Leukemia following Chemotherapy for Breast Cancer

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ABSTRACT

Leukemia following chemotherapy for breast cancer was studied among patients diagnosed during 1973–1985 within the population-based tumor registries in the Surveillance, Epidemiology, and End Results Program. Among 13,734 women given initial chemotherapy, 24 developed acute nonlymphocytic leukemia (ANLL) compared to 2.1 expected based on general population rates (observed/expected = 11.5; 95% confidence interval = 7.4–17.1). Overall, 58 excess ANLL occurred per 100,000 women-years at risk for patients treated with chemotherapy. The cumulative incidence was 0.7% at 10 years. Risk remained high over all periods of observation up to 9 years after treatment. Among 7974 women treated only with surgery during 1973 and 1974, a period before the widespread use of adjuvant chemotherapy for breast cancer, ANLL was not significantly increased (observed = 7, expected = 5.1). A case-control study was then conducted in Connecticut to evaluate more detail the risk associated with adjuvant chemotherapy in the general population. Among 20 cases (17 incident leukemias and 3 deaths due to preleukemia) and 60 matched controls, alkylating agents were linked to an 11.9-fold risk of ANLL and preleukemia (95% confidence interval = 2.6–55). Chemotherapy regimens including melphalan were related to a higher risk of leukemic conditions than those including cyclophosphamide.

These data suggest that women in the general population treated with adjuvant chemotherapy for breast cancer at an increased risk of leukemia, that the risk remains high among long-term survivors, and that risk differs by type of alkylating agent administered.

INTRODUCTION

Previous studies of breast cancer patients have linked acute leukemia and preleukemia to treatment with alkylating agents (1–3). However, the widespread use of adjuvant chemotherapy to treat women with operable breast cancer and regional lymph node involvement is relatively recent (4), and the risk among long-term survivors in the general population has not been determined. Further, the risks of chemotherapy-related leukemia by specific type of drug, age at treatment, and time since treatment are also not well defined. Approximately 50,000 breast cancer patients each year are potential candidates for adjuvant chemotherapy in the United States, and therefore, the late effects of these drugs present an important concern. To address these issues, a previous cohort study of breast cancer patients diagnosed during 1973 to 1980 within National Cancer Institute’s SEER2 cancer registration areas (3) was extended with 5 additional years of follow-up and new breast cancer cases, and a nested case-control study was conducted in the state of Connecticut.

SUBJECTS AND METHODS

SEER Cohort Study: Chemotherapy versus Surgery. Breast cancer patients diagnosed during 1973 to 1985 were identified from the incidence files of nine population-based cancer registries participating in the SEER program (5). The population-based registries cover approximately 10% of the United States population, and studies utilizing this data resource avoid the potential for selection bias associated with hospital referral patterns or protocol admission criteria. A total of 85,889 women were selected who had invasive breast cancer, either unilateral or bilateral, as their first primary cancer and who survived 18 months or more following their initial diagnosis. Altogether, 13,734 women were reported to SEER as receiving chemotherapy as part of their first course of therapy. This group was further subdivided into patients whose initial treatment included both chemotherapy and radiotherapy (n = 3961) and those receiving chemotherapy without radiotherapy (n = 9773). Women given chemotherapy for a second breast primary were included if treatment was initiated within 1 year from the diagnosis of the first breast cancer (n = 58). No information was available in SEER on specific drugs or on therapy given after the first course of treatment. The reporting of chemotherapy to registry personnel is known to be incomplete (3), since drug therapy is frequently administered at private physicians’ offices without notation in hospital charts. Due to considerable evidence of misclassification of chemotherapy status in the SEER data, we restricted the comparison group to patients diagnosed in 1973 and 1974, before the widespread use of adjuvant chemotherapy for breast cancer (6, 7). The comparison group consisted of 7974 women who were reported as receiving surgery only (no chemotherapy, no radiotherapy) for their first course of therapy.

