years = 15%, and 40 years = 22%) than among women in the general population (cumulative risk at 10 years = 1%, 20 years = 5%, 30 years = 10%, and 40 years = 15%). Similarly, among women older than 50 years at cervical cancer diagnosis, cumulative risks were statistically significantly higher among cervical cancer survivors compared with women in the general population. Among cervical cancer survivors, cumulative risks were generally higher when women were diagnosed with cervical cancer at younger ages (<50 years).

Internal Comparisons of Second Cancer Risk

Analysis of interval-specific hazard ratios from internal comparisons of risk between the radiotherapy group and no-radiotherapy group shows that compared with women who did not receive radiotherapy, cervical cancer survivors treated by radiation were at a statistically significant increased risk in each latency interval for second cancer at any site (Fig. 2, A) and for second cancers at heavily irradiated sites (Fig. 2, B). Additionally, the hazard ratio for any second cancer increased with increasing follow-up time, and the increase was statistically significant (P_{trend} = .011). There was also an increase in radiotherapy-related hazard ratios for heavily irradiated sites grouped together over follow-up (P_{trend} = .087). For second cancers of the rectum/anus (Fig. 2, C), genital sites (Fig. 2, D), and urinary bladder (Fig. 2, E), we did not observe statistically significant trends in hazard ratios over follow-up time. However, hazard ratios were generally higher than unity in all

Table 3. Observed numbers and SIRs for selected second cancers among cervical cancer patients treated with radiotherapy by time since diagnosis (latency interval)*

	Latency interval										
	1–9 y (n = 52 613; py = 91 877)		10–19 y (n = 23 780; py = 186 713)		20–29 y (n = 14 173; py = 99 547)		30–39 y (n = 6175; py = 36 551)		≥40 y (n = 1675; py = 7225)		P_{trend} excluding 1–9 y (direction of trend)†
Second cancer	Obs	SIR	Obs	SIR	Obs	SIR	Obs	SIR	Obs	SIR	
All cancers	2399	1.31‡	1977	1.27‡	1480	1.37‡	737	1.50‡	203	1.83‡	<.001 (+)
All solid cancers	2258	1.32‡	1859	1.28‡	1386	1.38‡	697	1.53‡	197	1.93‡	<.001 (+)
Heavily irradiated sites§	688	1.17‡	780	1.53‡	681	1.87‡	392	2.30‡	123	3.15‡	<.001 (+)
Small intestine	9	1.54	9	1.73	8	2.14	5	2.94	0	0.00	.692
Colon	225	1.25‡	184	1.13	155	1.23‡	78	1.19	28	1.67‡	.157
Rectum/anus‖	81	0.93	154	2.01‡	127	2.23‡	84	3.09‡	36	5.79‡	<.001 (+)
Urinary bladder	127	2.70‡	130	2.84‡	152	4.13‡	101	5.44‡	26	5.83‡	<.001 (+)
Uterine corpus	63	0.48‡	113	1.06	87	1.27‡	38	1.40	7	1.39	.089
Ovary/fallopian tubes	66	0.61‡	86	0.98	68	1.22	38	1.73‡	11	2.72‡	<.001 (+)
Other female genital¶	82	4.00‡	70	4.01‡	70	5.54‡	41	6.33‡	15	8.66‡	<.001 (+)
Bone	8	2.86‡	7	3.63‡	4	3.59	0	0.00	0	0.00	.288
Soft tissue	20	2.41‡	23	3.63‡	9	2.24‡	7	4.05‡	0	0.00	.433
Moderately irradiated sites#	307	1.29‡	256	1.22‡	212	1.37‡	101	1.40‡	21	1.37	.178
Stomach	127	1.32‡	99	1.34‡	62	1.30‡	24	1.18	5	1.23	.592
Pancreas	98	1.63‡	63	1.10	58	1.28	33	1.47‡	4	0.79	.453
Kidney	39	0.90	55	1.31	56	1.72‡	26	1.69‡	6	1.91	.159
Lightly irradiated sites**	1154	1.51‡	707	1.12‡	391	0.95	154	0.88	33	0.87	<.001 (–)
Trachea/bronchus/lung	591	4.23‡	298	2.34‡	160	1.73‡	63	1.54‡	7	0.80	<.001 (–)
Breast	393	0.78‡	282	0.70‡	150	0.60‡	60	0.59‡	20	0.90	.435
Other sites											
Acute non-lymphocytic leukemia	36	2.74‡	12	1.01	11	1.26	5	1.24	1	1.05	.699
Chronic lymphocytic leukemia	9	0.56	11	0.74	13	1.11	10	1.62	1	0.59	.221

* py = person-years; Obs = observed; SIR = standardized incidence ratio.

