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COHORT STUDY OF THE LONG-TERM EFFECT OF IRRADIATION FOR CARCINOMA OF THE UTERINE CERVIX

Second primary malignancies in the pelvic organs in women irradiated for cervical carcinoma at Radiumhemmet 1914–1965

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Abstract

The risk of second primary malignancy arising after therapeutic irradiation was evaluated in the Radiumhemmet series of carcinoma of the uterine cervix treated in 1914–1965. Only tumours appearing more than 10 years after irradiation were taken into account. Comparisons of observed with expected incidence showed excess of malignancies in urinary bladder, endometrium, ovaries and rectum, but not of colon carcinoma. Comparisons were made with cohorts from the Swedish Cancer Registry.

The carcinogenic effect of irradiation has been well documented in animal experiments and also following accidental or therapeutic irradiation of humans (1–3). Attempts to establish the long-term effect on various organs exposed to different radiation levels meet with several difficulties. These involve the accuracy of documented dose levels and the completeness of follow-up of study populations.

Women treated for carcinoma of the uterine cervix constitute an ideal study population. Treatment is relatively successful, and many of the patients are young and survive long enough to be at risk of late complications of radiation therapy. Most treated women are carefully observed for many years after irradiation. The administered doses, as intracavitary radium or cesium application or as external radiation, as a rule are accurately recorded, and it is possible to calculate the doses received by organs at differing distances from the irradiated field.

Cohort studies of irradiated cervical carcinoma seem to indicate an enhanced risk of second primary malignancy, and a recent collaborative study showed an increased risk of myeloid leukaemia arising 1 to 10 years after such treatment (6). Increased risk of new solid primary malignancy a long time after treatment has also been observed.

The aim of the present investigation was to evaluate the risk of second primary malignancy arising in heavily irradiated organs. Only tumours appearing more than 10 years after treatment of carcinoma of the uterine cervix were taken into account. Very few radiation induced solid tumours appear before 10 years and leukaemia, which often has a shorter latency time, was not included in the series. The study population was the Radiumhemmet Cervical Cancer Series, treated in the period 1914–1965. This series fulfils the criteria for duration and intensity of follow-up. The bladder, rectum, uterine corpus and ovaries, being close to the cervix, are heavily irradiated sites.

Material and Methods

The series comprises all the women who were treated for carcinoma of the uterine cervix from 1914 through 1965 and who survived the treatment for more than 10 years. Altogether 13041 women

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Table 1

Women treated for carcinoma of the cervix uteri at Radiumhemmet 1914–1965

	Years after treatment									
	0	5	10	15	20	25	30	35	40	45
No. surviving	13 041	6 076	5 000	3 389	1 893	998	494	131	54	13
Years after treatment		0–4	5–9	10–14	15–19	20–24	25–29	30–34	35–39	40–
Mean population at risk		9 500	5 538	4 195	2 640	1 446	746	312	93	33
Women years at risk		47 800	27 690	20 975	13 200	7 230	3 730	1 560	465	165

Table 2

Observed and expected numbers of second primaries in heavily irradiated sites

Years after treatment	Observed cases	Expected cases
10–14	41	40.4
15–19	48	31.5
20–24	30	20.6
25–29	7	11.9
30–34	9	5.2
35–39	6	1.1
40–44	4	0.6
Total	145	111.3

were treated, 5 000 of whom survived for the stipulated period.

Radiation exposure. Radiation therapy was given mainly by external beam, intracavitary application or a combination of both methods. Radium was the most widely used intracavitary source. A typical treatment comprised two 20 to 30 hour applications with 60 to 70 mg of radium in the uterus and vagina. External beam was used for uniform irradiation of the pelvic area and its lateral lymph nodes. Orthovoltage roentgen (200–400 kV) and ^{60}Co were the most common types of external irradiation during the period.