SEER registry incidence files were searched for leukemia that developed 18 months or more following the initial breast cancer diagnosis. Earlier investigations have indicated that the minimal latent period for chemotherapy-induced leukemia is approximately 1–2 years (1–3). Eleven cases diagnosed less than 18 months after the initial cancer were excluded. The histological type of leukemia was classified by the individual patient’s physician or hospital pathologist and was accepted as reported. Of primary interest was ANLL, defined as acute myelogenous leukemia, acute monocytic leukemia, erythroleukemia, and acute leukemia, not otherwise specified.

For each patient, PY were accrued 18 months after the breast cancer diagnosis until the date of death, date of last follow-up, date of diagnosis of (non-breast) subsequent primary cancer, or December 31, 1985, whichever came first. Sex-, age-, and calendar year-specific incidence rates for all leukemia combined and specific leukemia subtypes from SEER were applied to the appropriate PY to compute the expected number of leukemias had these women experienced the same rates as the general population included in the SEER registration areas (8). Tests of significance (2-sided) of the ratio of the observed to the expected number of subsequent leukemias and exact 95% CI were calculated assuming the observed number of leukemias followed a Poisson distribution (9). Cumulative probabilities were estimated by the Kaplan–Meier method (10).

Connecticut Case-Control Study: All Treatments. To obtain complete treatment information, including subsequent therapy, a nested case-control study of leukemic disorders was conducted in Connecticut. Chronic lymphocytic leukemia was excluded since this type of leukemia is not known to be induced by radiotherapy or chemotherapy. Between 1973 and 1985, 20 leukemic disorders were identified among 14,860 women with breast cancer, who survived at least 18 months, by record linkage with the incidence files of the Connecticut Tumor Registry and by searching Connecticut mortality files for an underlying cause of death reported as severe anemia or other blood disorder. Preleukemias recorded on the death certificate but not specified as the underlying cause of death were not included. All cases of leukemia and potential preleukemia were reviewed and reclassified by the study hematologist.
LEUKEMIA FOLLOWING CHEMOTHERAPY FOR BREAST CANCER

Table 1 Observed and expected number of leukemia cases by therapy and type of leukemia

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Surgery only</th>
<th>Any chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. patients</td>
<td>7,974</td>
<td>13,734</td>
</tr>
<tr>
<td>Average PY</td>
<td>7.0</td>
<td>2.7</td>
</tr>
<tr>
<td>Average age at diagnosis (yr)</td>
<td>60.5</td>
<td>53.9</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Leukemia type</th>
<th>O/E</th>
<th>95% CI</th>
<th>O/E</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>All leukemias</td>
<td>12</td>
<td>0.9</td>
<td>0.4-1.5</td>
<td>26</td>
</tr>
<tr>
<td>ANLL</td>
<td>7</td>
<td>1.4</td>
<td>0.5-2.8</td>
<td>24</td>
</tr>
<tr>
<td>CML ML NOS</td>
<td>1</td>
<td>0.4</td>
<td>0.01-2.3</td>
<td>1</td>
</tr>
<tr>
<td>CLL</td>
<td>3</td>
<td>0.6</td>
<td>0.1-1.7</td>
<td>1</td>
</tr>
<tr>
<td>ALL</td>
<td>1</td>
<td>2.6</td>
<td>0.06-13.9</td>
<td>0</td>
</tr>
</tbody>
</table>

* Patients who survived 18 months or more after diagnosis.
† PY accumulated beginning 18 months after breast cancer diagnosis.
‡ ML NOS, myelogenous leukemia, not otherwise specified; CLL, chronic lymphocytic leukemia.

(W. C. M.), using reports and slides available from peripheral blood studies and bone marrow samples. The 20 cases were classified as: 15 ANLL, 1 ALL, 1 CML, 1 acute myeloblastosis, 1 refractory anemia with an excess of blasts, and 1 refractory anemia with an excess of blasts in transformation to leukemia. One leukemia was rejected due to a history of preleukemia prior to the breast cancer diagnosis, and 3 of the 6 blood disorders were judged not to be preleukemia. For each eligible case, three controls were randomly selected from the pool of women in the Connecticut breast cancer cohort who were matched for exact age and calendar year of breast cancer diagnosis, race, and follow-up interval (without a second primary cancer). Controls were selected who survived at least as long as the interval between the breast cancer and leukemia diagnoses or, for preleukemia cases, the interval between breast cancer and death.

