Acta Oncologica 29 (1990) Fasc. 5

FROM THE DEPARTMENT OF GYNAECOLOGICAL ONCOLOGY, AND CANCER EPIDEMIOLOGY, RADIUMHEMMET, AND THE DEPARTMENT OF HOSPITAL PHYSICS, KAROLINSKA HOSPITAL, STOCKHOLM, SWEDEN.

MALIGNANT DISEASE AFTER RADIATION TREATMENT OF BENIGN GYNAECOLOGICAL DISORDERS

A study of a cohort of metropathia patients

M. RYBERG, M. LUNDELL, B. NILSSON and F. PETTERSSON

Abstract

One hundred and seven cases of malignant tumours occurred among 788 women irradiated 1912 to 1977 for metropathia. One hundred and seventy-three women out of 1 219 referred for the same diagnosis and not irradiated developed a malignant tumour. The tumours were diagnosed between 1958 and 1982. The relative risk of malignant tumours among the irradiated women was 1.22 and among the non-irradiated 1.09 compared to cancer registry data. A statistically non-significant increase of the relative risk was found in the irradiated patients for tumours of the rectum (1.58), colon (1.46), and the nervous system (1.67). A decreased overall relative risk was seen for cancer of the breast (0.92) after irradiation, but women treated at the age of 50 or more had an increased risk (2.08). The relative cancer risk of the heavily irradiated sites was not increased during the first 20 years after irradiation, but a statistically significant increase of the risk was seen after 30 years.

Key words: Radiation carcinogenesis, radiotherapy, metropathia, cohort study.

The carcinogenic effect of ionizing irradiation is well established. Tumours have thus been observed in humans after occupational radiation exposure (1), after the atomic bomb explosions in Hiroshima and Nagasaki (2) and also after radiotherapy for spondylitis (3–5) and several other types of medical radiation exposure. Still there are many unknown facts about dose response and individual organ sensitivity at different ages. Further data on these relationships in man are therefore of great interest. Women with benign uterine bleeding disorders—metropathia—have earlier been studied and the relative risk of malignant tumours after irradiation varies from 1.0 to 2.1 (6–11).

The aim of the present study is to evaluate the risk of malignant disease in a cohort of women with benign uterine bleeding disorders, comparing the risk among irradiated and non-irradiated women with the expected risk calculated from incidence data from the Swedish National Cancer Registry.

Material and Methods

During the period of 1912 to 1977, 933 women were treated with ionizing irradiation for metropathia at Radiumhemmet and between 1919 to 1979 1 530 women with the same diagnosis were referred for consultation without being irradiated. In the following discussion 145 women in the radiotherapy series and 311 women in the non-irradiated series have been excluded (Table 1). The remaining 788 irradiated cases and 1 219 non-irradiated cases form the basis of the present study. All women were followed through hospital records and population registers for vital status. Causes of death were registered and all women were followed up against data in the Swedish National Cancer Registry. The central cancer registration started in 1958. The reporting to the Cancer Registry of new diagnosed cases of cancer is compulsory by law for clinicians and pathologists. Quality control of the registered data has shown a high degree of accuracy (12).

The mean observation time in the radiotherapy series was 28.2 years (range 0–56 years) and in the control series 27.7 years (range 0–55 years). The 788 irradiated cases contributed 9 289 woman-years at risk and the 1 219 non-irradiated cases contributed 22 060 woman-years at risk during the period 1958 to 1982. Women younger than 50

Accepted for publication 22 July 1989.

Table 1

The Radiumhemmet metropathia series. Cases excluded

	Radiotherapy group n	Control group n
Previously treated for malignant tumour	28	59
Suspicion of malignant tumour in uterus at time of admission	9	21
Previous radiotherapy	55	81
Records missing	10	116*
Incomplete follow-up	43	29
Incorrect diagnosis	—	5
Total	145	311

*Part of the archives was not available during a period of reconstruction of the old Radiumhemmet building. No suspicion of biased selection.

years of age at diagnosis and treatment contributed 7 305 woman-years at risk in the radiotherapy series as against 18 607 in the control series during the same period. The correspondence figures for women aged 50 or older were 1 984 in the irradiated series and 3 453 in the control series. For each tumour site and period of observation, the expected numbers of malignant tumours were calculated for different age groups on the basis of incidence data from the Swedish National Cancer Registry.

