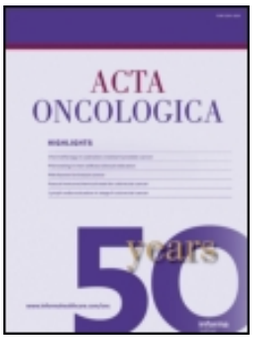

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LEUKEMIA IN PATIENTS WITH BREAST CANCER FOLLOWING ADJUVANT CHEMOTHERAPY AND/OR POSTOPERATIVE RADIATION THERAPY

PER HAHN, NORMA NELSON, and EDWARD BARAL

We investigated the possible etiological role of adjuvant chemotherapy and postoperative radiation therapy in the development of leukemia. A case–control design with four controls matched to each case of leukemia from a cohort of women who had been treated for breast cancer during the years from 1970 to 1985 was used. Thirteen (0.23%) of the women in this cohort developed leukemia over varying lengths of follow-up time, ranging from 3 to 14 years. A higher percentage of the leukemia cases previously had adjuvant chemotherapy compared to their matched controls (54% versus 13%) The relative odds estimate of developing leukemia after chemotherapy compared to no chemotherapy was 14.8 (95% C.I. (1.8; 125.3) $p < 0.01$). This estimate and the test of statistical significance was based on the likelihood function for matched sets with one case and more than one control. Approximately the same percentage of leukemia cases as their controls had received postoperative regional radiation therapy (28% versus 23%). No significant association was found between postoperative radiation therapy and development of leukemia. A combination of adjuvant chemotherapy and postoperative radiation therapy was found more frequently in the leukemia cases than in their matched controls (33% versus 9%). The leukemia developing in patients having received adjuvant chemotherapy was frequently therapy resistant, resulting in a short survival.

An increasing number of women with breast cancer receive adjuvant chemotherapy and radiation treatment after surgery. It has been shown that patients who have received chemotherapy with alkylating agents have an increased risk of leukemia (1, 2). Also, a combination of cyclophosphamide, 5-fluorouracil and methotrexate was reported to be associated with leukemia (3, 4). Such an effect (i.e. leukemogenesis) is of concern in the situation of adjuvant therapy, especially when these women's life expectancy is long. The incidence of leukemia in the general population of women in Manitoba is low; three cases of leukemia in 100 000 female population were observed in one year (5). We here present the results of a case–control study from a cohort of 5 535 breast cancer cases where 0.23% subsequently developed leukemia (6).

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Material and Methods

Between 1970 and 1985, 5 535 breast cancer were retrieved from the population-based provincial Manitoba Cancer Registry at the Manitoba Cancer Treatment and Research Foundation. The Manitoba Cancer Treatment and Research Foundation has been legally mandated to collect, register and maintain data on all cancer patients in Manitoba since 1937. Primary data sources for the registry are cytology and pathology departments in the province, admission and separation data from the provincial hospital, abstracting system, letters and reports of malignant neoplasm forms from physicians, vital statistics deceased listings, as well as hospital health records. The population of the Province of Manitoba is approximately 1 063 020 of which 539 240 are females. The registration of cases is very complete due in large part of the government run health

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care system, i.e. Manitoba Health. There is also an exchange of information between the provinces and territories of Canada to ensure cases diagnosed/treated elsewhere are registered within their home province. The occurrence of subsequent leukemia among registrants of the Manitoba Cancer Foundation was confirmed histologically.

Thirteen (0.23%) of the breast cancer cases diagnosed during the years 1970 through 1985 were diagnosed with second primary leukemia by the end of 1988. Some second primaries may have been lost due to migration, but it will be minimal. No attempt was made to distinguish myeloid dysplastic disease from leukemia.

A 1:4 matched set case–control study involving 13 second primary leukemia cases was carried out. Four controls were randomly selected from the cohort of 5 535 breast cancer cases. The matching criteria were age, year of first diagnosis and length of follow-up. Age was selected to within two years; year of first diagnosis to within one year, and follow-up time (without intervening death or occurrence of a second primary) to at least as long as that of the case. However, during analysis two controls were removed from one set since they died after too short follow-up. Another four sets were reduced by one control because stage was unknown. These six controls were not replaced.

A multivariate matched set analysis, described by Breslow & Day (6) was carried out with adjuvant chemotherapy usage or radiotherapy as the exposure variable and stage of the breast cancer diagnosis. While stage would be expected to be associated with chemotherapy as a chosen breast cancer treatment, it was not, however, expected to be independently associated with the development of leukemia.

The Fisher's score test based on the conditional likelihood function for matched sets as given by Breslow & Day (6, p. 260), was used to determine if an association between the exposure variable and the leukemia second primaries was statistically significant. In addition, exact probabilities based on the matched sets were calculated since the number of discordant sets was small. There was very close agreement in the p-values. Maximum likelihood estimates of the odds ratio of leukemia occurrences, with its 95% confidence interval, were also obtained (6, p. 176–7). For the cases we also estimated the median lapse of time to leukemia diagnosis and the median survival after leukemia diagnosis.

Results

Among the 13 cases, there were 2 chronic leukemias, 2 acute nonlymphocytic leukemias, 2 acute monocytic leukemias and 7 myeloid leukemias. The median lapse of time between the breast cancer diangosis and the leukemia diagnosis of the cases was 5.2 years (Table 1), whereas median duration of time between diagnosis of leukemia and death for the case was one month with a maximum of 27 months (2.25 years). The controls survived much longer than the cases even after subtracting the time between diagnosis of breast cancer and the diagnosis of leukemia for the case from its control's survival time.

