

## CANCER RISK FOLLOWING RADIOTHERAPY FOR INFERTILITY OR MENSTRUAL DISORDERS

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**A cohort of 968 Israeli women treated with radiotherapy for infertility was followed up for cancer incidence. The majority of the subjects were irradiated to both the ovaries and the pituitary gland. Mean doses to the brain, colon, ovary and bone marrow were 0.8, 0.6, 1.0 and 0.4 Gy, respectively. More than 10 years after radiation treatment, 60 cancers were observed compared with 74.5 expected based on national cancer incidence rates (standardized incidence ratio 0.81, 95% confidence interval 0.61–1.04). No statistically significant excess or deficit was seen for any individual type of cancer; however, a non-significant 60% increased risk of colon cancer was observed. Risk of colon cancer was higher among women with 2 or more treatments and increased with length of follow-up. A decreased risk of breast cancer was suggested. Neither age at exposure nor attained age modified subsequent cancer risk. No clear excess of any cancer site was observed among women at organ doses above the median compared with subjects at doses below the median, except a slight increase in colon cancer. No significant excess incidence of cancer was demonstrated in this small cohort of patients treated with radiotherapy for infertility. Our results are consistent with those from an earlier study of cancer mortality among women receiving radiotherapy for infertility conducted in New York City. *Int. J. Cancer* 82:795–798, 1999. Published 1999 Wiley-Liss, Inc.†**

Low-dose radiotherapy of the ovaries and the pituitary gland for bleeding disorders and infertility was introduced around 1910. The treatment was never widely used, but from the 1920s until the 1950s it gained some popularity for patients with underlying ovarian dysfunction (Kaplan, 1958). It was considered an effective form of treatment, with conception rates reported between 25% and 71% (Wolfe, 1950). Although the mechanisms of action were not known, radiotherapy was thought to induce ovulation by “stimulation” (*i.e.*, acceleration of ovarian function and increase in hormone production), resolution of persistent corpus luteum or destruction of granulosa cysts (Kaplan, 1957).

Radiotherapy for this purpose was discontinued mostly because of potential but undemonstrated genetic effects (Kaplan, 1957). An increased risk of pelvic cancer among patients with benign pelvic diseases was first recognized in the 1940s and later attributed to therapeutic irradiation (Speert and Peightal, 1949).

### MATERIAL AND METHODS

A cohort study of Israeli women irradiated between 1940 and 1972 for infertility or menstrual disorders was conducted. Study subjects were identified from the records of 5 out-patient radiotherapy clinics: Zamenhoff, Tugendreich, Linn, Hadassah and Tel Hashomer hospitals. After exclusion of duplicate records, 5 subjects not resident in Israel, 10 with unknown dates of treatment and 4 treated for other conditions, 1,209 women were eligible for the study.

Patients were traced using medical records, medical insurance records, army records and the Central Population Registry to obtain unique national identity numbers. The tracing criteria used were last name, year of birth, country of origin, year of immigration and

father's name. Of the original 1,209 women, 968 (80%) were traced, 802 (66%) with a perfect match and 166 (14%) with a probable match. Probable matches (subjects matched for most but not all factors) were treated as matches in the analysis. Loss from follow-up was due mainly to incomplete or lost records at one of the hospitals with a tracing rate of only 53%, whereas for other clinics it was between 80% and 90%. Tracing was most complete (80% or more) for subjects born in Israel, later periods of treatment (1950 onward) and later years of birth (1920 onward). Untraced subjects did not differ from traced patients in terms of age at irradiation; type of irradiation; mean radiation dose to the uterus, colon or active bone marrow; or number of children. The only detectable difference between traced and untraced subjects was that the indication for treatment was amenorrhea more frequently among traced patients than among untraced patients. Subjects were followed up for death or emigration through the Central Population Registry.

Cancer incidence data were obtained through the Israel Tumor Registry, a nationwide, population-based cancer registry established in 1960 with a very high degree of completeness of coverage (Iscovich, 1992). A computerized record linkage based on national identity numbers and names was performed to identify incident cancer cases in the cohort. All diagnoses were verified through pathology reports.