Detailed data on all treatment courses (surgical procedures, radiotherapy, chemotherapy, and hormonal therapy) were abstracted from hospital charts, radiotherapy clinics, oncology clinics, physician’s offices, and registry files. Six patients were seen regularly at an oncology clinic during the time of interest. For the remaining 74 women, we attempted to contact all physicians who may have administered therapy or who had knowledge of the patient’s treatment. When available, the daily dose of each drug received and treatment schedules were abstracted. Successful contact was made with at least one physician (or clinic) knowledgeable of the patient’s primary treatment for 85% of the cases and 87% of the controls. Yearly follow-up reports of disease status and treatment status from the individual hospital tumor registries were used for an additional 10% of the cases and 3% of the controls as confirmation of the treatment information available in the medical records.

Among 26 women who were identified from physician and hospital medical records as receiving an alkylating agent as part of their first course of therapy, chemotherapy was not recorded in SEER registry files for 3 of 13 cases (23%) and 7 of 13 controls (54%).

Comparisons between cases and matched controls were made using conditional logistic regression methods (11, 12). When the matched analysis produced an infinite relative risk, i.e., for melphalan, exact methods were used to calculate the lower confidence boundary (13). In addition, an unmatched relative risk was calculated using unconditional logistic regression. The degree of uncontrolled confounding introduced by breaking the matching was estimated by comparing the unmatched with the matched relative risk for all alkylating agents combined (11); the unmatched estimate was shown to be conservative (i.e., closer to 1.0) but similar in magnitude to the matched relative risk. Treatment with an alkylating agent was included in the analysis up to 1 year prior to the development of leukemia (or death due to preleukemia) for the case or the corresponding interval for each matched control. Relative risks for individual alkylating agents were restricted to agents given for at least 1 month and were adjusted for exposure to other alkylating agents.

Detailed information on the dose of each alkylating agent was available for 9 of 13 exposed cases (69%) and 10 of 13 exposed controls (77%). Although estimation of a dose-response relationship for each alkylating agent would have been desirable, the small number of subjects exposed to individual agents made these analyses unreliable.

RESULTS

SEER Cohort Study. Breast cancer patients reported to SEER as receiving chemotherapy for their first course of treatment were younger at mean age of diagnosis than the comparison group of women treated with surgery alone (54 versus 61 years, Table 1). Practically all women receiving chemotherapy were diagnosed during 1975 or later (97%). The average PY at risk for leukemia development (accrued from 18 months after the breast cancer diagnosis) was 2.7 years for the chemotherapy group as compared to 7.0 years for those treated with surgery only; this difference is largely due to the longer follow-up period possible for patients diagnosed in 1973 and 1974 (11-12 years).

Compared with the general population, breast cancer patients treated with chemotherapy had a 5-fold risk of developing leukemia, whereas no increased risk was observed for those treated with surgery only (Table 1). The leukemia excess following chemotherapy was entirely due to the 11.5-fold risk of ANLL. No elevation in risk was observed for chronic lymphocytic leukemia, ALL, CML, or other myelogenous leukemia.

Table 2 Observed and expected ANLL following chemotherapy for breast cancer by time since initial diagnosis

<table>
<thead>
<tr>
<th>Time since diagnosis (yr)</th>
<th>No. of patients</th>
<th>PY</th>
<th>O</th>
<th>E</th>
<th>O/E</th>
<th>95% CI</th>
<th>Excess risk*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.5-2.4</td>
<td>13,734</td>
<td>11,563</td>
<td>3</td>
<td>0.6</td>
<td>5.0</td>
<td>1.0-15</td>
<td>21</td>
</tr>
<tr>
<td>2.5-4.9</td>
<td>9,887</td>
<td>16,368</td>
<td>12</td>
<td>0.9</td>
<td>13.3</td>
<td>6.9-23</td>
<td>68</td>
</tr>
<tr>
<td>5.0-7.4</td>
<td>4,198</td>
<td>6,961</td>
<td>6</td>
<td>0.4</td>
<td>14.6</td>
<td>5.3-32</td>
<td>80</td>
</tr>
<tr>
<td>7.5-11.0</td>
<td>1,746</td>
<td>2,621</td>
<td>3</td>
<td>0.2</td>
<td>16.7</td>
<td>3.4-49</td>
<td>108</td>
</tr>
<tr>
<td>All</td>
<td>13,734</td>
<td>37,513</td>
<td>24</td>
<td>2.1</td>
<td>11.5</td>
<td>7.4-17</td>
<td>58</td>
</tr>
</tbody>
</table>

* Excess risk = (O - E) / PY × 100,000.
Substantial analyses were confined to the ANLL subtype.