† (+) denotes increasing trend and (–) denotes decreasing trend across follow-up intervals.

‡ Denotes statistically significant at $P<.05$.

§ Heavily irradiated sites (>3 Gy average radiation dose) (11).

‖ Includes cancers of the rectal junction.

¶ Includes cancers of the vagina, vulva, and other unspecified genital sites.

Moderately irradiated sites (1–3 Gy average radiation dose) (11).

** Lightly irradiated sites (<1 Gy average radiation dose) (11).

follow-up intervals (10–19, 20–29, 30–39, and ≥40 years). For colon cancer (Fig. 2, F), radiotherapy-related hazard ratios increased to a statistically significant extent over follow-up time, being highest in the period ≥40 years of follow-up (HRs for 10–19 years = 1.33, 20–29 years = 1.52, 30–39 years = 3.32, and ≥40 years = 8.30; P_{trend} = .017).

Evidence for effect modification of radiotherapy-related risk by age at cervical cancer diagnosis was observed for second cancers of rectum/anus, genital sites, and urinary bladder (Fig. 3; P_{trend} = 0.002, <.001, and .005, respectively). For these sites, hazard ratios (for patients who received radiotherapy versus those who did not) were highest among women diagnosed with cervical cancer before the age of 40 and were lowest among women diagnosed with cervical cancer after the age of 59 years. There was less evidence of effect modification by age for colon cancer (P_{trend} = .186).

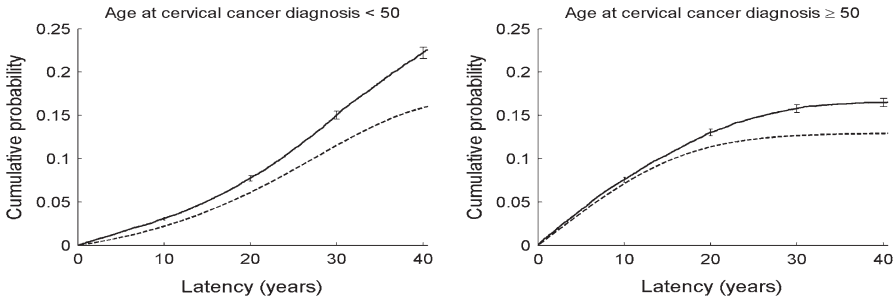

Fig. 1. Cumulative risk of all second cancers (excluding cancer of the cervix) after adjustment for competing risks of death. Results are shown for cervical cancer patients (**solid line**) and women in the external general population (**dashed line**) who were less than 50 years old at the time of diagnosis (**left panel**) or 50 years or older (**right panel**).

