Second Primary Cancer after Treatment for Cervical Cancer

An International Cancer Registries Study

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Background. **The pattern of second cancers after treatment for cervical cancer provides important information on the risk of radiation-induced malignancies. Large numbers of women survive many years and can be studied for late effects.**

Methods. **Incident second cancers in 86,193 patients with cervical cancer reported to 13 population-baaed cancer registries in 5 countries were evaluated to estimate the risk of second cancer among very long term survivors.**

Results. **Overall, 7543 second cancers were observed versus 6015 cancers expected based on population rates (observed/expected = 1.2). Lung cancer accounted for nearly half of the excess cancers. Among the 49,828 women treated with radiation, 3750 survived 30 or more years and a two-fold risk of cancers of heavily irradiated organs was seen. Most of the excess cancers were of the rectum, vagina, vulva, ovary, and bladder. Patterns of risk over time since treatment were consistent with a radiation etiology. Significant increases of nonchronic lymphocytic leukemia and cancers of the bone and kidney were also linked to radiotherapy. Women treated surgically were also at significant risk of second cancers, in all likelihood related to cigarette smoking and risk factors similar to those of cervical cancer,**

Conclusions. **Curative therapy for cervical cancer results in large numbers of long term survivors who develop second cancers very late in life. Radiation is an important cause of this increase and there is no evidence that risk returns to normal levels. *Cancer* 1995;76:442-52.**

Key words: cervical cancer, radiotherapy, second cancer, late effects.

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Supported in part by Public Health Service Contracts NO1-CP-85638-02, N01-CP-85639 -03, N01-CP-85626-01, and NOl-CP-85604 between the Division of Cancer Etiology and the Finnish Cancer Registry, Danish Cancer Registry, University of Iowa and Westat, respectively.

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The authors thank Mr. Dave Hacker and Ms. Patty Griffin of IMS for computer support; Ms. Diana Wagner and Mr. Dan Olson of the State Health Registry of Iowa for computer programming; and Ms. Rebecca Albert for manuscript preparation.

Received October 25, 1994; revision received April 6, 1995; accepted April 6, 1995.

Patients with cervical cancer provide an excellent opportunity to study the late effects of radiotherapy, because sufficiently large numbers of patients are available for study, treatment usually succeeds so that patients survive for long periods of time,[1] nonirradiated patients can be compared, and radiation doses to organs other than the cervix can be estimated accurately.[2] Radiotherapy results in organ doses that range from tens of Grays (thousands of rads) for those organs nearest to the cervix to tenths of Grays (tens of rads) for those farthest away. Organs that receive 1 Gy are of special interest, because cell-killing effects are minimal..

A large international study of patients with cervical cancer has extensively evaluated the risk of second cancer development in cohort and case-control studies.[3-7] Follow-up for the international study ended in 1980,

and the number of long term survivors, although sufficient to detect increased relative risks for some cancers, was not large, and the number of nonexposed comparison subjects was small. We extended the follow-up of patients with cervical cancer for an additional 10 years for several registries and added others to increase the number of nonexposed comparison subjects. Data are provided on the pattern of risk of second cancers over time and by age group after treatment for cervical cancer.

Materials and Methods

Study Population

The cohort involved women diagnosed with a primary invasive cancer of the cervix uteri (ICD8 -180) who survived at least 2 months after diagnosis and reported to 1 of 13 cancer registries. We excluded all patients with cervical cancer who had had a previous invasive cancer or in situ bladder cancer. The participating cancer registries included Denmark, Finland, Norway, Sweden, Connecticut, and Iowa and seven areas of the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program. General information on each registry has been reported.[8] The cancer registries of Denmark, Finland, Norway, Sweden, and Connecticut participated in the previous study.[3] All registries except Sweden identified which women had received radiotherapy for cervical cancer, although most Swedish women were probably irradiated.[9]

Ascertainment of Second Cancers

Each cancer registry identified second cancers by linking their cohort with registry records based on specific identifying information for each subject. For a second cancer to be included, it must have occurred at least 2 months after the diagnosis of the cervical cancer. We accepted all registry reports of second cancers without further review, and they were coded to the seventh or eighth revision of the International Classification of Diseases.[10,11] Histologic confirmation was noted for 92% of all second cancers and ranged from 74% for cancer of the pancreas to 100% for Hodgkin's disease and cancers of the larynx and vulva.

Radiation Treatment

Radiation treatment for cervical cancer usually consisted of external beam radiotherapy; brachytherapy using an intracavitary radiation source, such as radium or cesium or a combination of both modalities. The choice of radiotherapy usually depended on the stage of disease.[12] Radiotherapy for cervical cancer resulted in very high doses of radiation (>30 Gy) to organs in the pelvic region, such as the ovaries, rectum, and bladder, whereas organs in the abdominal cavity, such as the stomach and pancreas, received between 1 and 3 Gy.[2] The dose to the colon was heterogeneous and ranged from 4 Gy for the transverse colon to 24 Gy for the sigmoid colon. Doses varied widely due to differences in treatment practices as well, Table 1 shows the range of doses likely to be received by specific organs and the active bone marrow.