Information sources. The main documentary sources were the clinical records from Radiumhemmet, supplemented with data from other hospitals in which patients were treated or where they died. Information was obtained also from population registrars who, for instance, provided copies of requested death certificates. Contact was made with doctors who had signed death certificates, or with associated health service units, and additional records from such sources were included in the Radiumhemmet files. A system was also in force whereby doctors throughout Sweden regularly reported to Radiumhemmet on any examinations of our patients. Furthermore, Radiumhemmet maintained contact with patients via personal correspondence. Table 1 surveys the cohort under study for periods up to 45 years after treatment. The mean cohort population at risk in the various intervals is stated.

Pathology. All pathology reports were originally reviewed at the radiopathology department of Karolinska Sjukhuset, and for the present study one of the authors undertook a new review. All old tissue specimens were rescrutinized, to distinguish as precisely as possible between new primary tumours and recurrence of the original cervical carcinoma.

Expected numbers of new primary malignancies. The expected numbers of new primary malignancies in the urinary bladder, uterine corpus, ovaries, colon and rectum were calculated from data on incidence received from the Swedish Cancer Registry, which was established in 1958. Since the registered incidence of carcinoma in nearly all of these sites has increased in Sweden since 1958, the calculated expected numbers may be too high for the early period of the cohort under study.

Results

The observed and expected numbers of second primary tumours in the heavily irradiated sites (uterine corpus, ovaries, colon, rectum and bladder, considered collectively) are shown in Table 2. The total of 145 observed cases exceeded the expected number by about 30 per cent.

Urinary bladder carcinoma, observed and expected, is reported in Table 3. The number of observed tumours was almost double that expected. The long-term survivors seemed to be at highest risk, with 11

Table 3

Bladder carcinoma after treatment for cervix carcinoma, observed and expected numbers in relation to age at treatment

Bladder ca., years after cervix ca. treatment	Age at treatment for cervix carcinoma						Observed bladder malignancy	Expected bladder malignancy
	30–34	35–39	40–44	45–49	50–54	55–59		
10–14			1	1			2	2.6
15–19		1		1	1	2	5	2.6
20–24	1		1		1		3	1.9
25–29		1			1		2	1.2
30–34	1						1	0.6
35–39	2	1					3	0.2
40–44	1						1	0.1
45–49		1					1	–
Total							18	9.2

Table 4

Endometrial (corpus uteri) carcinoma after treatment for cervix carcinoma, observed and expected numbers in relation to age at treatment

Corpus uteri ca., years after cervix ca. treatment	Age at treatment for cervix carcinoma									Observed corpus uteri malignancy	Expected corpus uteri malignancy
	25–29	30–34	35–39	40–44	45–49	50–54	55–59	60–64	65–69		
10–14	1			2	2	2	4	2	1	14	10.4
15–19		1		3	2	3	1			10	7.5
20–24			3		2	2	2			9	4
25–29				1		1				2	2
30–34			1	1						2	1
35–39			2							2	0.3
Total										39	25.2

Table 5

Ovarian carcinoma after treatment for cervix carcinoma, observed and expected numbers in relation to age at treatment

Ovarian ca., years after cervix ca. treatment	Age at treatment for cervix carcinoma										Observed ovarian malignancy	Expected ovarian malignancy
	25–29	30–34	35–39	40–44	45–49	50–54	55–59	60–64	65–69	70–74		
10–14	1	1		2	1		1	2	1	1	10	11
15–19	3	1		3	2	3	1				13	7.3
20–24	1	1	1		1			1			5	4.1
25–29											0	1.9
30–34				1	2						3	0.8
35–39				1							1	0.3
40–44				2							2	0.1
Total											34	25.5

of the 18 cases manifest 20 years or more after radiation therapy.

Carcinoma of the endometrium occurred in 39 cases, but was expected in only 25.2 (Table 4). Most cases (24/39) appeared between 10 and 19 years after radiation therapy. Notably, 8 of the 39 endometrial tumours were of mixed Müllerian type (Figure).