Substantial ANLL excesses following chemotherapy were apparent throughout all follow-up periods with the last two leukemias observed in the 9th year after breast cancer diagnosis (Table 2). After 30 months from initial diagnosis, the O/E rose to about 15-fold and remained constant at this high level throughout the remainder of the follow-up period. The overall excess risk of leukemia associated with chemotherapy was 58 cases of ANLL/100,000 woman-years at risk, and the cumulative probability of developing ANLL after 10 years was 0.7 ± 0.2% (rate ± SE). By comparison, patients treated with surgery (no radiotherapy or chemotherapy) had a cumulative incidence of ANLL of 0.1% at 10 years.

The risk of ANLL by age at chemotherapy was evaluated in both relative and absolute terms (Fig. 1). On a relative scale, the observed number of leukemias divided by the expected number decreased significantly with age at treatment (for trend, $P = 0.006$). On an absolute scale, the observed number of leukemias minus the expected number, divided by PY, remained relatively constant (for trend, $P = 0.76$). Because the underlying rate of disease can change dramatically with age, it is often recommended that the absolute scale be used when making inferences about the modifying effect of age.

ANLL excesses were most prominent for breast cancer patients treated during the early years of adjuvant chemotherapy use (Table 3). A significant negative trend over the calendar years 1975 to 1982 was detected (for trend, $P = 0.014$). Differences in duration of patient follow-up did not account for the lower risk in the most recent time periods. After restricting the analysis to women followed for 2.5 years or more (a period over which the risk was relatively constant), patients treated during 1979 to 1982 remained at lower risk of ANLL ($O = 3, E = 0.5$) as compared to women receiving chemotherapy during 1975 to 1978 ($O = 18, E = 0.9$).

Since SEER data on the first course of therapy is routinely updated in the years following a cancer diagnosis, we evaluated our breast cancer cohort for a possible bias in the method of reporting treatment. In a sample of breast cancer patients treated with chemotherapy who did not develop a second primary cancer, 8.4% had their drug therapy reported to SEER retrospectively, i.e., at some time after the initial treatment for breast cancer. In a comparable group of breast cancer patients who later developed ANLL, 23% had their chemotherapy reported to the registry in a retrospective manner, presumably as the result of the detailed treatment history taken at the time of the leukemia diagnosis. The effect of this bias is to overestimate the ANLL risk. A crude estimate of the ANLL risk in the absence of retrospective reporting was obtained by reducing the observed and expected numbers of ANLL by 23 and 8.4%, respectively, resulting in a decrease in the $O/E$ ratio from 11.5 to 9.7.

**Connecticut Case-Control Study: All Treatments.** The mean age at diagnosis of breast cancer for the 20 cases of leukemia and preleukemia and 60 age-matched controls was 63 years (range 48–87 years). Only 4 subjects were less than 50 years of age at the time of initial treatment. A large proportion of the leukemia and preleukemia cases and matched controls were treated for breast cancer during 1975 and 1976 (60%), the calendar years found to be associated with the highest risks in the SEER cohort analysis described above. One-half of the leukemic conditions occurred 5 years after initial diagnosis for breast cancer (range 23–102 months). The cases and controls differed in stage of breast cancer at initial presentation: 75% of the cases had cancer involvement of the regional lymph nodes (stage II and III) versus 52% of the controls; only 3 women (all controls) had distant metastases (stage IV) at the time of their initial breast cancer diagnosis.