Malignant tumours were found in 166 of the 788 irradiated women and in 212 of the 1 219 non-irradiated. Thirteen women in the irradiated series and 13 women in the control series had more than one malignant tumour. One hundred and seven of the incident cases in the irradiated cohort and 173 in the control cohort occurred in the period 1958 to 1982. In the further discussion only the first malignancy will be taken into account. Due to limitations in available cancer registry data no tumours diagnosed before 1958 will be considered in the following calculations and discussions. The relative risks (RR) given below are the calculated ratio between the observed and the expected number of tumours.

Based on the Poisson distribution, two-tailed 95% confidence intervals were calculated for the statistical evaluation of relative risk data. 95% upper and lower confidence limits are given within parentheses ( ).

Treatment. The treatment modalities for the 788 women in the studied group were intracavitary brachyradium therapy, external radiotherapy or a combination of these techniques (13). The intracavitary treatment was administered as a uterine, a vaginal or a combined application. The uterine radium treatment was usually delivered by four sources, each containing 370–555 MBq, which were either applied into a rubber tube or into an applicator of a metal alloy. The treatment time was about 16 h.

Table 2

The Radiumhemmet metropathia series. Estimated organ doses during standard treatments

	Uterine application Gy	Vaginal application Gy	External irradiation Gy
Uterus	10	2.5	5
Ovary	4	3.5	6
Rectum	8	9	6
Urinary bladder	9.5	11	4.5
Colon	0.1	0.1	0.02
Pancreas	0.05	0.09	0.02
Stomach	0.04	0.07	0.02
Breast	0.02	0.03	<0.01
Thyroid	<0.01	<0.01	<0.01

For the vaginal application, two radium capsules (with a total of 2.6 GBq) were applied to the vaults with a spacer in between. The application time was usually 24 h. Later on, a vaginal radium-cyclinder (5.6 GBq) was also frequently used instead of the capsule technique. The treatment time was then reduced to 12 h.

The external therapy was given with ortho-voltage x-rays (175 kVp, HVL 1 mm Cu) and was usually delivered by three portals: two anterior portals over the ovaries and one posterior. Each portal was treated once per treatment course.

Brachyradiumtherapy was given in 657 women, of which 33 had more than one application, while 115 women were treated with x-rays and 19 had more than one course. Sixteen women were treated with both brachytherapy and external irradiation.

In order to estimate the absorbed doses in different body regions, the mean distances from the uterus and the vagina to the various organs of an average patient in the cohort were determined using information about height and weight from the hospital records.

The absorbed doses in different organs were then calculated for the three different standard treatment techniques. The mean absorbed dose in the pelvis was 6.5 Gy (range 2.5–11 Gy). In organs outside the pelvis the absorbed doses were less than 0.1 Gy (Table 2).

Results

During the period 1958 to 1982, 107 irradiated women and 173 women in the control series developed a malignant tumour. The relative risk of developing a malignant tumour was 1.22 (1.00; 1.47) in the radiotherapy cohort and 1.09 (0.94; 1.27) in the control cohort. The relative risk increased after 20 years of observation among the irradiated women but not among the controls (Table 3). In the irradiated cohort the risk of developing a malignant tumour was 1.23 (0.98; 1.53) and 1.17 (0.76; 1.71) respectively if the women were treated before or after the age of 50.

Table 3

The Radiumhemmet metropathia series. Relative risk by observation time in the radiotheraphy cohort (R) and the control cohort (C)

Observation time years	All sites						Heavily irradiated sites						Female genital tract tumours					
	R			C			R			C			R			C		
	O	RR	95% CI	O	RR	95% CI	O	RR	95% CI	O	RR	95% CI	O	RR	95% CI	O	RR	95% CI
0–9	10	1.37	(0.66; 2.52)	26	1.35	(0.88; 1.98)	1	0.43	(0.01; 2.42)	7	1.08	(0.43; 2.22)	1	0.48	(0.01; 2.65)	7	1.23	(0.49; 2.53)
10–19	14	0.70	(0.38; 1.17)	45	0.95	(0.69; 1.27)	5	0.93	(0.30; 2.16)	18	1.40	(0.83; 2.21)	4	0.93	(0.25; 2.38)	18	1.68	(1.00; 2.66)
20–29	39	1.20	(0.86; 1.65)	72	1.25	(0.97; 1.57)	10	1.54	(0.74; 2.83)	15	1.17	(0.66; 1.93)	8	1.78	(0.77; 3.50)	11	1.18	(0.59; 2.12)
30–39	35	1.58	(1.10; 2.20)	24	0.79	(0.50; 1.17)	9	2.50	(1.14; 4.75)	3	0.53	(0.11; 1.54)	5	2.27	(0.74; 5.30)	2	0.56	(0.07; 2.01)
40–49	9	1.61	(0.73; 3.05)	6	1.94	(0.71; 4.21)	5	7.14	(2.32; 16.67)	3	7.50	(1.55; 21.92)	3	7.50	(1.55; 21.92)	0	—	(—)
Total	107	1.22	(1.00; 1.47)	173	1.09	(0.94; 1.27)	30	1.62	(1.09; 2.31)	46	1.20	(0.88; 1.60)	21	1.56	(0.96; 2.38)	38	1.29	(0.91; 1.77)