Table 1. Typical Average Organ Dosas Associated With Radiotherapy for Cervical Cancer*

Second cancer	Average organ dose (Gy)
Heavily irradiated site (dose >3 Gy)	
Small intestine	10-20
Colon	24
Rectum	30-60
Uterus	165
Ovary	32
Vagina	66
Bladder	30-60
Bone	22
Connective Tissue	7
Moderately irradiated site (1 Gy < dose <3 Gy)	
Liver	2
Stomach	2
Pancreas	2
Kidney	2
Lightly irradiated site (dose <1 Gy)	
Esophagus	0.3
Lung	0.3
Breast	0.3
Thyroid	0.1
Hematologic site	
Leukemia	7‡
Hodgkin's disease†	7‡
Non-Hogkin's Iymphoma†	7‡
Multiple myeloma	7‡

* From Boice et al. 1988, Radiat Res.
† Dose to lymphoid tissue could not be estimated, so the active bone marrow dose was used as a surrogate.
‡ Average dose to active bone marrow.

Data Analysis

Registries determined expected numbers of cancers by applying 5-year-age and calendar-year incidence rates for the general female population to the corresponding number of person years (PY). Accrual of PY began 2

Table 2. Number of Women with Cervical Cancer and Person-Years at Risk, by Treatment and Registry

		Invasive cervical cancer					
		Radiotherapy		*No radiotherapy*		*All**	
Registry	Diagnosis years	*No. of women*	*PYR*	*No. of women*	*PYR*	No. of *women*	*PYR*
Denmark	1943-89	19,191	235,692	6524	83,577	25,715	319,269
Finland	1953-89	7002	76,257	931	11,230	8329	89,741
Sweden†	1958-88	—	—	—		17,754	185,998
Norway‡	1953-90	8112	100,769	1744	18,332	11,341	127,044
United States							
Connecticut	1935-88	5595	54,038	1664	17,593	7259	71,632
Iowa	1935-89	3758	37,100	1094	9383	4862	46,524
SEER program (excl. CT and IA)	1973-89	6170	28,884	4756	28,356	10,933	57,259
Total§		49,828	532,740	16,713	168,472	86,193	897,467

PYR: person-years.

* Includes 19,652 women with missing treatment data (17,754 from Sweden; 1,485 from Norway; 396 from Finland; 10 from Iowa; and 7 from SEER).

† No treatment data are available.

‡ Treatment data are not available for diagnosis years 1981-85.

§ Total excludes first year of follow-up after cervical cancer.

months after the date of diagnosis of cervical cancer and continued until the diagnosis of a second cancer, date of death, or date of last follow-up, whichever occurred first. Most registries linked their mater of patientsa with cervical cancer with population and/or death registries to determine vital status, date of death, and date of emigration from their respective country. The ratio of observed to expected incident second cancers was calculated, and exact and approximate 95% confidence intervals were computed,[13] assuming that the observed number of cancers followed a Poisson distribution. Tests of homogeneity and trend over time since cervical cancer diagnosis were performed according to methods described by Breslow et al.[14] and one-sided *P* values presented. We computed the absolute risk as the difference between observed and expected events divided by PY.

Results

The cohort comprised 86,193 women with invasive cervical cancer contributing 897,467 PY of observation (Table 2). Years of cervical cancer diagnosis ranged from 1935 to 1990, and the average period of observation was 10.4 years Radiotherapy was reported for 49,828 women (532,740 PY), and treatment other than radiotherapy was noted for 16,713 women (168,472 PY), Treatment information was unavailable for 19,652 women, the majority of whom were from Sweden (17,754) and were probably treated with radiotherapy. There were 1485 women from Norway, for whom treatment data were not available from 1981 to 1985, and 396 women from Finland, 10 women from Iowa, and 7 women from SEER with missing treatment information.

The cohort contained 18,093 women alive 20 years or more after their cervical cancer diagnosis (70,312 PY) and 4801 women who were followed for 30 years or more after their cervical cancer diagnosis, accruing 22,451 PY (Table 3). Most long term survivors resided in Connecticut and Denmark, because these two registries have been operating longer than any of the others,

Overall, we noted a 20% significant increase of all second cancers excluding cervix and nonmelanoma skin cancer (7543 observed [O] vs. 6015 expected [E]) after all treatments for cervical cancer (Table 4). Lung cancer contributed nearly half of the excess cancers. The risk of second cancers after radiotherapy (0/E = 1.2) appeared similar to that after other treatments (0/E = 1.1). Relative risks for most second cancers ranged from 1.1 to 3.0 after all treatments. Risks did not differ appreciably by treatment for most second cancers, with the exception of bone cancer, which occurred only after radiotherapy. We observed the highest risks for cancer of the vagina (10.6 for irradiated, 19.7 for nonirradiated) and vulva (4.4 for irradiated, 3.5 for nonirradiated). Compared with general population rates, significant deficits for cancers of the ovary (0.9 and 0.5), uterine corpus (0.9 and 0.2), and breast (0.7 and 0.9) were noted for both irradiated and nonirradiated groups, Respectively.

Table 5 presents patterns of risk of second cancers over time by treatment. Organ sites are grouped by

Table 3. Number of Women and Person-Years at Risk by Time Since Diagnosis of Cervical Cancer

	Invasive cervical cancer					
	Radiotherapy		*No radiotherapy*		*All"*	
Time since diagnosis (yr)	No. women *starting interval*	*PYR*	No. women *starting interval*	*PYR*	No. women *starting interval*	*PYR*
<1	60,689	52,013	19,637	16,535	103,329	89,247
1-4	49,828	147,155	16,713	54,153	86,193	262,641
5-9	29,756	128,835	11,265	46,697	53,808	228,486
10-14	22,443	96,691	7709	30,288	38,824	164,184
15-19	16,311	68,652	4593	17,980	27,208	112,400
20-24	11,317	45,698	2778	10,518	18,093	70,312
25-29	7110	26,677	1507	5554	10,338	36,991
30+	3750	19,031	793	3281	4801	22,451
Total†	49,828	532,740	16,713	168,472	86,193	897,467

PYR: person-years.