Overall, 26 patients received chemotherapy which included an alkylating agent (13 cases, 65%; 13 controls, 22%). Table 4 describes the cytotoxic agents given to patients for their primary (first course) therapy and any subsequent treatment and the cumulative dose of alkylating agent. To enable comparison with other studies, cumulative doses are presented without adjustment for patient size (range, 1.33–2.15 m$^3$). The overall RR of leukemia and preleukemia associated with alkylating agent therapy was 8.1 (Table 5). The increased risk associated with chemotherapy was most evident for ANLL and preleukemia (ANLL + PL: RR = 11.9). The unmatched estimate of the ANLL + PL risk was similar to the matched estimate (unmatched RR = 9.1, 95% CI = 2.7–31). Neither the ALL nor the CML case received chemotherapy.

Duration of alkylating agent therapy appeared to influence the risk of ANLL + PL (Table 5). In comparison with patients with no exposure, the RR associated with less than 18 months of therapy was 8.8, and the RR for 18 months or more of therapy was 14.7. The test of linear trend for increasing risk with increasing duration was highly significant ($P = 0.001$).

The ANLL + PL risk following alkylating agent therapy, adjusted for adjuvant radiotherapy, increased to 20-fold (Table 6). Radiotherapy was associated with a nonsignificant 3.6-fold risk of leukemic conditions after adjusting for chemotherapy.

![Fig. 1. Observed (O) to expected (E) ratio and excess risk ((O - E)/PY x 100,000) of ANLL following chemotherapy for breast cancer, according to age at first treatment (95% confidence intervals are presented for O/E ratios).](image-url)

**Table 3** Observed and expected ANLL following chemotherapy for breast cancer by year of breast cancer diagnosis

<table>
<thead>
<tr>
<th>Year of diagnosis</th>
<th>No. of patients</th>
<th>PY</th>
<th>O</th>
<th>E</th>
<th>O/E</th>
<th>95% CI</th>
<th>Excess risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>1973–1974</td>
<td>433</td>
<td>1873</td>
<td>0</td>
<td>0.1</td>
<td>0.0</td>
<td>0.0–31</td>
<td>–6</td>
</tr>
<tr>
<td>1975–1976</td>
<td>2010</td>
<td>9828</td>
<td>13</td>
<td>0.6</td>
<td>21.7</td>
<td>11.5–37</td>
<td>126</td>
</tr>
<tr>
<td>1977–1978</td>
<td>2252</td>
<td>9256</td>
<td>7</td>
<td>0.5</td>
<td>14.0</td>
<td>5.6–29</td>
<td>70</td>
</tr>
<tr>
<td>1979–1980</td>
<td>2598</td>
<td>7815</td>
<td>1</td>
<td>0.4</td>
<td>2.5</td>
<td>0.06–14</td>
<td>8</td>
</tr>
<tr>
<td>1981–1982</td>
<td>3678</td>
<td>6959</td>
<td>3</td>
<td>0.4</td>
<td>8.1</td>
<td>1.7–24</td>
<td>38</td>
</tr>
</tbody>
</table>

*See footnotes a, b to Table 1 and a to Table 2.
*For trend, calendar years 1975–1982, $P = 0.014$.
*For trend, calendar years 1975–1982, $P = 0.008$. 

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patients (22-25) by providing details on over 13,000 women treated for calendar years 1979-1982, which likely reflects the introduction areas goes beyond previous registry studies of breast cancer and that long-term therapy was associated with the greatest risk.

Our evaluation of leukemia within the SEER cancer registration areas goes beyond previous registry studies of breast cancer patients (22-25) by providing details on over 13,000 women treated with chemotherapy by year of observation and age and calendar year of diagnosis. Risk of leukemia was found to be highest during 1975-1976. Substantially lower risks were observed for women in the general population treated with alkylating agents for breast cancer. Risk was highest for patients treated in the mid-1970s and remained elevated throughout all periods of observation, up to 9 years after initial treatment. Age at first treatment was not an important modifier of risk with younger patients being at similar excess risk as older patients. A nested case-control study showed that the risk of leukemic conditions was higher for melphalan than cyclophosphamide and that long-term therapy was associated with the greatest risk.