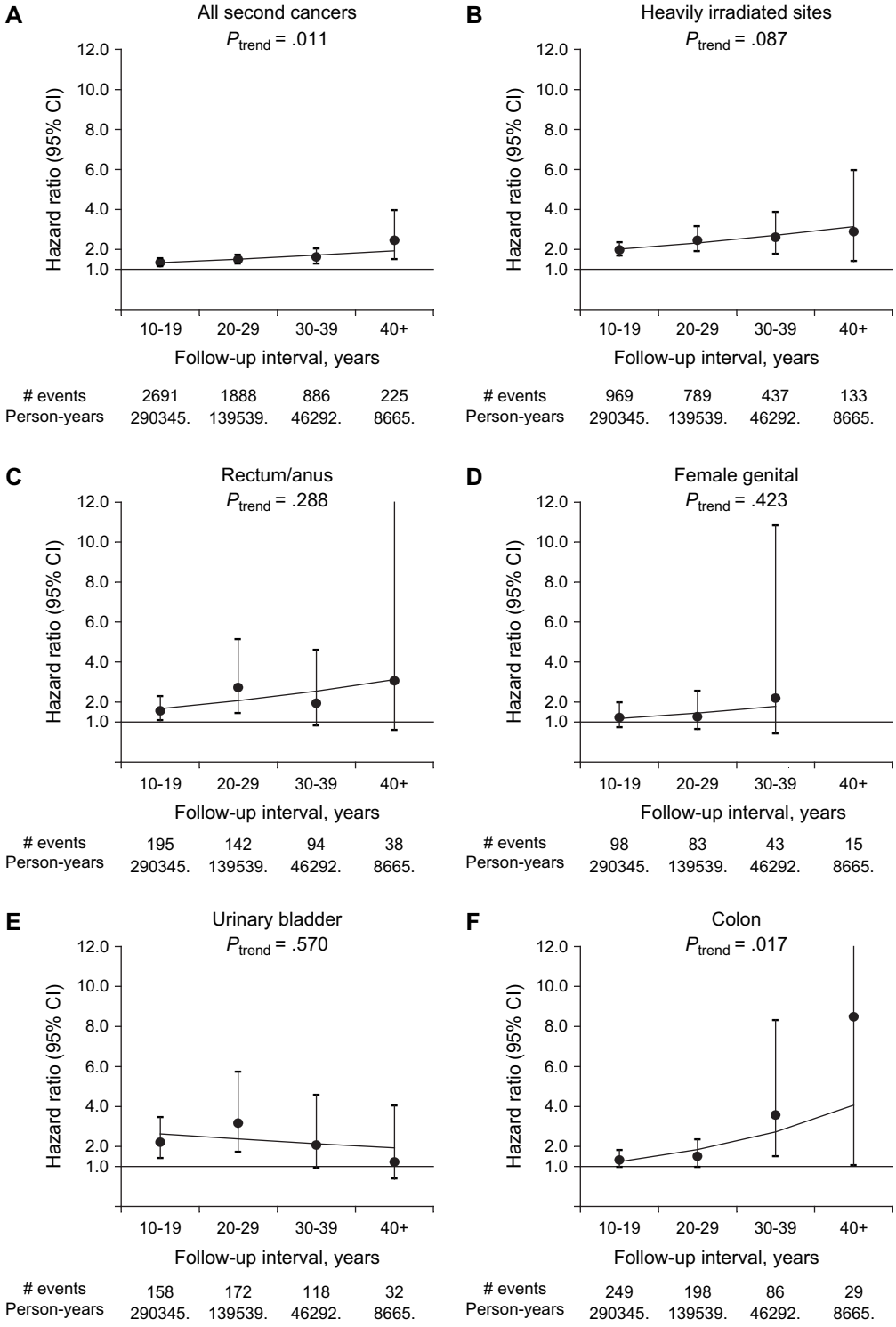

Fig. 2. Hazard ratios and 95% confidence intervals (CIs) comparing outcomes in cervical cancer patients who received radiotherapy with cervical patients who did not receive radiotherapy calculated from Cox regression models. **A**) All second cancers. **B**) Cancers at heavily irradiated sites. **C**) Cancers of the rectum/anus. **D**) Female genital cancers. **E**) Cancers of the urinary bladder. **F**) Colon cancer. All models incorporated terms for treatment, treatment by latency, age, treatment by age, calendar year, treatment by calendar year, and registry. The exponential trend line indicates the log-linear relationship (interaction) between treatment variable (radiotherapy versus no radiotherapy) and follow-up interval (10–19, 20–29, 30–39, and ≥40 years of follow-up). The *P* value for the interaction term is denoted in each panel. The total number of events and person-years within each latency interval (including both radiotherapy and no-radiotherapy groups) are also shown. The hazard ratio and 95% confidence intervals for female genital sites in the latency interval ≥40 years after cervical cancer diagnosis could not be estimated owing to zero events in the no-radiotherapy group. The upper 95% CIs for the hazard ratios for cancers of the rectum/anus and colon at ≥40 years of follow-up were 15.4 and 67.8, respectively.

Discussion

Based on 12 496 second cancers in our population-based study of more than 100 000 cervical cancer patients, we have shown for the first time, to our knowledge, that following radiotherapy for cervical cancer treatment, risk for all second cancers continues to increase over time and remains elevated for more than 40 years. We extend findings in previous studies (4–8,11,15–18) by showing that risks for second cancers of the rectum/anus, colon, urinary bladder, ovary, and female genital sites other than cervix remain elevated to a statistically significant extent for at least 40 years after radiotherapy.

Evidence of a high-dose radiation effect following radiotherapy for anogenital cancers has been inconsistent for second cancers of the colon and stomach (4,6,7,12,19–22). We found that when compared with risk in the general population, risk for cancers of the stomach and colon was increased to a statistically significant