Information on treatment-related factors and medical history was obtained from the radiation therapy records. Indications for radiotherapy were infertility, amenorrhea and other menstrual disorders (Table I). The majority of traced patients (749, or 77%) received radiotherapy to both the pituitary and the ovaries. In addition, 88 patients (9%) were irradiated to the pituitary gland only and 3 to the ovaries only. Specific type of treatment was unavailable for 128 women (13%) because the radiation records were destroyed due to lack of storage space. Sixty-six women had received radiotherapy more than once. The mean age at irradiation was 28 years (range 13–45). Among the 49% of study subjects for whom parity status was recorded on the radiotherapy record, 62% were nulliparous at the time of treatment and 38% had at least one child.

The typical method of treatment consisted of delivering 60 to 100 R with orthovoltage X-rays to the ovaries and 225 R to the pituitary gland in 3 fractions over 3 weeks (Kaplan, 1958). The dose to the ovaries is 10% to 15% of the dose required for sterilization (Hendry, 1989). The organ doses to the brain, thyroid, breast, colon (by subsite), uterus, ovary and active bone marrow were estimated individually for 633 patients with complete radia-

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**TABLE I** – NUMBER OF PATIENTS AND PERSON-YEARS BY DIAGNOSIS, TYPE OF TREATMENT AND AGE AT TREATMENT

	Subjects		Person-years at risk		
	Number	%	Total	2-year lag	10-year lag
Diagnosis					
Infertility	301	31	8,254	7,652	5,244
Amenorrhea	473	49	10,902	10,182	7,311
Other or unknown	194	20	5,679	5,291	3,744
Type of treatment					
Ovarian	3	<1	92	86	62
Pituitary	88	9	2,319	2,143	1,445
Both	749	77	21,160	19,662	13,680
Unknown	128	13	4,702	4,446	3,422
Age at treatment (years)					
<25	316	33	9,140	8,508	5,984
25–29	293	30	8,438	7,852	5,514
30+	359	37	10,696	9,978	7,111
Total	968	100	28,273	26,338	18,609

tion records using phantom simulations. The dose to the total active bone marrow was calculated based on estimates of active bone marrow distribution (Cristy, 1981).

Person-years at risk were calculated from the date of treatment or January 1, 1960 (date of the establishment of the Israel Tumor Registry), whichever was later, and the date of death, cancer diagnosis, emigration or December 31, 1990, whichever occurred first. A lag period of 2 years was used for leukemia (*i.e.*, the first 2 years of follow-up after treatment were excluded). For other cancers, a lag period of 10 years was used. Only first primary malignancies were included in the analyses.

The expected numbers of cases were calculated based on national cancer incidence rates among females specific to 5-year age group, ethnicity and 5-year calendar period. The standardized incidence ratio (SIR) was calculated as the ratio of observed to expected numbers of cases. The 95% confidence intervals (CIs) were calculated assuming that the observed numbers followed a Poisson distribution. Tests for trend were carried out using the likelihood ratio test.

## RESULTS

There were a total of 28,274 person-years at risk among the 968 traced, irradiated women (Table I). Using a 2-year lag for the leukemia analysis and a 10-year lag for the solid cancer analysis, there were 26,338 and 18,609 person-years at risk, respectively. The most common diagnosis was amenorrhea (49%), followed by infertility (31%). Subjects were treated mostly during the 1950s (595 women, or 61%). Fewer than 10% were treated in the 1940s and the remaining 30% in the 1960s. The mean year of treatment was 1955, the mean age at treatment was 28 years (range 13–45) and the mean length of follow-up was 29 years.

Organ doses were estimated for a sample of 633 women. Average doses to the brain, ovary and uterus as well as sigmoid colon were between 0.5 and 1.0 Gy (Table II). The mean dose to the active bone marrow was 0.36 Gy. Doses to the thyroid and breast were much lower.

A total of 60 cancer cases were observed during the follow-up period compared with 74.5 expected (SIR 0.8, 95% CI 0.6–1.0) (Table III). The deficit was due mainly to a low risk of breast cancer (SIR 0.7, 95% CI 0.4–1.1). Low incidence rates were observed for both pre-menopausal (SIR 0.6, 95% CI 0.2–1.1 for ages <50 years) and post-menopausal (SIR 0.7, 95% CI 0.4–1.3 for ages ≥50 years) breast cancer. Of the most heavily exposed sites, there was a suggestion of increased risk for cancers of the colon (SIR 1.6, 95% CI 0.6–3.3) and uterine corpus (SIR 1.4, 95% CI 0.5–3.1), especially among women treated for infertility (SIR 3.8, 95% CI 1.2–8.8). No excess was observed for leukemia (SIR 1.2 based on 2