* Includes 19,652 women with missing treatment daa.

† Excludes first year of follow-up after cervical cancer.

proximity to the cervix and therefore by relative amount of radiation received.

Heavily Irradiated Sites (Organ Doses >3 Gy)

Excess cancer incidence 30 or more years after radiotherapy was due mainly to cancers of the rectum (0/E = 4.0), bladder (6.2), vagina (39.4), vulva (7.9), and ovary (1.7). We noted no excess of colon cancer despite high doses to parts of the colon. Trends of increasing risk of cancer of the bladder, rectum, and ovary with time since irradiation were observed, supporting a radiation etiology for these cancers. Risks for cancer of the vulva and vagina were elevated for irradiated and nonirradiated cervical cancer patients. Although risks for vaginal cancer were almost twice as high for the nonirradiated patients, risk increased with time only for irradiated patients. By 20 years after cervical cancer, vaginal and vulvar cancers appeared only in the radiotherapy group, An overall deficit of uterine corpus cancer accompanied by a trend of increasing risk with time since cervical cancer diagnosis occurred for both treatment groups.

Bone cancer was increased after radiotherapy only. Risk was highest within the first 20 years after treatment and then appeared to decrease among long term survivors. Connective tissue cancer risk was elevated for all time periods in both treatment groups.

Moderately Irradiated Sites (Organ Doses = 1-3 Gy)

Of the organs receiving between 1 and 3 Gy, only the risk for cancer of the kidney (1.9) was significantly elevated among irradiated 30-year survivors, which was accompanied by a trend of increasing risk over time. Risks for cancers of the stomach (1.2) and pancreas (1.2) were significantly increased after radiotherapy. Cancer of the pancreas was also increased, however, in the nonirradiated group (1.5). The number of stomach cancers was less than expected among long term survivors in both treatment groups. Liver cancer did not occur above expectation in either treatment group, but significant trends of increasing risk over time were noted for both groups.

When we combined the risks for cancer of heavily and moderately irradiated sites, a pattern of increasing risk over time emerged, which rose from a 10% excess risk of second cancer in the first 10 years after radiotherapy to a 100% excess risk at 30 or more years. The same sites were grouped for the nonirradiated women, and all of the risks remained close to one, except for a 50% excess risk of second cancers occurring 30 or more years later.

Lightly Irradiated Sites (Organ Doses <1 Gy)

Two of the most radiosensitive organ sites in women, the breast and thyroid gland, as well as other organs in the upper chest, head, and neck region, received incidental doses of less than 1 Gy from radiotherapy for cervical cancer. Observed numbers of cancers of the thyroid, esophagus, larynx, and breast were less than expected among 30-year irradiated survivors. Compared with the general population, breast cancer occurred less often than expected over all time intervals for the irradiated women and just below or at expectation for the nonirradiated women. Thy-

Table 4. Observed and Expected Numbers of Second Cancers* by Treatment for Cervical Cancer

