

Second primary cancer following treatment for cervical cancer

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A follow-up study of 7535 women in Ontario was carried out to assess the occurrence of second primary cancers following the treatment of invasive carcinoma of the cervix between 1960 and 1975. The study was part of a larger international investigation of late radiation effects in patients with cervical cancer. Data were collected on the date and the type of treatment for cervical cancer and on the occurrence of second primary cancers diagnosed before 1980. Observed and expected numbers of second primary cancers, the latter determined according to Ontario incidence rates, were compared for individual sites and for all sites combined. There were significantly more primary cancers of the lung than expected (64 v. 15.52) but significantly fewer second primary cancers of the breast (56 v. 105.01) and colon (27 v. 43.31). Overall, there were significantly fewer ($p < 0.05$) observed second primary cancers than expected (280 v. 394). Although the

median follow-up period was less than 10 years there was no marked evidence of an excess of radiation-induced second primary cancers.

Dans le dessein de connaître le taux de survenue d'un second cancer primitif après le traitement d'un cancer envahissant du col utérin, on a suivi 7535 femmes traitées pour cette raison en Ontario de 1960 à 1975. Ceci s'inscrit dans une vaste enquête internationale sur les effets tardifs des rayonnements ionisants chez de telles patientes. Il a été tenu compte de la date et du genre de traitement de la première tumeur et de la survenue de toute seconde tumeur primitive avant 1980. Pour chaque localisation de celle-ci, et pour l'ensemble, on a comparé le taux observé au taux attendu selon les fréquences connues en Ontario. Ainsi la fréquence des cancers du poumon est plus grande que le chiffre attendu (64 contre 15,52), au contraire des cancers du sein (56 contre 105,01) et du côlon (27 contre 43,31) et de l'ensemble des seconds cancers primitifs (280 contre 394; $p < 0,05$); toutes ces différences sont significatives. Bien que la durée médiane de la période d'observation soit inférieure à 10 ans, on peut dire qu'on n'a pas fait la preuve qu'il existe un excès de seconds cancers radiogènes.

The issue of whether cancer therapy causes cancer is obviously not trivial; yet answers are slow to emerge. Previous studies have attempted to address the issue of cancer following radiotherapy by evaluating the risk of second primary cancers in women with cervical cancer treated by radiation. The large number of these

studies indicates that many of these women are treated successfully by radiotherapy and survive sufficiently long for second primary cancers to develop. The focus of these studies has been the search for radiation-induced tumours that are distant from the primary site. Reported numbers that exceeded expectation have included those for cancers of the oral cavity, respiratory tract, corpus uteri, ovary, urinary bladder, kidney and rectum.¹⁻⁵ However, the findings from these studies and from larger clinical series⁶⁻⁹ have differed as a result of the definition of second primary neoplasms,¹⁰ the method and length of follow-up of patients with cervical cancer, the different treatment methods, the size of the patient series and the different incidence rates used to derive the expected number of second primary cancers.

Explanations of the observed excesses detract from the radiation induction hypotheses. A higher incidence than expected at certain sites may be due to misdiagnosis of cervical cancer metastases as new primary cancers (e.g., in the lung)² or may result from common risk factors for different sites^{3,11-13} (e.g., smoking-related cancers).

This study was part of a large international study of late radiation effects in patients with cervical cancer who were examined for second primary carcinomas. The Ontario Cancer Registry was used to follow up a large series of patients.

Methods

The cohort of cancer patients included 7535 women in whom inva-

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sive carcinoma of the cervix was diagnosed between 1960 and 1975 who were treated at one of the seven regional treatment centres of the Ontario Cancer Treatment and Research Foundation and the Ontario Cancer Institute, incorporating the Princess Margaret Hospital, Toronto. As 88% of all patients with cervical cancer diagnosed in Ontario from 1969 to 1971 were referred within 1 year of diagnosis to one of these treatment centres, the cohort was almost a complete enumeration of cases of cervical cancer occurring in Ontario.

Excluded from the cohort were women who were not residents of Ontario; women who had received their initial treatment for cervical cancer outside of Ontario; women with a diagnosis of cancer at any time prior to, or simultaneous with, the diagnosis of cervical cancer; and women with two or more subsequent diagnoses of other cancers in addition to the cervical cancer. Follow-up, through the treatment centres' records, was carried on until 1980. Only 5.5% of the 7535 women were lost to follow-up before 1976, and 79% of the cohort were followed up until they died or until 1980, whichever was earlier.