**TABLE II** – ESTIMATED ORGAN DOSES (Gy) BASED ON A SAMPLE OF 633 WOMEN

Organ	Dose (Gy)			
	Mean	Median	10th percentile	90th percentile
Brain	0.80	0.74	0.55	1.10
Cranium and face	0.58	0.55	0.35	0.75
Colon, average	0.65	0.67	0.001	0.81
Colon, sigmoid	1.18	1.10	0.001	1.60
Ovary	1.04	0.94	0.001	1.40
Uterus	0.97	0.81	0.001	1.40
Active bone marrow	0.36	0.37	0.11	0.43
Thyroid	0.01	0.01	0.007	0.016
Breast	0.01	0.01	0.003	0.011

**TABLE III** – OBSERVED AND EXPECTED NUMBERS OF INCIDENT CANCER CASES IN 1960–1990 AMONG 968 ISRAELI WOMEN IRRADIATED FOR INFERTILITY OR MENSTRUAL DISORDERS (USING A 10-YEAR LAG)

Site	Observed	Expected	SIR (95% CI)
Head and neck <sup>1</sup>	1	1.05	0.95 (0.01–5.30)
Gastro-intestinal	13	14.60	0.89 (0.47–1.52)
Colon	7	4.42	1.58 (0.63–3.27)
Rectum	2	3.96	0.51 (0.06–1.83)
Respiratory	2	3.33	0.60 (0.07–2.17)
Bone and connective tissue	—	0.65	0.00 (0.00–5.68)
Breast	18	25.75	0.70 (0.41–1.11)
Uterine corpus	6	4.17	1.44 (0.52–3.13)
Ovary	7	5.02	1.39 (0.56–2.87)
All female genital	14	11.29	1.24 (0.68–2.08)
Urinary organs	1	2.54	0.39 (0.01–2.08)
All pelvic organs <sup>2</sup>	24	22.21	1.08 (0.69–1.61)
Brain and nervous system	2	3.07	0.65 (0.07–2.35)
Thyroid	1	2.14	0.47 (0.01–2.61)
Leukemia <sup>3</sup>	2	1.61	1.25 (0.14–4.50)
Other lymphatic and hemato-poietic	3	3.07	0.98 (0.20–2.86)
All cancers	60	74.53	0.81 (0.61–1.04)

<sup>1</sup>Includes buccal cavity, tongue, salivary glands, mouth, oropharynx, nasopharynx, larynx, nose and paranasal sinuses. <sup>2</sup>Includes ovary, uterine cervix, uterine corpus, bladder, colon and rectum. <sup>3</sup>Two-year lag.

cases), cancers of the thyroid (SIR 0.5 based on 1 case), brain (SIR 0.6 based on 2 cases), head and neck (SIR 0.9 based on 1 case of nasopharyngeal cancer) or pelvic sites combined (ovary, uterine cervix, uterine corpus, bladder, rectum and colon (SIR 1.1, 95% CI 0.7–1.6).

There was some suggestion of an increasing risk with age at exposure (Table IV) for all cancers combined ( $P_{\text{trend}}$  0.15) and for all pelvic sites ( $P_{\text{trend}}$  0.28), but no trend with attained age was observed. No clear pattern of risk emerged by time since exposure; however, the risk of colon cancer was significantly increased 20 to 29 years after treatment (SIR 3.1, 95% CI 1.1–6.7).

There were too few subjects irradiated only to the pituitary gland or ovaries to meaningfully assess cancer risk by type of treatment. The data were also too sparse for detailed dose–response analysis. An organ dose above the median was not associated with a statistically significantly higher risk than an organ dose below the median for any of the sites (pelvic, brain, colon, head and neck, leukemia) (Table V). However, there was a suggestion of increased risk of colon cancer among the 66 women who received multiple treatments: SIR 1.2 (95% CI 0.4–2.8) and 8.0 (95% CI 0.9–28.9) for 1 and 2 or more treatments, respectively.