Second cancer (ICD-7)	Treatment: *Radiotherapy*	*No radiotherapy*	*All† treatments*
Esophagus (150)			
Obs	51	8	72
Exp	32.9	5.9	45.4
O/E(95% CI)	1.6(1.2, 2.0)	1.4 (0.6, 2.7)	1.6(1.2, 2.0)
Stomach (151)			
Obs	266	32	367
Exp	214.7	31.2	303.0
O/E(95% CI)	1.2 (1.1, 1.4)	1.0(0.7, 1.4)	1.2 (1.1, 1.3)
Small intestine (152)			
Obs	22	2	33
Exp	12.3	2.7	20.8
O/E(95% CI)	1.8(1.1, 2.7)	0.7(0.1, 2.7)	1.6(1.1, 2.2)
Colon (153)			
Obs	474	95	712
Exp	427.3	90.4	624.2
O/E(95%CI)	1.1 (1.0, 1.2)	1.1 (0.8, 1.3)	1.1 (1.1, 1.2)
Rectum (154)			
Obs	340	58	504
Exp	205.5	43.1	302.0
O/E(95%CI)	1.7(1.5, 1.8)	1.3(1.0, 1.7)	1.7(1.5, 1.8)
Liver (155.0)			
Obs	32	7	52
Exp	28.7	6.2	47.1
O/E(95%CI)	1.1 (0.8, 1.6)	1.1 (0.4, 2.3)	1.1 (0.8, 1.4)
Pancreas (157)			
Obs	167	42	273
Exp	139.6	28.0	211.3
O/E(95%CI)	1.2 (1.0, 1.4)	1.5 (1.1, 2.0)	1.3 (1.1, 1.4)
Larynx (161)			
Obs	28	7	41
Exp	11.5	3.8	17.2
O/E(95%CI)	2.4 (1.6, 3.5)	1.8(0.7, 3.8)	2.4(1.7, 3.2)
Lung (162-3)			
Obs	720	162	1081
Exp	241.7	75.3	370.1
O/E(95%CI)	3.0(2.8, 3.2)	2.2 (1.8, 2.5)	2.9 (2.7, 3.2)
Breast (170)			
Obs	694	248	1246
Exp	961.3	270.7	1575.6
O/E(95%CI)	0.7(0.7, 0.8)	0.9(0.8, 1.0)	0.8(0.8,0.8)
Uterine corpus (172)‡			
Obs	249	12	329
Exp	271.4	71.1	426.0
O/E(95%CI)	0.9(0.8, 1.0)	0.2(0.1, 0.3)	0.8(0.7, 0.9)
Vagina (176.1)			
Obs	51	18	88
Exp	4.8	0.9	8.2
O/E(95%CI)	10.6(7.9, 13)	19.7(12,31)	10.7(8.6, 13)
Vulva (176.0)			
Obs	70	9	114
Exp	16.0	2.6	27.8
O/E(95%CI)	4.4 (3.4, 5.5)	3.5(1.6,6.6)	4.1 (3.4, 4,9)
Ovary (175)[3]			
Obs	199	29	295
Exp	231.5	58.6	376.7
O/E(95%CI)	0.9(0.7, 1.0)	0.5 (0.3, 0.7)	0.8 (0.7, 0.9)
Kidney (l80)			
Obs	127	40	227
Exp	99.4	22.8	162.3
O/E(95%CI)	1.3(1.0, 1.5)	1.8 (1.2, 2.4)	1.4 (1.2, 1.6)
Bladder(18)			
Obs	377	47	562
Exp	110.2	25.2	167.6
O/E(95% CI)	3.4(3.1,3.8)	1.9(1.4, 2.5)	3.4(3.1, 3.6)
Thyroid (194)			
Obs	46	12	72
Exp	36.7	10.6	64.1
O/E(95%CI)	1.3 (0.9, 1.7)	1.1 (0.6, 2.0)	1.1 (0.9, 1.4)
Bone (196)			
Obs	17	0	20
Exp	5.7	1.2	8.8
O/E(95% CI)	3.0 (1.7, 4.8)	0.0(0.0,2.9)	2.3 (1.4, 3.5)
Connective tissue (197)			
Obs	33	10	68
Exp	16.0	3.7	27,9
O/E(95% CI)	2.1 (1.4, 2.9)	2.7(1.3,5.0)	2.4 (1.9, 3.1)
Non-Hodgkin's lymphoma (200, 202)			
Obs	95	25	169
Exp	87.4	22.0	139.8
O/E(95%CI)	1.1 (0.9, 1.3)	1.1 (0.7, 1.7)	1.2 (1.0, 1.4)
Hodgkin's disease (201)			
Obs	15	5	25
Exp	15.5	4.0	25.3
O/E(95% CI)	1.0 (0.5, 1.6)	1.2(0.4, 2.9)	1.0 (0.6, 1.5)
Multiple myeloma (203)			
Obs	47	2	61
Exp	51.4	10.4	79.3
O/E(95%CI)	0.9(0.7, 1.2)	0.2 (0.0, 0.7)	0.8 (0.6, 1.0)
Leukemia (204)			
Obs	107	23	177
Exp	91.6	19.8	137.3
O/E(95%CI)	1.2 (1.0, 1.4)	1.2 (0.7, 1.7)	1.3 (1.1, 1.5)
Nonchronic lymphatic leukemia (204.2, 204.3)			
Obs	82	15	136
Exp	59.3	13.2	89.4
O/E(95% CI)	1.4 (1.1, 1.7)	1.1 (0.6, 1.9)	1.5 (1.3, 1.8)
Chronic lymphatic leukemia(204.0)			
Obs	25	8	41
sap	32	9	48
O/E(95%CI)	0.8(0.5, 1.1)	1.2 (0.5, 2.4)	0.9 (0.6, 1.2)
All sites excluding cervix and other skin (140-204)			
Obs	4820	1053	7543
Exp	3854	938	6015
O/E(95% CI)	1.2 (1.2, 1.3)	1.1 (1.0, 1.2)	1.2 (1.2, 1.3)
No. women	49,828	16,713	86,193
Person year	532,740	168,471	897,467

Obs: observed; Exp: expected; CI: confidence interval.

* For all time periods excluding first year of follow-up after cervical cancer.

† Includes subjects with missing treatment data.

‡ Data not available for oophorectomy and hysterectomy in the cohort, therefore expected values are not adjusted for organs at risk.

roid cancer was elevated overall in both treatment groups, more so in the radiotherapy group, but without accompanying trends of increasing risk over time. Cancers of the larynx and esophagus were both significantly increased after radiotherapy, but there were no trends of increasing risk over time, and risks were modestly elevated among the nonirradiated women. Lung cancer risk was significantly increased in both treatment groups (3.0, irradiated; 2.2, nonirradiated) and decreased over time for the irradiated women, whereas risks stayed relatively constant over time for the nonirradiated women with the highest observed risk (3.1) for 30-year survivors.

Hematopoietic Sites

Risks for non-Hodgkin's lymphoma, Hodgkin's disease, and multiple myeloma were all near expectation after radiotherapy, A similar pattern was noted for the nonirradiated women, including a significant deficit of multiple myeloma.