In the control group the corresponding risks were 1.11 (0.93; 1.32) and 1.04 (0.73; 1.42) respectively (Table 4).

The relative risks calculated for different sites (Table 5) were not statistically significant, due probably to the small size of each subgroup. A higher risk than estimated according to the rates in the Swedish National Cancer Registry for both the irradiated and non-irradiated women was found for cancer of the pancreas, the ovary, the corpus uteri, the kidney and the urinary bladder. For the sites brain, colon, rectum, uterine cervix as well as for lymphatic leukemia an elevated relative risk was seen in the radiotheraphy group but not in the control group. A lower or equal risk was found for cancer of the breast and the stomach in the radiotheraphy cohort. Women irradiated before 50 years of age had a relative risk of 0.54 (0.23; 1.06) for cancer of the breast compared to 2.08 (1.00; 3.83) for women irradiated at the age of 50 or more.

For tumours in the heavily irradiated sites (cancer of the urinary bladder, rectum, ovary, cervix uteri and corpus uteri) the relative risk was more pronounced among the irradiated than the controls. The risk increased over time for the radiotheraphy cohort and was statistically significant after 30 years (Table 3).

Discussion

The expected numbers of malignant tumours in the present study were calculated from the incidence data in the Swedish National Cancer Registry. To get reliable data for comparison, the study was restricted to the period 1958 to 1982.

The overall relative risk in the control group of developing a malignant tumour was equal to the expected risk. Cancers of the breast (women ≥ 50 years of age), ovary,

Table 4

Radiumhemmet metropathia series. Relative risk by age at treatment for different sites

Site	Radiotherapy cohort			Control cohort		
	Observed	Expected	RR (95% CI)	Observed	Expected	RR (95% CI)
All sites						
< 50 years of age	81	65.8	1.23 (0.98–1.53)	135	121.4	1.11 (0.93–1.32)
≥ 50 years of age	26	22.3	1.17 (0.76–1.71)	38	36.7	1.04 (0.73–1.42)
Breast						
< 50 years of age	8	14.9	0.54 (0.23–1.06)	35	30.5	1.15 (0.80–1.60)
≥ 50 years of age	10	4.8	2.08 (1.00–3.83)	9	7.9	1.14 (0.52–2.16)
Ovary						
< 50 years of age	6	3.8	1.58 (0.58–3.44)	15	8.2	1.83 (1.02–3.02)
≥ 50 years of age	0	1.1	—	1	2.1	0.48 (0.01–2.65)

Table 5

Radiumhemmet metropathia series. Observed and expected numbers of malignant tumours (ICD-7)

Sites	Observed	Expected	RR	95% CI
All sites				
R	107	88.0	1.22	1.00–1.47
C	173	158.2	1.09	0.94–1.27
Brain (193)				
R	4	2.4	1.67	0.45–4.27
C	5	4.8	1.04	0.34–2.43
Thyroid (194)				
R	1	0.9	1.11	0.03–6.19
C	2	1.8	1.11	0.13–4.01
Trachea, bronchus (162)				
R	2	2.3	0.87	0.11–3.14
C	4	4.5	0.89	0.24–2.28
Breast (170)				
R	18	19.5	0.92	0.55–1.46
C	44	38.5	1.14	0.83–1.53
Stomach (151)				
R	7	6.8	1.03	0.41–2.12
C	11	9.2	1.20	0.60–2.14
Colon (153)				
R	12	8.2	1.46	0.76–2.56
C	10	13.1	0.76	0.37–1.40
Rectum (154)				
R	6	3.8	1.58	0.58–3.44
C	5	6.4	0.78	0.25–1.82
Pancreas (157)				
R	6	3.4	1.76	0.65–3.84
C	7	5.4	1.30	0.52–2.67
Ovary (175)				
R	6	4.8	1.25	0.46–2.72
C	16	10.2	1.57	0.90–2.55
Cervix uteri (171)				
R	3	2.7	1.11	0.23–3.25
C	7	7.1	0.99	0.58–2.03
Corpus uteri (172)				
R	7	4.4	1.59	0.64–3.28
C	12	9.5	1.26	0.65–2.21
Kidney (180)				
R	6	2.8	2.14	0.79–4.66
C	9	4.9	1.84	0.84–3.49
Urinary bladder (181)				
R	4	2.2	1.82	0.50–4.66
C	5	3.9	1.28	0.42–2.99
Lymphatic leukemia (204)				
R	3	2.0	1.50	0.31–4.38
C	3	2.8	1.07	0.22–3.13
Heavily irradiated sites[1]				
R	30	18.5	1.62	1.09–2.31
C	46	38.3	1.20	0.88–1.60
Female genital tract tumours[2]				
R	21	13.5	1.56	0.96–2.38
C	38	29.5	1.29	0.91–1.77