There were 34 ovarian carcinomas, as against 25.5 expected (Table 5). Most (23/34) were detected in the first 20 years after irradiation.

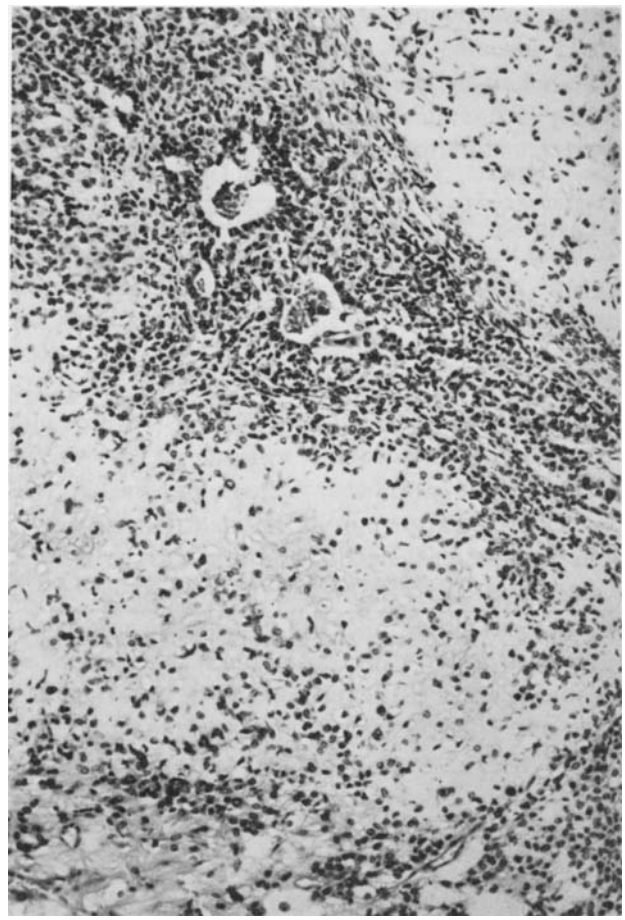
Table 6

Colon carcinoma after treatment for cervix carcinoma, observed and expected numbers in relation to age at treatment

Colon ca., years after cervix ca. treatment	Age at treatment for cervix carcinoma								Observed colon malignancy	Expected colon malignancy
	25–29	30–34	35–39	40–44	45–49	50–54	55–59	60–64		
10–14	1		1			2		1	5	10.9
15–19			1		5	3	1		10	9.3
20–24	1			1		1	2		5	7.4
25–29				1					1	5.1
30–34				1			1		2	2.1
35–39									0	0.6
40–44	1								1	0.2
Total									24	35.6

Carcinoma of the colon appeared during follow-up in 24 patients, but the expected number was 35.6 (Table 6).

Rectal carcinoma occurred in 31 patients, though the expected number was only 16.3 (Table 7). The observed incidence thus was almost double the expected.



Malignant mixed mesodermal tumour of the uterus with mixture of chondroid (light areas), non-specific sarcoma (highly cellular areas) and adenocarcinoma (glandular structures). Hematoxylin-eosin. ×500.

Discussion

The findings in the present investigation agree only partially with those in an extensive international collaborative cohort study (4, 6) based on cancer registries in several countries (Table 8). As in that study, we found an excess of rectal and bladder carcinomas occurring more than 10 years after radiation therapy. On the other hand, a slight deficit of ovarian and uterine corpus carcinomas was found in the international collaborative study, whereas excess numbers were found in the present investigation. Colon carcinoma in the international study was at roughly the expected level, whereas we found a deficit.