Because radiation-induced leukemia usually starts to appear 2 years after exposure and often peaks within 10 years of exposure, risks for leukemia were calculated for 5-year time intervals since cervical cancer treatment (Table 6). Significantly elevated risks of acute and nonlymphocytic leukemia excluding chronic lympocytic leukemia occurred in the 1-4 year(l.9) and 5-9 year (l.7) intervals after radiotherapy, whereas deficits were observed for these same time periods in the unexposed group. Chronic lymphocytic leukemia, which has never been reported to be associated with radiation, occurred less often than expected among irradiated patients (0.77) and slightly more than expected among nonirradiated women (1.22).

Age at Radiotherapy

On a relative scale, the risk for second cancers of heavily and moderately irradiated sites was inversely related to age at treatment for women who survived at least 10 years after cervical cancer (Table 7). Absolute risks for these cancers appeared relatively constant with age at treatment, suggesting that the decrease in O/E ratios over time may be in large part related to an increase in the background rates of cancer with increasing age.

Discussion

The primary purpose for conducting this study was to evaluate the risk of second cancer among very long term survivors of cervical cancer. The current study extended previous cancer registries studies[3] by increasing the number of 30-year survivors by sixfold, from 682 to 4801, and increasing the PY by more than 38%, from 1.709 PY to 22.451 PY. We combined data from 13 population-based cancer registries using their general population rates to derive expected numbers of cancers to calculate relatively precise risks of second cancer after radiotherapy for cervical cancer.

Overall, we noted similar elevations and deficits in risks for second cancers in both treatment groups with few exceptions. However, we did see increasing risks with the time after radiotherapy, not paralleled after surgery, supporting a radiation etiology.

High dose radiotherapy increased cancer of the rectum after cervical cancer, but not colon cancer in previous studies.[3,5] In contrast, for women treated for benign gynecologic disease with much lower doses on the order of 1.3 Gy, increased mortality from cancer of the colon but not rectum was reported.[15] The incidence of colon cancer, but not rectal cancer incidence, was increased among A-bomb survivors.[16] Deaths from colon cancer were elevated among patients with ankylosing spondylitis who received mean doses of 2.5-3.0 Gy to the intestines, but this increase has been attributed to underlying ulcerative colitis.[17] In our study, we observed no association between colon cancer and high dose radiotherapy, but a strong time response for cancer of the rectum persisted. Conceivably, the much higher dose received by the rectum accounted for the difference in the risk of cancer in these organs.

The strength of the trend of increasing risk of bladder cancer with time among irradiated women and the consistency of this finding with previous studies of irradiated populations[5,15,18,19] strongly point to radiation as a cause for part of this excess. Both bladder and cervical cancer are linked to cigarette smoking[20,21] and smoking may also have played a contributory role.

Our data support a radiation-related risk for ovarian cancer but were not convincing for uterine corpus cancer. Differential rates of organ removal make comparisons with the general population difficult for these two cancers. For example, the rate of oophorectomy was 15% in an earlier cervical cancer study[6] compared with rates of 7%-10% in the U.S. general population.[22] The elevated risk of ovarian cancer many years after radiotherapy is similar to the pattern previously reported.[3] For uterine cancer, an increase overtime for the nonexposed was also seen.

Cancer of the vulva and vagina share common risk factors with cervical cancer, although vulvar cancer is thought to be more closely related to cervical cancer than is vaginal cancer.[23,24] Human papilloma virus, which is strongly associated with cervical cancer,[25] may also be related to vulvar cancer.[26] The observed excesses are then likely related to both viral factors and radiotherapy.

Table 5. Observed and Expected Numbers of Second Cancers by Treatment and Time Since Diagnosis for 1-Year Survivors of Cervical Cancer