A second primary cancer was defined as a cancer found at another site at least 1 month after the diagnosis of cervical cancer. Subsequent tumours with different cell types from those of the original cervical cancer were considered to be second primary cancers. The charts of patients with second primary tumours with the same cell type as the cervical cancer were reviewed independently by a physician. The review evaluated the operative and pathological reports on the second primary tumour and the clinical progress of the patient since the initial treatment. Of the potential second primary cancers 31% were determined to be metastatic after this detailed review and were excluded from the study by a clinical consultant. Skin cancers other than melanoma were not included as second primary carcinomas in this study.

Woman-years for the length of follow-up for each case of cervical cancer were calculated from the date of first treatment of cervical cancer (or date of admission to a

clinic, whichever was earlier) to one of the following: the date of diagnosis of the second primary cancer, the date of death or the date when the patient was last known to be alive. The woman-years of the entire cohort were then tabulated by 5-year age groups and 5-year calendar periods. The observed number of second primary cancers was compared with the expected number derived from cancer incidence rates in Ontario.¹⁴ Site-specific rates for 1966 were used to calculate expected numbers

for the two earlier 5-year periods of the study, 1960 to 1964 and 1965 to 1969. Incidence rates for 1971 were used for the two later periods, 1970 to 1974 and 1975 to 1979. Significance testing in the analysis assumed a Poisson distribution.¹⁵

The initial treatment for cervical carcinoma between 1960 and 1975 was usually radiotherapy (in 94% of the patients). Only 10% of the women had undergone surgery as part of their initial treatment, and less than 1% had received chemo-

Table I—Observed and expected numbers, and their ratios, of second primary cancers diagnosed between 1960 and 1979 in patients with previously diagnosed cervical cancer, by site and type of therapy for the cervical cancer

Site or type of cancer	All therapy			Radiotherapy only		
	No. of cancers		Ratio	No. of cancers		Ratio
	Observed	Expected		Observed	Expected	
Stomach	10	15.17	0.66	10	14.73	0.68
Colon	27	43.31	0.62*	26	41.96	0.62*
Rectum	13	17.55	0.74	13	16.99	0.77
Pancreas	7	10.35	0.68	7	10.03	0.70
Lung	64	15.52	4.12†	61	14.94	4.08†
Breast	56	105.01	0.53†	54	100.42	0.54†
Uterus	16‡	26.56	0.60	16	25.53	0.63
Ovary	12	17.43	0.69	12	16.69	0.72
Bladder	15	9.68	1.55	15	9.41	1.59
Kidney	5	5.45	0.92	5	5.26	0.95
Leukemia	6	7.58	0.79	6	7.34	0.82
Other	49	120.48	0.41†	47	116.19	0.40†
Total	280	394.02	0.71†	272	379.41	0.72†

*p < 0.025.

†p < 0.01.

‡Two were uterine sarcomas.

Table II—Ratios of observed to expected numbers of second primary cancers, by site of cancer and length of follow-up, for the patients treated by radiotherapy only

Site or type of cancer	Length of follow-up (yr); ratio				Overall ratio
	< 1	1-4	5-9	≥ 10	
Stomach	1.99	1.45	0.00	0.00	0.68
Colon	0.46	0.58	0.94	0.36	0.62
Rectum	0.00	0.35	1.37	0.93	0.77
Pancreas	2.02	0.62	0.32	0.74	0.70
Lung	0.71	4.59	6.17	2.23	4.08
Breast	0.83	0.49	0.62	0.37	0.54
Uterus	0.00	0.12	0.76	1.40	0.63
Ovary	0.00	0.69	0.98	0.76	0.72
Bladder	0.00	1.30	2.46	1.57	1.59
Kidney	3.88	1.17	0.00	0.72	0.95
Leukemia	0.00	1.21	1.38	0.00	0.82
Other	0.46	0.22	0.57	0.42	0.40
Total	0.62	0.63	0.95	0.60	0.72

therapy. Radiotherapy usually consisted of radium or cesium applications and external beam irradiation with cobalt 60. The radiation application averaged 7769 mg•h and ranged from 3960 to 12 000 mg•h. The dose of external irradiation delivered to the cervix averaged 3907 rad and ranged from 3000 to 5000 rad.

Results

The mean age of the women was 52.1 (standard error 0.16) years. About 3% were less than 30 years old and nearly 12% were 70 years old or more. The cohort was followed up for a total of nearly 57 000 woman-years. For women who were lost to follow-up while they were still alive the woman-years were calculated exactly, to the date they were last known to be alive. The mean length of follow-up was 7½ years (median nearly 6 years).