[1] ovary (175), corpus uteri (172, 174), cervix uteri (171), rectum (154) and urinary bladder (181).
[2] ovary (175), corpus uteri (172, 174), cervix uteri (171), vulva and vagina (176).
R = Radiotherapy group; C = Control group

uterine corpus, and pancreas were found in excess both in the irradiated series and the non-irradiated control series. Common etiologic factors such as hormonal unbalance and high fat intake could well play a role in this female subgroup. Benign bleeding disorders are probably a symptom of an unbalanced ovarian function, which might explain the excess risk found even in the non-irradiated group for these sites.

The relative risk of a malignant tumour in the irradiated cohort compared with the risk in the whole population was 1.22, which is comparable with that reported from other studies among women irradiated for metropathia (6–11). An increased risk of malignant disease after radiotherapy has also been reported among persons treated for ankylosing spondylitis, the atomic bomb survivors and women irradiated for a carcinoma of the uterine cervix (2–5, 14, 15). Compared with the control group we found an excess risk of 10%.

For some tumour sites supposed to be hormonally influenced or related to high fat intake the risks were more pronounced in the radiotheraphy group than in the control group (uterine corpus, pancreas and colon). A lower risk was, however, found among the irradiated women than among the non-irradiated ones with regard to cancer of the breast and ovary. A decreased risk of developing a cancer of the breast after pelvic irradiation agrees with earlier reports (6, 7, 9–11, 16, 17). An increased risk of breast cancer after irradiation to other parts of the body than the pelvis has been reported among women treated for ankylosing spondylitis and fibroadenomatosis and among the atomic bomb survivors (2, 4, 5, 15, 18). The increased breast cancer risk found in women irradiated after menopause in our study should support these observations. A difference in the relative risk of cancer of the breast among women irradiated pre- and postmenopausally has been reported earlier (10, 14, 17). Our findings of a substantially reduced breast cancer risk among women irradiated premenopausely confirms earlier findings. Oestrogen hormones are probably of importance for breast cancer development and the reduced risk can be explained by oestrogen hormonal withdrawal. A relative risk of ovarian cancer varying from 1.0–3.1 has been reported in many metropathia studies after radiotheraphy (7, 9, 10, 16). The women in our control series experienced a 26% higher risk of ovarian cancer than women in the irradiated cohort. It is plausible that undiagnosed early ovarian neoplasms in some cases might have been responsible for the bleeding disorders and also that the radiotherapy might have cursed some of these conditions. Both decreased and increased risk of ovarian cancer after radiotherapy has been reported among women treated for carcinoma of the uterine cervix (14, 16, 19). Atomic bomb survivors have experienced an increased risk (20).

An increased risk of cancer of the colon and the uterine corpus after irradiation for metropathia and ankylosing

spondylitis has been reported (3–5, 11, 14, 16, 19). An increased risk of cancer of the colon but not of cancer of the uterine corpus was seen among atomic bomb survivors (2). Several studies of benign bleeding disorders and of ankylosing spondylitis recognize an increased risk of both urinary bladder cancer and kidney cancer (4, 5, 9, 11, 16). An increased risk of urinary tract cancers has also been found among atomic bomb survivors (2). A carcinogenic effect of radiation on the urinary bladder has also been reported after treatment for cervical carcinoma (14, 19) but no excess of renal cancer was found (14).

Although the different subgroups are too small to give statistically significant proof of a carcinogenetic effect of irradiation in the present study, our findings suggest such an effect in several sites.