		Radiotherapy							No radiotherapy						
Second cancer (ICD-7)	Parameter	*Total*	*1–9 yr*	*10–19 yr*	*20–29 yr*	*30+ yr*	*P value for homogeneity*	*P value for trend*	*Total*	*1–9 yr*	*10–19 yr*	*20–29 yr*	*30+ yr*	*P value for homogeneity*	*P value for trend*
Heavily irradiated sites (>3 Gy)															
Small intestine (152)	Obs	22	9	8	4	1	0.958	0.657	2	1	1	0	0	0.888	0.707
	Exp	12.3	4.9	4.1	2.5	0.9			2.7	1.2	0.9	0.5	0.1		
	O/E	1.8*	1.8	2.0	1.6	1.2			0.7	0.9	1.1	0.0	0.0		
Colon (153)	Obs	474	178	153	99	44	0.974	0.375	95	39	32	17	7	0.977	0.469
	Exp	427.3	162.7	137.2	90.2	37.2			90.4	37.3	29.8	17.3	5.9		
	O/E	1.1*	1.1	1.1	1.1	1.2			1.1	1.0	1.1	1.0	1.2		
Rectum (154)	Obs	340	66	125	90	59	0.000	0.000	58	25	20	8	5	0.613	0.501
	Exp	205.5	81.5	67.6	41.5	14.9			43.1	18.0	14.7	8.1	2.4		
	O/E	1.7*	0.8	1.8*	2.2*	4.0*			1.3*	1.4	1.4	1.0	2.1		
Uterine corpus (172)	Obs	249	64	102	63	20	0.000	0.000	12	2	5	2	3	0.001	0.002
	Exp	271.4	119.9	90.5	47.6	13.5			71.1	32.3	24.6	11.7	2.6		
	O/E	0.9	0.5*	1.1	1.3*	1.5			0.2*	0.1*	0.2*	0.2*	1.2		
Vagina (176.1)	Obs	51	11	20	12	8	0.000	0.000	18	17	1	0	0	0.022	0.996
	Exp	4.8	2.3	1.5	0.8	0.2			0.9	0.5	0.3	0.1	0.0		
	O/E	10.6*	4.8*	13.3*	15.6*	39.4*			19.7*	31.9*	3.6	0.0	0.0		
Vulva (176.0)	Obs	70	32	20	12	6	0.443	0.290	9	6	3	0	0	0.684	0.867
	Exp	16.0	7.1	5.3	2.8	0.8			2.6	1.4	0.8	0.3	0.1		
	O/E	4.4*	4.5*	3.8*	4.3*	7.9*			3.5*	4.3*	3.7	0.0	0.0		
Ovary (175)	Obs	199	64	65	50	20	0.000	0.000	29	15	7	5	2	0.541	0.414
	Exp	231.5	101.9	77.7	40.2	11.7			58.6	27.2	20.3	9.0	2.0		
	O/E	0.9*	0.6*	0.8	1.2	1.7*			0.5*	0.6*	0.3*	0.6	1.0		
Bladder (181)	Obs	377	112	102	104	59	0.000	0.000	47	24	10	8	5	0.121	0.693
	Exp	110.2	40.1	36.2	24.3	9.6			25.2	9.8	8.6	5.2	1.6		
	O/E	3.4*	2.8*	2.8*	4.3*	6.2*			1.9*	2.4*	1.2	1.6	3.2*		
Bone (196)	Obs	17	7	8	2	0	0.488	0.564	0	0	0	0	0	1.000	
	Exp	5.7	2.8	1.8	0.9	0.2			1.2	0.7	0.4	0.1	0.0		
	O/E	3.0*	2.5	4.5*	2.3	0.0			0.0	0.0	0.0	0.0	0.0		
necti tissue	Obs	33	15	14	4	0	0.401	0.786	10	5	2	1	2	0.016	0.086
	Exp	16.0	7.5	5.2	2.6	0.7			3.7	2.0	1.2	0.4	0.1		
	O/E	2.1*	2.0*	2.7*	1.5	0.0			2.7*	2.5	1.7	2.2	18.4*		
Moderately irradiated sites (1–3 Gy)															
Stomach (151)	Obs	266	123	83	50	10	0.535	0.781	32	13	15	3	1	0.368	0.719
	Exp	214.7	95.4	69.5	37.7	12.1			31.2	13.7	10.5	5.4	1.6		
	O/E	1.2*	1.3*	1.2	1.3	0.8			1.0	1.0	1.4	0.6	0.6		
Liver (155.0)	Obs	32	7	10	11	4	0.261	0.029	7	0	4	2	1	0.218	0.041
	Exp	28.7	10.1	9.5	6.6	2.5			6.2	2.3	2.2	1.3	0.4		
	O/E	1.1	0.7	1.0	1.7	1.6			1.1	0.0	1.8	1.5	2.6		
Pancreas (157)	Obs	167	75	41	34	17	0.056	0.777	42	15	18	7	2	0.683	0.625
	Exp	139.6	51.5	46.1	30.6	11.5			28.0	10.8	9.6	5.8	1.8		
	O/E	1.2*	1.5*	0.9	1.1	1.5			1.5*	1.4	1.9*	1.2	1.1		