Some descriptive observations are presented in Table 2. Slightly more than one-third of the leukemia cases and their controls were less than 50 years of age at the time of their breast cancer diagnosis (38% and 35%). There was a lower proportion of leukemia cases with stage I breast cancer compared with the controls (23% and 48%). This would occur if chemotherapy increased the risk of leukemia, and if chemotherapy was less often used in the

Table 1

Distribution of cases according to type of leukemia and years since diagnosis of breast cancer

Stage		Type of leukemia	Age	Diagnosis to leukemia yrs	Leukemia to death
Surgery only					
1	I	Acute nonlymophocyte leuk.	82	3	1 mo.
2	II	Acute myeloid leukemia	48	9	1 mo.
3	IV	Chronic lymphocytic leuk.	81	1	2 yr.
Radiotherapy only					
1	I	Chronic lymphocytic leuk.	68	9	10 mo.
2	I	Acute myeloid leukemia	62	5	10 mo.
3	II	Acute myeloid leukemia	46	5	5 mo.
Chemotherapy only					
1	II	Acute monocytic leukemia	71	2	1 mo.
2	II	Acute myeloid leukemia	60	8	1 mo.
3	II	Acute myeloid leukemia	45	3	2 yrs.
4	II	Acute monocytic leukemia	44	14	1 mo.
5	II	Acute nonlymphocytic leuk.	76	1	10 mo.
Chemotherapy & Radiotherapy					
1	II	Acute myeloid leukemia	61	4	1 mo.
2	II	Acute myeloid leukemia	49	12	6 mo.

Table 2

Distribution of variables by leukemia cases and controls

Variable	Breast cancer leukemia case variable (n = 13)		Breast cancer control variable (n = 46)	
Stage 1	3	23.1	22	47.8
Stage 2	9	69.2	20	43.5
Stage 3	0	0.0	4	8.7
Stage 4	1	7.7	0	0.0
Chemotherapy	7	53.8	6	13.0
Radiotherapy w/o chemo[b]	3	23.1	17	38.6
Radiotherapy with chemo[a]	4	33.3	4	8.7
Among those with surgery[c]				
Chemotherapy	7	70.0	6	22.2
Radiotherapy w/o chemo	3	50.0	17	44.7
Radiotherapy with chemo	2	40.0	4	16.0
Among those with chemotherapy				
Single chemotherapy*[d]	3	42.9	1	33.3

* Single chemotherapy as opposed to combination chemotherapy.
[a] One unknown in cases.
[b] Two unknowns in control.
[c] three leukemia cases had surgery only; 21 controls had surgery only.
[d] Three controls with chemotherapy could not be broken down to single or combination.

treatment of stage I breast cancer. The cases had a lower precentage of radiotherapy without chemotherapy than that of the controls (23% vs 39%). Conversely, the leukemia cases had a higher proportion with the combination of radiotherapy and chemotherapy than the controls (33% vs 9%). Over all, only 13% of the controls had received chemotherapy whereas 7 (53.8%) of the 13 cases had chemotherapy as treatment for breast cancer.

A statistically significant difference in exposure to adjuvant chemotherapy was found between the leukemia cases and the controls. The matched set score test, and the calculation of the exact probability based on the matched sets, gave statistical significance at $p < 0.01$. From the likelihood function for the matched sets, it is estimated that those breast cancer cases who received chemotherapy had an incidence rate of a diagnosed second primary leukemia per person per year at risk that was 14.8 times that of the breast cancer cases without chemotherapy (95% C.I.; 1.8 to 125.3).

In Table 3, a multivariate adjustment for exposure to adjuvant chemotherapy with radiotherapy and stage still showed an increased risk of 12.2 (95% C.I.; 1.3 to 114.4). We recognise the limitation of our small sample size, but the results are evident and straightforward.

Table 3

Estimate of odds ratios

Factors	Unadjusted O.R.	Adjusted O.R.
Chemotherapy	14.8 (1.8, 125.3)	12.2 (1.3, 114.4)
Radiotherapy	1.6 (0.4, 6.5)	1.1 (0.3, 4.1)
Stage	2.3 (0.8, 6.5)	1.2 (0.2, 5.9)

Discussion

The value of adjuvant chemotherapy in premenopausal women with stage II breast cancer is well established (7, 8). The leukemia incidence in the general population in Manitoba is low; three cases in 100 000 female population between the ages of 40–60 years (5). The occurrence of treatment-related leukemia in primary breast cancer after adjuvant chemotherapy represents a problem. In the present study, we have observed an increase of the incidence of leukemia in patients having received adjuvant chemotherapy compared to the incidence in controls, about as much as 15 times. Among the patients who were given chemotherapy and developed leukemia, 57% had CMF combination chemotherapy and 43% received melphalan as single drug. N. Einhorn et al. (1) demonstrated the leukemogenic effect of the use of melphalan for ovarian cancer. Boice (9) and Curtis et al. (10) reported that ionizing radiation is leukemogenic, but there are few reports which have shown such events following postoperative radiotherapy for breast cancer and the results of our study could not confirm such association between the use of regional radiation therapy and leukemia.

Leukemia developing in the patients who had recieved adjuvant chemotherapy had, in our analysis, poor prognosis as no survivors were found beyond 11 months. The

association of leukemia persists even after adjusting for both radiotherapy and the stage of breast cancer. In the treatment of Hodgkin's disease, age was found to be a risk factor for the occurrence of treatment-related leukemia (12). Such a correlation could not be tested in this study as we have matched by age, although Hodgkin's disease patients are generally younger than the patients studied in this analysis.

Having recognized the benefits of adjuvant chemotherapy in the management of the carcinoma of the breast (1), further research on a larger number of cases will have to continue with the focus on developing less toxic regimens and identifying the patients who are more susceptible to leukemogenic action of certain types of chemotherapy.

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