The deficit of uterine corpus and ovarian carcinoma in the vast material of the international study might have been due to a relatively frequent performance of hysterectomy and oophorectomy, so that the women were no longer at risk for these tumour types. As the traditional Radiumhemmet method of treatment in cervical carcinoma included no surgery, most of these organs remained at risk in the Radiumhemmet series. We observed no excess of colon carcinoma, which accords with other reports in the literature (2, 4, 6, 7, 9). A deficit of colon carcinoma was, in fact, found in one series. Although a partial explanation could have been misclassification of colon and rectal carcinomas, this cannot account for the excess rectal carcinoma shown in our study, a risk observed also in the international collaborative study (4, 6). The sugges-

Table 7

Rectal carcinoma after treatment for cervix carcinoma, observed and expected numbers in relation to age at treatment

Rectal ca., years after cervix ca. treatment	Age at treatment for cervix carcinoma									Observed rectal malignancy	Expected rectal malignancy
	25–29	30–34	35–39	40–44	45–49	50–54	55–59	60–64	65–69		
10–14				2	2	3	2	1		10	5.5
15–19	1	1		1	2	2		2	1	10	4.8
20–24		1	3	2	1	1				8	3.2
25–29		1	1							2	1.7
30–34		1								1	0.7
35–39										0	0.3
40–44										0	0.1
Total										31	16.3

Table 8

*Observed and expected numbers of second primary cancers in 10-year survivors after cervical carcinoma**

Second primary malignancy	Invasive cervical carcinoma						In situ carcinoma		
	Radiation therapy			No radiation therapy					
	O	E	O/E	O	E	O/E	O	E	O/E
Colon	145	133	1.1	23	18	1.3	21	22	0.9
Rectum	118	69	1.7	14	9.8	1.4	11	11	1.0
Uterine corpus	78	83	0.9	2	14	0.1	10	22	0.5
Ovary	69	76	0.9	6	12	0.5	14	19	0.7
Bladder	112	33	3.4	5	4.3	1.2	11	5.0	2.2

* Extracted from 'Second cancer in relation to radiation treatment for cervical cancer', from the International Radiation Study Group on Cervical Cancer (6).
O=observed, E=expected.

tion has been made that apparent absence of risk for colon carcinoma following radiation therapy for cervical carcinoma may result from cellular inactivation caused when high doses of radiation are delivered to rapidly dividing cells (2, 6).

Women with carcinoma of the cervix differ from the general female population as regards factors other than irradiation that may influence risk of second malignancies. Specifically, these women tend to smoke more (5), to have more children and to be of lower socioeconomic status than the average in women. A previous study showed that use of oral contraceptives also was associated with heightened cigarette consumption (10). Co-variation has been demonstrated between alcohol consumption and cigarette smoking. Occupation was found to influence the cancer panorama in women (11). A network of direct and indirect factors thus may characterize a group of women with basically above-average risk for cancer of the bladder, cervix, lungs and oral cavity (9).

In order to designate any increased risk as an effect of radiation, it is necessary to study incidence trends in chronologic relationship to treatment and to compare irradiated with non-irradiated cervix cancer patients. Table 9 shows the observed and expected numbers of new primary malignancies in colon, rectum, uterine corpus, ovaries and bladder among 14760 women recorded in the Swedish Cancer Registry as having carcinoma of the uterine cervix. Table 10 presents corresponding data concerning 43971 women found to have carcinoma in situ of the uterine cervix. For colon cancer, the observed and expected values were strikingly similar in the cohort of invasive carcinomas, and also in the women with in situ carcinoma. Rectal carcinoma exceeded the expected rate by 60 per cent among the women treated for in situ cervix carcinoma and

Table 9

The Swedish Cancer Registry cohort of invasive carcinoma of the uterine cervix (8)

	Years since diagnosis of primary cervical carcinoma										Total minus <1 year	
No. of women starting interval	<1 14 760		1–4 12 075		5–9 7 066		10–14 4 033		≥15 1 491			
	O	E	O	E	O	E	O	E	O	E	O	E
Colon	4	4.45	11	12	12	10.81	7	6.58	1	1.80	31	31.19
Rectum	3	2.18	9	5.96	9	5.37	9	3.23	1	0.88	28	15.43
Uterine corpus	8	4.04	3	11.67	7	10.66	5	6.07	1	1.52	16	29.92
Ovary	8	4.63	6	13.14	7	11.61	9	6.48	2	1.57	24	32.75
Bladder	1	1.24	10	3.43	3	3.22	6	2.04	1	0.57	20	9.26

O=observed, E=expected.