Kidney (180)	Obs	127	39	42	32	14	0.186	0.015	40	14	17	7	2	0.838	0.470
	Exp	99.4	37.3	33.6	21.2	7.3			22.8	8.9	8.1	4.6	1.2		
	O/E	1.3*	1.0	1.2	1.5*	1.9*			1.8*	1.6	2.1*	1.5	1.6		
Lightly irradiated sites (< Gy)															
Esophagus (150)	Obs	51	29	14	7	1	0.137	0.988	8	3	5	0	0	0.277	0.783
	Exp	32.9	13.7	10.7	6.3	2.1			5.9	2.5	2.0	1.1	0.3		
	O/E	1.6*	2.1*	1.3	1.1	0.5			1.4	1.2	2.5	0.0	0.0		
Larynx (161)	Obs	28	14	6	8	0	0.211	0.714	7	3	2	1	1	0.553	0.270
	Exp	11.5	4.9	3.8	2.2	0.7			3.8	1.7	1.3	0.7	0.1		
	O/E	2.4*	2.9*	1.6	3.7*	0.0			1.8	1.7	1.5	1.5	6.8		
Lung (162-3)	Obs	720	444	175	75	26	0.000	1.000	162	71	57	22	12	0.254	0.618
	Exp	241.7	94.0	78.4	50.8	18.6			75.3	31.9	25.5	14.1	3.9		
	O/E	3.0*	4.7*	2.2*	1.5*	1.4			2.2*	2.2*	2.2*	1.6	3.1*		
Breast (170)	Obs	694	328	230	101	35	0.207	0.971	248	134	76	29	9	0.568	0.865
	Exp	961.3	428.4	313.1	166.1	53.7			270.7	135.0	89.2	37.1	9.3		
	O/E	0.7*	0.8*	0.7*	0.6*	0.7*			0.9	1.0	0.9	0.8	1.0		
Thyroid (194)	Obs	46	24	15	7	0	0.474	0.902	12	7	2	2	1	0.358	0.167
	Exp	36.7	16.8	12.1	6.1	1.6			10.6	6.4	3.0	1.0	0.2		
	O/E	1.3	1.4	1.2	1.1	0.0			1.1	1.1	0.7	2.0	4.2		
Hematopoietic sites															
Lymphoma (200, 202)	Obs	95	37	35	19	4	0.538	0.778	25	12	10	1	2	0.356	0.708
	Exp	87.4	34.3	28.3	18.0	6.8			22.0	10.0	7.2	3.7	1.2		
	O/E	1.1	1.1	1.2	1.1	0.6			1.1	1.2	1.4	0.3	1.7		
Hodgkin's disease (201)	Obs	15	7	5	1	2	0.244	0.283	5	4	1	0	0	0.765	0.854
	Exp	15.5	7.6	5.0	2.3	0.6			4.0	2.4	1.1	0.4	0.1		
	O/E	1.0	0.9	1.0	0.4	3.3			1.2	1.7	0.9	0.0	0.0		
Multiple myeloma (203)	Obs	47	16	16	11	4	0.937	0.261	2	1	1	0	0	0.877	0.734
	Exp	51.4	19.5	17.3	10.8	3.7			10.4	4.3	3.6	2.0	0.6		
	O/E	0.9	0.8	0.9	1.0	1.1			0.2*	0.2	0.3	0.0	0.0		
All sites excluding cervix & other skin	Obs	4820	1957	1514	950	399	0.000	0.000	1053	490	353	146	64	0.017	0.606
	Exp	3854.5	1601.6	1262.3	735.4	255.2			938.0	426.1	314.2	155.0	42.7		
	O/E	1.3*	1.2*	1.2*	1.3*	1.6*			1.1*	1.2*	1.1*	0.9	1.5*		
Heavily & moderately† irradiated sites	Obs	2424	802	793	567	262	0.000	0.000	401	176	135	60	30	0.088	0.443
	Exp	1783.1	724.8	585.9	349.4	123.0			387.7	166.0	132.1	69.8	19.8		
	O/E	1.4*	1.1*	1.4*	1.6*	2.1*			1.0	1.1	1.0	0.9	1.5*		

Obs: observed; Exp: expected

* $P < 0.05$.

† Includes cancers of the small intestine, colon, rectum, uterus, vagina, vulva, ovary, bladder, kidney, pancreas, stomach, ecti tiss

Table 6. Observed and Expected Numbers of Leukemia by Treatment and Time Since Diagnosis for 1-Year Survivors of Cervical Cancer

Second cancer (ICD-7)	Radiotherapy									No radiotherapy								
	Total	*1-4 yr*	*5-9 yr*	*10-14 yr*	*15-19 yr*	*20-24 yr*	*25-29 yr*	*30+ yr*	*Total*	*1-4 yr*	*5-9 yr*	*10-14 yr*	*15-19 yr*	*20-24 yr*	*25-29 yr*	*30+ yr*
Chronic lymphatic leukemia (204.0)																
Obs	25	3	4	4	4	5	2	3	8	3	2	0	2	0	1	0
Exp	32.33	6.00	6.17	5.53	4.81	4.00	2.90	2.91	6.56	1.26	1.32	1.18	0.98	0.80	0.56	0.44
O/E	0.77	0.50	0.65	0.72	0.83	1.25	0.69	1.03	1.22	2.38	1.51	0.00	2.03	0.00	1.79	0.00
95% CI	(0.50, 1.14)	(0.10, 1.46)	(0.17, 1.66)	(0.19, 1.85)	(0.22, 2.13)	(0.40, 2.92)	(0.08, 2.49)	(0.21, 3.01)	(0.52, 2.40)	(0.48, 6.96)	(0.17, 5.46)	(0.00, 3.12)	(0.23, 7.34)	(0.00, 4.58)	(0.02, 9.94)	(0.00, 8.38)
Acute and nonlymphocytic leukemia (204.2, 204.3)																
Obs	82	24	21	8	9	11	3	6	15	3	2	5	1	1	2	1
Exp	59.28	12.68	12.43	10.54	8.48	6.58	4.50	4.05	13.24	3.09	3.08	2.45	1.81	1.31	0.85	0.65
O/E	1.38*	1.89*	1.69*	0.76	1.06	1.67	0.67	1.48	1.13	0.97	0.65	2.04	0.55	0.76	2.35	1.54
95% CI	(1.10, 1.72)	(1.21, 2.82)	(1.05, 2.58)	(0.33, 1.50)	(0.48, 2.01)	(0.83, 2.99)	(0.13, 1.95)	(0.54, 3.22)	(0.63, 1.87)	(0.19, 2.83)	(0.07, 2.35)	(0.66, 4.77)	(0.01, 3.08)	(0.01, 4.24)	(0.26, 8.47)	(0.02, 8.57)

Obs: observed; Exp: expected; CI: confidence interval.

High dose radiotherapy increases the risk of bone and connective tissue cancer after adult cancers.[3,17,27] Specific information on the site of the bone and connective tissue cancers in the current study was not available, and thus it was not possible to evaluate whether these cancers occurred within or near the radiation field, In our series, osteosarcomas but not necessarily soft-tissue sarcoma were elevated after radiation treatment.