Cancer incidence was roughly similar among patients with different indications for treatment. There was, however, some indication of increased risk of genital cancers among women treated for infertility (SIR 2.3, 95% CI 0.9–4.8), including a statistically significantly increased risk of ovarian cancer (SIR 3.8,

**TABLE IV** – SIR WITH 95% CI BY AGE AT TREATMENT AMONG 968 ISRAELI WOMEN IRRADIATED FOR INFERTILITY OR MENSTRUAL DISORDERS

Cancer site	Age at treatment (years)			p (trend)
	<25	25–29	30+	
Colon	1.77 (0.02–9.84)	0.96 (0.01–5.35)	1.78 (0.57–4.15)	0.81
Female genital	0.49 (0.01–2.71)	1.56 (0.50–3.65)	1.33 (0.57–2.61)	0.46
Pelvic organs <sup>1</sup>	0.57 (0.06–2.07)	1.03 (0.38–2.24)	1.24 (0.71–2.02)	0.28
Breast	0.83 (0.27–1.93)	0.66 (0.21–1.53)	0.66 (0.29–1.30)	0.72
All malignancies	0.55 (0.24–1.09)	0.75 (0.42–1.23)	0.93 (0.65–1.28)	0.15

<sup>1</sup>Includes ovary, uterine cervix, uterine corpus, bladder, colon and rectum.

**TABLE V** – SIR BY ORGAN DOSE AMONG 968 ISRAELI WOMEN IRRADIATED FOR INFERTILITY OR MENSTRUAL DISORDERS

Cancer site	Median dose (Gy)	SIR (95% CI)		p
		SIR below median	SIR above median	
Colon	0.67	1.50 (0.17–5.42)	5.00 (0.56–18.0)	0.24
Ovary	0.94	2.70 (0.54–7.90)	2.58 (0.52–7.53)	0.96
Uterus	0.94	3.24 (0.65–9.47)	1.10 (0.01–6.13)	0.35
Female genital	0.94 <sup>1</sup>	2.04 (0.66–4.76)	1.90 (0.61–4.43)	0.91
Pelvic organs <sup>2</sup>	0.94 <sup>1</sup>	1.31 (0.48–2.86)	1.63 (0.70–3.22)	0.69

<sup>1</sup>Ovary dose.–<sup>2</sup>Includes ovary, uterine cervix, uterine corpus, bladder, colon and rectum.

95% CI 1.2–8.8) and of colon cancer (SIR 2.1, 95% CI 0.7–4.8) among women treated for menstrual disorders.

To address concerns about the influence of incomplete follow-up, we conducted 2 additional analyses. We excluded all subjects from the one hospital with a large proportion of incomplete tracing and patients with only a “probable” match. In both of these analyses, the results were practically identical with those presented above.

DISCUSSION

The results of a cohort study of almost 1,000 women treated with radiotherapy for infertility or menstrual disorders are reported. Even though the number of subjects was modest, we were able to follow up the women for over 3 decades and to identify incident cancer cases from a population-based cancer registry.

National cancer incidence rates were used as a reference. These rates are statistically stable but not necessarily representative of the study population. Had it been available, a comparison group of women diagnosed with the same conditions but without radiotherapy would have been more valid. However, reference rates from an internal comparison group would be less stable because of the small number of expected cancer cases. The use of population rates could bias the results if the cancer risk for women with infertility or menstrual disorders is different from that for the general population. In the only study of benign gynecologic disease with a non-treated control group, breast cancer and total cancer incidence rates among unexposed controls were comparable to those for the general population, but there was an excess of ovarian cancer (Ryberg *et al.*, 1990). Among 2,496 infertile Israeli women not treated with radiation, the incidence of endometrial carcinoma was significantly elevated (SIR 4.8, 95% CI 3.0–74), and an increased risk of breast cancer of borderline statistical significance (SIR 1.3, 95% CI 0.96–1.6) was observed (Modan *et al.*, 1998).

Information on cancer incidence was not available before 1960, which may have led to some under-ascertainment but no bias since it would affect the observed and expected rates similarly. The risk of solid cancers following exposure to ionizing radiation becomes manifest after a relatively long latency period, after which the excess risk persists for decades. Hence, no profound effect on risk estimates can be expected. For leukemia, which has a shorter latency period, the lack of cancer incidence data before 1960 might be a larger problem. However, survival for adult leukemia gener-

ally is very poor, and there were no deaths before 1964. This suggests that we did not miss any early leukemias.

Twenty percent of the eligible subjects were not traced due to lack of identifying information. Subjects lost to follow-up were similar to traced women in terms of most demographic and treatment-related characteristics. Further, results obtained after exclusion of the hospital with the lowest follow-up rate were practically identical to those based on the entire material. Therefore, bias is unlikely.

The indications for radiotherapy were closely related gynecologic disorders, including infertility, amenorrhea and other menstrual disorders. Infertility of ovarian origin was the primary reason for a patient to seek treatment, but the most common indication for treatment was amenorrhea, usually secondary. Endocrine disorders underlying secondary amenorrhea resemble those related to ovarian infertility and include ovarian failure, polycystic ovary syndrome, hypogonadotropic hypogonadism and hyperprolactinemia (Crosignani and Vegetti, 1996).