ACKNOWLEDGEMENTS

This work was supported by grants from NCI, IARC No. RA/81/031, Swedish Cancer Society—project Nos. 87:405, 88:212, the Cancer Society in Stockholm, No. 87:22 and King Gustaf V's Jubilee Foundation, No. 87:592.

Request for reprints: Dr Marianne Ryberg, Department of Gynaecological Oncology, Radiumhemmet, Karolinska Hospital, S-104 01 Stockholm, Sweden.

REFERENCES

1. Seltser R, Sartwell PE. The influence of occupational exposure to radiation on the mortality of American radiologists and other medical specialists. Am J Epidemiol 1965; 81: 2–22.
2. Kato H, Schull WJ. Studies of the mortality of A-bomb survivors. 7. Mortality, 1950–1978: Part 1. Cancer mortality. Radiat Res 1982; 90: 395–432.
3. Court Brown WM, Doll R. Mortality from cancer and other causes after radiotheraphy for ankylosing spondylitis. Br Med J 1965; 2: 1327–32.
4. Darby SC, Doll R, Smith PG. Long-term mortality after a single treatment course with x-rays in patients treated for ankylosing spondylitis. Br J Cancer 1987; 55: 179–90.
5. Smith PG, Doll R. Mortality among patients with ankylosing spondylitis after a single treatment course with x-rays. Br Med J 1982; 284: 449–60.
6. Alderson MR, Jackson SM. Long-term follow-up of patients with menorrhagia treated by irradiation. Br J Radiol 1971; 44: 295–8.
7. Brinkley D, Haybittle JL. The late effects of artificial menopause by X-radiation. Br J Radiol 1969; 42: 519–21.
8. Corscaden JA, Fertig JW, Gusberg SB. Carcinoma subsequent to the radiotherapeutic menopause. Am J Obstet Gynecol 1946; 51: 1–12.
9. Doll R, Smith PG. The long-term effects of x-irradiation in patients treated for metropathia haemorrhagica. Br J Radiol 1968; 41: 362–8.
10. Smith PG, Doll R. Late effects of x-irradiation in patients treated for metropathia haemorrhagica. Br J Radiol 1976; 49: 224–32.
11. Wagoner JK. Leukemia and other malignancies following radiation therapy for gynecological disorders. in: Boice JD Jr, Fraumeni JF Jr, eds. Radiation carcinogenesis: Epidemiology and biological significance. New York: Raven Press 1984: 153–9.
12. Mattsson B. Cancer registration in Sweden. Studies on completeness and validity of incidence and mortality registers. Stockholm: Karolinska Institute, 1984.
13. Ryberg M, Lundell M, Pettersson F. Radiotherapy in benign uterine bleeding disorders. The Radiumhemmet metropathia cohort 1912–1977. Short- and long-term results. Ups J Med Sci 1989; 94: 161–9.
14. Boice JD, Jr, Day NE, Andersen A, et al. Second cancers following radiation treatment for cervical cancer. An international collaboration among cancer registries. J Natl Cancer Inst 1985; 74: 955–75.
15. Schull WJ. Atomic Bomb Survivors: Patterns of cancer risk. In: Boice JD Jr, Fraumeni JF Jr, eds. Radiation carcinogenesis: Epidemiology and biological significance. New York: Raven Press 1984: 21–36.
16. Palmer JP, Spratt DW. Pelvic carcinoma following irradiation for benign gynecological diseases. Am J Obstet Gynecol 1956; 72: 497–505.
17. Feinlab M. Breast cancer and artificial menopause: A cohort study. J Natl Cancer Inst 1968: 41: 315–29.
18. Baral E, Larsson LE, Mattsson B. Occurrence of breast carcinoma in women treated with x-rays for benign diseases of the breast. In: Nieburgs HE, ed. Prevention and detection of cancer. Part II. Detection. Vol 2, Cancer detection in specific sites. New York, Basel: Marcel Dekker Inc 1980: 1731–40.
19. Pettersson F, Fotiou S, Einhorn N, Silfverswärd C. Cohort study of the long-term effect of irradiation for carcinoma of the uterine cervix. Acta Radiol Oncol 1985; 24: 145–51.
20. Tokuoka S, Kawai K, Shimizu Y, et al. Malignant and benign ovarian neoplasms among atomic bomb survivors, Hiroshima and Nagasaki, 1950–80. J Natl Cancer Inst 1987; 79: 47–57.