Pancreatic cancer was not clearly related to radiotherapy, because similar small increases were seen among the nonexposed. Our findings for a modest increase for cancer of the kidney, but not liver, after radiotherapy are similar to those from the earlier registry study.[3] Unlike the previous cohort study, there was a small increase of stomach cancer in the current study. In a cohort of women irradiated for benign gynecologic disease, deaths due to stomach, liver, and kidney cancer were close to expectation, whereas pancreatic cancer was increased, but this was attributed to reasons other than radiation.[15] The number of deaths due to kidney cancer was greater than expected among 5-year survivors after an estimated total body dose of 1.9 Gy during radiotherapy for ankylosing spondylitis.[17] Liver cancer is known to occur in excess after high-linear energy transfer irradiation from Thorotrast,[28,29] but the liver until recently was not considered to be susceptible to radiation-induced carcinogenesis after x- or gamma-rays.[16]

Similar to an earlier study,[3] breast cancer was diagnosed less frequently than expected in irradiated women for all time periods and occurred below or close to expectation in the nonirradiated women. Perhaps radiation to the ovaries should provide a protective effect against breast cancer. In these data, the effect lasts 30 years, possibly due to irradiation of the ovary[30] or the adrenal glands.[31] Data on oophorectomy status and other risk factors for breast cancer were absent for our cohort. Several risk factors for cervical cancer clearly oppose those for breast cancer, such as panty and age at first delivery, so that patients with cervical cancer would be expected to be at lower risk of breast cancer than the general population.[20]

Most of the evidence for radiosensitivity of the thyroid gland comes from studies of children who underwent head and neck irradiation for various medical conditions[32] rather than adults, It is unclear from these registry data that thyroid cancer is increased in adult women after radiotherapy for cervical cancer.

Although radiation induces lung cancer[33] and we noted increases in our cohort, the lungs received only very low doses of radiation, on the order of 0.1 Gy. Several other factors point to a tobacco rather than a radiation etiology. Patients with cervical cancer tend to

Table 7. Observed and Expected Cancers of Heavily and Moderately Irradiated Organ Sites* by Age at Exposure Among 10-Year Survivors

	Age at exposure (yrs)				
Category	<40	40-49	50-59	>=60	Total
No. of women	5062	7172	6074	4135	22,443
Observed	361	581	457	223	1622
Expected	175.6	367.6	329.4	185.5	1058
Observed/expected	2.1†	1.6†	1.4†	1.2†	1.5§
Person-years‡	76,142	95,917	60,310	24,383	256,752
Absolute risk§	24.3	22.2	21.2	15.4	22.0

PY: person years.

* Small intestines, colon, rectum, uterus, vagina, vulva, ovary, bladder, kidney, pancreas, stomach, liver, bone, and connective tissue.

† $P < 0.05$.

‡ Discrepancy between totals of person years in this table and Table 2 is due to rounding.

§ [(Observed-expected)/PY] x 10^4.

smoke more than the general population,[20] although we did not have information on smoking for this cohort. Risks were increased for other smoking-related cancers in both treatment groups, such as bladder, kidney, and pancreatic cancers. Also, human papillomavirus has been postulated to be associated with cancers of the lung, larynx, and esophagus,[34] and perhaps this accounts for the increased risk for these cancers seen in both treatment groups.

Leukemia has been associated with radiation exposure in many studies,[33] and the relationship to partial-body exposure is complicated. Twofold risks of leukemia have been reported after doses of less than 1 Gy in women irradiated for benign gynecologic disease,[35,36] and threefold risks were reported after 3 Gy in the ankylosing spondylitis cohort,[17] whereas much higher doses—7 Gy—received by patients with cervical or uterine cancer have also resulted in twofold relative risks.[4,37] Cell killing in conjunction with the protracted nature of radiotherapy has been postulated as a possible explanation for fewer leukemias than expected occurring in patients with cervical cancer based on predicted radiation risk estimates.' Consistent with the previous studies,[4,37] risk for leukemia other than chronic lymphocytic leukemia was significantly increased during the first 9 years after radiotherapy.

Non-Hodgkin's lymphoma and Hodgkin's disease have not been convincingly related to radiation exposure,[38] whereas multiple myeloma has been reported to be in excess after radiation exposure in some studies[19,39,40] but not in others.[5,35,41,42] Our data show no association with radiotherapy for cervical cancer and any of these hematologic malignancies. Studies of most populations exposed to therapeutic radiation do not show an increase in these cancers, with the exception of patients with ankylosing spondylitis, for whom non-Hodgkin's lymphoma was significantly increased among 5-year survivors.[17] Incidence data from the A-bomb survivors do not support a radiation association with non-Hodgkin's lymphoma or multiple myeloma.[42]

In summary, the current study demonstrates that the risk of radiation-induced second cancers appears to persist 30 or more years after treatment for cervical cancer for organs receiving more than 1 Gy, including the rectum, vagina, vulva, bladder, and ovary. Patterns of risk over time for heavily irradiated organs were consistent with a radiation etiology. Significant increases of leukemia and cancers of the bone and kidney were also linked to radiotherapy, Surgically treated patients were at significant overall risk of second cancers, related in all likelihood to shared risk factors with cervical cancer and increased smoking rates. Because the risk of developing a new primary cancer remains high even 40 years after initial diagnosis of cervical cancer, it is prudent to consider active follow-up of such patients for life.

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