Table 10

The Swedish Cancer Registry cohort of in situ carcinoma of the uterine cervix (8)

	Years since diagnosis of primary cervical carcinoma										Total minus <1 year	
No. of women starting interval	<1 43 971		1–4 40 640		5–9 25 243		10–14 6 448		≥15 843			
	O	E	O	E	O	E	O	E	O	E	O	E
Colon	2	3.44	20	13.54	9	11.65	–	3.40	2	0.55	31	29.14
Rectum	2	1.63	8	6.65	11	6.02	4	1.78	1	0.28	24	14.73
Uterine corpus	5	4.02	12	17.50	17	16.56	5	4.71	–	0.64	34	39.41
Ovary	8	6.05	20	23.67	24	19.55	4	4.96	–	0.66	48	48.84
Bladder	1	0.87	6	3.59	7	3.35	5	1.06	–	0.18	18	8.18

O=observed, E=expected.

by 80 per cent among those with invasive carcinoma (8). As in situ carcinoma only exceptionally was irradiated, only a small part of the observed excess could have been attributable to irradiation.

Endometrial carcinoma was found in excess incidence in the present Radiumhemmet series 10 years or more after treatment of cervical carcinoma. In the Swedish Cancer Registry study (8) there was slight deficit of observed compared with expected number of endometrial carcinomas after in situ cervix carcinoma. Among the cohort with invasive cervix cancer in that study, the observed/expected ratio was only 16/29.9. Limitation of that comparison to 10-year survivors, however, reduces the ratio to 6/7.6. Moreover, the Radiumhemmet cohort upon which our study was based, and which originated in the period 1914–1965, differed from the Cancer Registry cohort with origin 1958–1976 in that in recent time hysterectomy has increasingly been performed after radiation therapy at some Swedish centres. The collective evidence from the Radiumhemmet cohort indicates irradiation as a cause of the excess of endometrial carcinomas. The remarkably high proportion of mixed Müllerian tumours among the endometrial neoplasms is in line with previous reports (2).

Carcinoma of the ovary was observed in 34 of the Radiumhemmet cases, as against 25.5 expected. In the Swedish Cancer Registry cohort the ratio was 24/33 (Table 9). Ten years or more after treatment the figures were 11/8, i.e. expectation was exceeded by roughly 35 per cent, as in the Radiumhemmet study. Among the in situ cervix carcinomas (Table 10) there was no excess of observed ovarian carcinoma. These findings strongly suggest a late radiation effect in ovarian carcinogenesis.

Carcinoma of the urinary bladder showed an observed/expected ratio during follow-up of cervix

carcinoma, amounting to 18/9.2 in the Radiumhemmet series. In the Cancer Registry series of invasive cervix carcinoma the figures were 20/9.3 for the whole period and 7/2.6 for the 10-year survivors (Table 9). For in situ carcinoma (Table 10) the corresponding ratios were 18/8.2 and 5/1.2. These data do not necessarily suggest an exclusively radiation induced carcinogenesis, but probably were partly explainable by other factors, such as smoking habits and occupational exposure. Studies of various irradiated populations have yielded equivocal results as to an association of radiation with bladder carcinoma. The International Radiation Study group on Cervical Cancer nevertheless concluded that, although roughly half of the observed excess risk could be explained by influence of smoking, an increase of risk with time and the level of relative risk among long-term survivors suggested a radiation effect (6).

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