Overall, cancer incidence was slightly below the expected level. Despite a large proportion of nulliparous women in the cohort, breast cancer incidence was lower than in the general population. A decreased risk of breast cancer accounted for approximately half of the deficit in cancer incidence. Radiation doses to the breast were negligible and not expected to influence breast cancer risk. Ovarian doses were also too small to affect ovarian function and account for the decreased risk of breast cancer (Hendry, 1989). Data are sparse and results inconsistent regarding the effects of menstrual disorders, including amenorrhea, on the risk of breast cancer (Parazzini *et al.*, 1993; den Tonkelaar and de Waard, 1996). There is some indication that polycystic ovary syndrome may be associated with a decreased risk of breast cancer and increased risk of ovarian cancer, though the results are not clear (Schildkraut *et al.*, 1996; Anderson *et al.*, 1997). There is little or no evidence that hyperprolactinemia affects the risk of breast cancer (Helzlsouer *et al.*, 1994; Hankinson *et al.*, 1995). Functional disorders of the hypothalamus associated with low gonadotropin and estrogen levels are also relatively common causes of secondary amenorrhea. Although no empirical studies have been published, such a hormonal profile might decrease the risk of breast cancer. Several endocrine factors related to amenorrhea may have contributed to the decreased risk of breast cancer.

Cancers of the endometrium and ovary were slightly but not statistically significantly increased compared with the general population. We were not able to conduct dose–response analyses because of the narrow radiation dose distribution and small numbers of cases, but no differences were observed between women with organ doses below vs. above the median or between women with one vs. multiple radiation treatments. Previous studies have suggested that infertility is not strongly associated with overall cancer risk but is associated with an elevated risk of endometrial cancer (Escobedo *et al.*, 1991; Brinton *et al.*, 1992; Modan *et al.*, 1998) and possibly ovarian cancer (Whittemore *et al.*, 1992; Rossing *et al.*, 1994). A link between breast cancer and infertility or subfecundity was observed in one study (Modan *et al.*, 1998) but not in others (Gammon and Thompson, 1990; Sellers *et al.*, 1993). Although an increased risk of breast, ovarian and

endometrial cancer, and possibly colon cancer, has been associated with nulliparity or a low frequency of live births, no clear difference in cancer risk was observed between women who were parous or nulliparous at the time of treatment in this cohort. Our finding, however, has to be tempered by the fact that information on parity status was known for only half the cohort.

There was some indication of an increased incidence of colon cancer in the cohort, with a higher risk associated with high radiation doses and long follow-up. A small number of births may also be associated with an increased risk of colon cancer, and the risk was slightly higher among nulliparous than parous women. Detection bias is a potential alternative explanation, but it is unlikely given the temporal pattern and association with the number of treatments that are compatible with a radiation effect. In addition, the low incidence of breast cancer does not support a role for detection bias.

There was little evidence for an increased risk of leukemia associated with radiation exposure in our study. The confidence interval, however, was wide, and we could not rule out an excess of similar magnitude to that observed among atomic bomb survivors with the same level of doses (Preston *et al.*, 1994). Fractionation of exposure also may have reduced the risk of leukemia by up to 50% compared with a single dose.

An earlier study of mortality among women treated with radiotherapy for infertility or amenorrhea in New York showed increased risks of colon cancer and non-Hodgkin's lymphoma (Ron

*et al.*, 1994). As in this study, no excess was observed for leukemia or brain cancer. Mortality from breast cancer was similar to rates in the general population of New York.

Other studies of cancer risk following pelvic irradiation for benign gynecologic disease have generally shown increased risks of leukemia with bone marrow doses of 1 Gy or higher, but no dose-response relationship has been established (Ryberg *et al.*, 1990; Inskip *et al.*, 1993; Darby *et al.*, 1994). Some studies also have shown increased risks of pelvic cancers, including bladder, colon, uterus and ovary, and a decreased risk of breast cancer. The bone marrow doses in our study, however, were less than half of those in these studies, and doses to pelvic organs were even lower.

Our results provide little evidence that radiotherapy for infertility is associated with an increased risk of cancer, though there was a suggestion of an excess of colon cancer incidence. Modest effects for individual sites could not be excluded, however, due to the small sample size.

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