Two hundred and eighty women were identified in whom a second primary cancer had developed by 1980. Observed and expected numbers of second primary cancers were tabulated by site of the cancer and type of therapy (Table I). Though cancers at nearly all the sites were observed less frequently than expected, most of these differences were not statistically significant. Exceptions were cancer of the lung, which occurred more often than expected, and cancers of the colon and the breast, which occurred less often

than expected.

Radiotherapy for the cervical cancer was given to 94% of the women and to 97% of those in whom a second cancer developed. The same pattern of observed and expected numbers of cancers was evident in this major subgroup treated by radiotherapy: an overall deficit of observed second primary cancers, an excess of observed lung cancers, and a deficit of observed colon and breast cancers, all statistically significant (Table I). In addition, in this subgroup an excess of observed bladder cancers and a deficit of observed uterine and ovarian cancers were noted; however, these were not statistically significant. While the subgroup of women who had not been given radiotherapy was small ($n = 422$), it too showed a statistically significant excess of lung cancers (3 observed v. 0.58 expected). The deficit of observed breast cancers in these women was not statistically significant.

The ratios of observed to expected numbers of second primary cancers by site and latency are shown in Table II for the women who received radiotherapy. The excess of lung cancers appeared as early as 1 to 4 years after the cervical cancer had been diagnosed, and it persisted through the follow-up period. The deficits of colon and breast cancers were also consistent.

Discussion

The analysis of second primary

cancers in a cohort of 7535 women who had had cancer of the cervix identified a higher incidence rate of cancer of the lung and a lower incidence rate of cancers of the breast and colon than expected in the general female population of Ontario. Several explanations for these observations are offered.

Since there were significantly more lung cancers than expected in both the group that received radiotherapy and the group that did not, the excess of lung cancer seems not to be related to radiation. Other factors, such as cigarette smoking or misdiagnosis of metastases, might explain the excess of observed primary cancers of the lung and bladder.^{3,11-13} Unfortunately, historical data on cigarette smoking by the women were not available.

The deficit of second primary cancers of the colon, as well as of the stomach and rectum, could be related to a failure to report some of these cancers to the treatment centres associated with the Ontario Cancer Treatment and Research Foundation. Digestive tract cancers are principally treated by surgery, whereas the treatment centres are tertiary referral centres for radiotherapy or chemotherapy; follow-up of patients with cervical cancer by these centres may not have identified every cancer of the digestive tract.

The deficit of uterine and ovarian second primary cancers might be related to the surgical removal of

Vafia

In hypertension,

CAPOTEN
(captopril)



Music in the office

Having background music in the reception room is a good idea. Not only is it soothing to nervous patients, but it also helps to protect the privacy of conversations in offices which aren't completely soundproofed. If conversations can be overheard between exam rooms, music can be beneficial in these areas as well. Just be sure to install volume controls in each room to avoid being distracted by the music while you are examining the patient.

these organs as part of the initial or subsequent treatment. Thus, not all patients with cervical cancer would be at risk for these types of cancer. The extent of surgery was not known for the entire cohort, so the analysis of these sites could not be adjusted for the number of women at risk.

There are a few possible explanations for the twofold deficit of observed breast cancers in this study. Patients with cervical cancer tend to have had their first pregnancy at an early age, a situation that has been shown to protect against breast cancer.¹⁶ Ablation of ovarian function by the high doses of radiotherapy also decreases the risk of breast cancer later in life.¹⁷ In addition, cervical cancer occurs predominantly among lower socioeconomic groups and breast cancer among higher socioeconomic groups. While it was not possible to analyse the observed and expected numbers of cancers by social class, it is known that the magnitude of the effect of social class on the risk of breast cancer is approximately two fold in the general population.¹⁶ These differences could account for the overall deficit of observed second primary cancers of the breast.

Even with the high doses of radiation to the pelvic region and the resultant low level of exposure to radiation at distant body sites, it appears from this study that radiation-induced cancer should not be a concern in determining whether women with cervical cancer should undergo radiotherapy. Support for the use of radiotherapy for cervical cancer comes from several sources. A similar follow-up study on more than 28 000 patients with cervical cancer failed to document any excess of radiation-induced leukemias.¹⁸ Seven years after initial treatment with radiation, patients with cervical cancer in a large clinical series had a life expectancy similar to that of the general population.¹⁹

The findings of our study should be viewed with caution. The women were not followed up long enough for us to be able to identify additional cancers occurring more than 20 years later, as has been reported in other studies.²⁰⁻²³ Therefore, the possibility that long-term radiogenic ef-

fects would not be seen in this cohort cannot be ruled out. However, that the second primary cancers in the women in our study occurred shortly after radiotherapy for cancer of the cervix supports the hypothesis that these cancers arose from causes other than radiation.

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