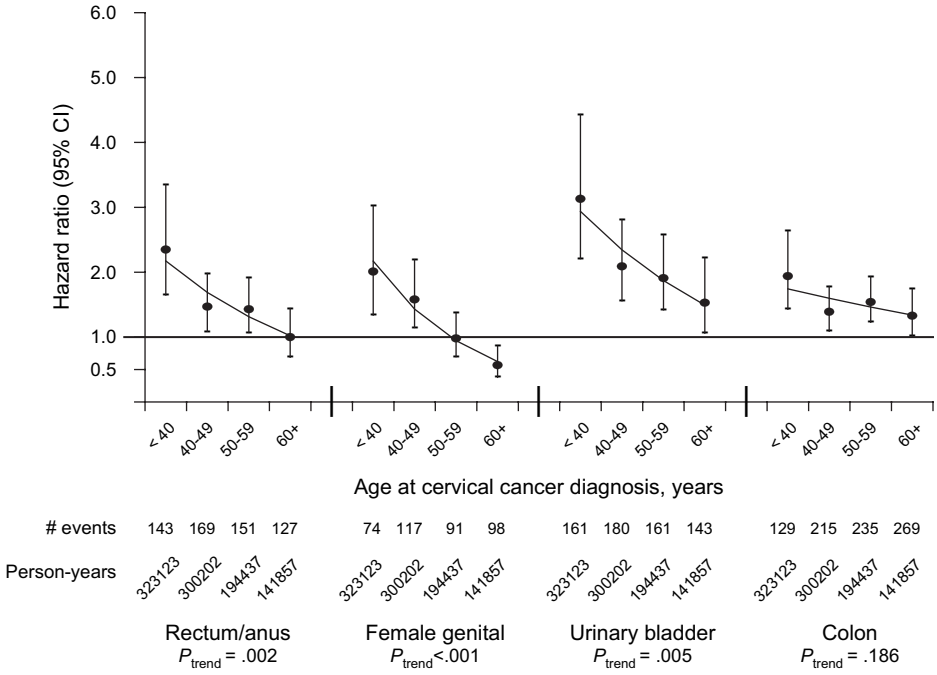

Fig. 3. Hazard ratios of second cancers at specific sites for women who received radiotherapy versus those who did not receive radiotherapy according to age at cervical cancer diagnosis. All models incorporated terms for treatment, age, treatment by age, calendar year, treatment by calendar year, and registry. The exponential trend line indicates the log-linear relationship (interaction) between treatment variable (radiotherapy vs no radiotherapy) and age at cervical cancer diagnosis. The *P* value for the interaction term is denoted in each panel.

extent only among women initially treated with radiotherapy. Furthermore, internal comparisons of risk showed that following radiotherapy, colon cancer risk was statistically significantly increased with increased follow-up time. The large number of women contributing extended follow-up in our study may have afforded statistical power needed to detect moderate excesses.

Our observation of a deficit of breast cancer (SIR = 0.77) among cervical cancer survivors is similar to those of previous reports (7,23). This deficit may arise from several factors, including factors related to pregnancy and surgical and radiation treatments. Cervical cancer patients in general are younger at first delivery and of higher parity than women in the general population, and both characteristics are associated with a lower risk of breast cancer (7). Additionally, hysterectomy and ovarian ablation through irradiation may alter hormonal exposure of the breast tissue and thereby reduce subsequent breast cancer risk (7). Although we could not assess the population not at risk for cancers of uterine corpus and ovary/fallopian tubes owing to hysterectomies, we observed that among women treated by radiotherapy, after an initial deficit (in 1–9 years of follow-up), SIRs for second cancers of ovary/fallopian tubes increased to above unity over follow-up beyond 10 years.

We also observed a statistically significant deficit of melanoma in both the radiotherapy and no–radiotherapy treatment groups (5). Although the reasons are unclear, the deficit of melanoma may be related to factors among cervical cancer patients such as low socioeconomic status that are associated with lower risk of melanoma (24). Consistent with previous studies of cervical cancer patients treated with radiation, statistically significant risks of acute non-lymphocytic leukemia were seen only 1–9 years after radiotherapy (SIR = 2.74) whereas risk of chronic lymphocytic leukemia was not statistically significantly increased at any time after exposure (4,7).

HPV is the primary cause of invasive cervical cancer (3), and it plays a role in the etiology of cancers of the vagina, vulva, anus, and a subset of cancers in the oropharynx (25–27). Consistent with an etiologic role for HPV, risk of these cancers was increased to a statistically significant extent in both the radiotherapy and no-radiotherapy groups. The increased risk of HPV-related cancers among cervical cancer survivors may reflect transmission of HPV by sexual behavior to sites other than the cervix, a genetic susceptibility to oncogenic effects of HPV, or shared risk factors such as smoking. We also observed increased risks for smoking-related cancers (pharynx, trachea/bronchus/lung, pancreas, and urinary bladder) in both the radiotherapy and no-radiotherapy groups, reflecting the previously observed increased cigarette smoking among cervical cancer patients (28,29).

Previous investigations have also assessed temporal patterns in radiotherapy-related risk by examining trends in SIRs over follow-up time (4,7,8). Attributing trends in SIRs (which are derived through external comparisons with the general population) to a radiotherapy effect may be prone to confounding biases because in addition to receiving radiotherapy, cervical cancer patients have more HPV infections and smoke more than women in the general population (12). Therefore, for sites in close proximity to the cervix as well as for the aggregated groups of all second cancers and cancers of heavily irradiated sites, we performed internal comparisons of second cancer risk between the radiotherapy group and the no-radiotherapy group.

Our observations of statistically significant increases in hazard ratios over follow-up time for second cancer at any site when comparing women who received radiotherapy versus those who did not and borderline statistically significant increases in hazard ratios over follow-up time for heavily irradiated sites considered together (Fig. 2) are consistent with trends in SIRs derived from external comparisons (Table 3). Whereas SIRs for rectum/anus,

female genital sites, and urinary bladder cancers were increased to a statistically significant extent with increasing follow-up time among women who received radiotherapy, our internal comparisons for these sites indicated no evidence for trends in hazard ratios over follow-up time. Additionally, no trends in SIRs over follow-up time were observed for colon cancer, whereas internal comparisons indicated that hazard ratios did increase to a statistically significant extent over follow-up time. These discrepancies between external and internal comparisons may have arisen from better control of confounding by HPV infections (for rectum/anus and other female genital sites) and smoking (for bladder cancer) in internal comparisons.

Hazard ratios for second cancers of rectum/anus, genital sites, and urinary bladder among women who received radiotherapy compared with women who did not were statistically significantly higher for women who underwent irradiation at younger ages. These observations are similar to previous reports that indicated that the risk of radiotherapy-induced cancers among adults is higher when treated at younger ages and that the increased risk may persist throughout life (11).

Consistent with the presence of several established cancer risk factors among cervical cancer survivors, including radiation, HPV, and smoking, we found a high cumulative risk of any second cancer among long-term survivors (40-year cumulative risk = 22%). Furthermore, excess absolute risks were high for sites in close proximity to the cervix that receive high doses of radiation (EAR = 22.7 per 10 000 person-years). Radiotherapy and smoking have been shown to interact in a multiplicative fashion to increase lung cancer risk among Hodgkin lymphoma survivors (30–32). It is not known whether radiotherapy interacts with HPV infection or cigarette smoking to increase second cancer risk among cervical cancer survivors. We could not assess risk factor interactions in this study because we did not have information on smoking behaviors among cervical cancer survivors. However, we note that SIRs for cancers at sites in close proximity to the cervix, such as the rectum/anus and urinary bladder—although increased to a statistically significant extent among women who did not receive radiotherapy—were even higher among women who received radiotherapy. Further studies are required to assess whether these differences in risk arise from risk factors acting either independently or synergistically. The effects of radiation, HPV, and smoking may interact through common cellular pathways such as the p53 tumor suppressor pathway (32,33).

Several limitations of this study should be mentioned. Treatment information recorded in cancer registries is not always accurate, and radiotherapy status may have been misclassified in some instances. Furthermore, the availability of information regarding initial cancer therapy but not subsequent treatment may have also resulted in misclassification. Previous studies of cervical cancer patients, however, have not found misclassification of treatment to be a serious complication (11). We also could not take into account differences in radiation doses across treatment modalities or changes in treatments over calendar time. Because radiation doses were not available for individual patients, categories of doses were based on results from case–control studies previously conducted on many of the patients that had been included in the current investigation (11). Finally, multiple statistical comparisons were performed in this study, which could have led to false-positive associations.

In conclusion, we found that the risk of second cancers at sites in close proximity to the cervix, which receive high doses of radiation, increased with time and the increase extended beyond 40 years after treatment. Although we did not evaluate either HPV infections or history of smoking, we also found that the risks of HPV- and smoking-related cancers were increased to a statistically significant extent among cervical cancer survivors. The high cumulative risk of second primary cancers in cervical cancer survivors should prompt screening efforts in this group of women.

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Funding

Intramural Research Program, National Cancer Institute, National Institutes of Health.

Notes

We wish to thank Jeremy Miller, Information Management Services, Rockville, MD, for expert computer support and data management.

The authors take full responsibility for the study design, data collection, analysis and interpretation of the data, the decision to submit the manuscript for publication, and the writing of the manuscript.

Manuscript received December 8, 2006; revised July 26, 2007; accepted September 24, 2007.