### Discussion

Consistent with studies of patients treated with alkylating agents for other malignancies (14–21), a high leukemia risk was found for women in the general population treated with alkylating agents for breast cancer. Risk was highest for patients treated in the mid-1970s and remained elevated throughout all periods of observation, up to 9 years after initial treatment. Age at first treatment was not an important modifier of risk with younger patients being at similar excess risk as older patients. A nested case-control study showed that the risk of leukemic conditions was higher for melphalan than cyclophosphamide and that long-term therapy was associated with the greatest risk.
of observation among 5299 breast cancer patients treated with chemotherapy including melphalan who were enrolled in the National Surgical Adjuvant Breast and Bowel Project clinical trials (1). Additional years of observation will be needed to learn whether the leukemia excess will be limited to the first decade after exposure as suggested in some studies of Hodgkin's disease (16).

When measured on a relative scale, the risk of ANLL after chemotherapy was highest for women treated at ages younger than 55 years, and risk declined with increasing age at diagnosis. Other large studies of breast cancer patients have also reported higher relative risks of leukemia among young women treated with chemotherapy (1, 2). However, the absolute excess risks in our study did not vary markedly by age at initial treatment. Women under 55 years of age experienced approximately the same number of excess leukemia cases/person-years of follow-up as older women. Thus, younger women may not be more susceptible to chemotherapy-induced leukemia than older women, but instead their higher relative risk may simply reflect their lower underlying risk.

Although available data are limited, melphalan has been related to a higher leukemia risk than cyclophosphamide in studies of ovarian cancer and multiple myeloma (26, 27). Our case-control study also found a substantial difference in risk between these two agents when administered at the lower dose levels used in adjuvant chemotherapy for breast cancer. Therapy with melphalan was associated with a large risk of leukemic conditions (conservatively estimated as RR = 45 but based on only one exposed control). These results are consistent with the 24-fold risk reported from the National Surgical Adjuvant Breast and Bowel Project patients treated with approximately 550 mg of melphalan (cumulative risk at 10 years = 1.68%) (1). Similar to reports from clinical trials (28, 29), we did not find a significant leukemia risk for treatments including cyclophosphamide. However, the numbers are small, and increases as much as 6-fold could not be rejected at the 5% level. One case-control study in Germany reported 2.7-fold risk of leukemia among breast cancer patients treated with cyclophosphamide, with the highest risk seen among those receiving more than 30,000 mg (2). Within our series, no other drug was administered frequently enough to provide quantitative estimates of risk.

Risk of leukemia has been found to be highest among patients with the largest cumulative exposure to alkylating agents (26, 30). Breast cancer patients treated with alkylating agents for 18 months or more had the highest risk of leukemic conditions, presumably due to a larger cumulative dose. Few patients in this case-control study received chemotherapy for less than 12 months, and thus, we were unable to evaluate the risk associated with short-term therapy which is frequently recommended in current treatment practice (4).

Radiotherapy for breast cancer has been reported to increase the risk of leukemia in some (1, 25) but not all studies (2, 31). A nonsignificant 3.6-fold risk was observed in our case-control study, but the estimate of risk was consistent with a wide range of values, including that of no risk at all. Because such a small proportion of active bone marrow is exposed during radiation treatment of breast cancer, it has been suggested that high doses to these limited volumes result more in cellular killing of potentially leukemic cells than in transformation (31).

Several strengths and limitations of our series should be considered in interpreting our results. An important advantage of the SEER cancer registries is the large numbers of patients available for evaluation. Moreover, the use of population-based registry data minimizes any bias due to selection or referral patterns that may occur in clinical or hospital series. However, there are potential problems in the accuracy of the treatment designations reported to cancer registries (31, 32). In the current SEER analysis we found a higher rate of retrospective reporting of chemotherapy for patients with a second primary leukemia as compared to women who did not develop a second primary cancer, a bias which resulted in overestimating the leukemia risk due to chemotherapy. This bias was eliminated in the case-control study which obtained treatment records from private physicians as well as from hospital and oncology clinic charts. We found that it was difficult to determine chemotherapy exposure within the general population, because treatment is not centralized as it often is for radiotherapy. By undertaking an extensive search we were able to verify with a physician the treatment administered for about 85% of the patients, although detailed dose records could not be located for 30% of study subjects who received chemotherapy.

The use of adjuvant chemotherapy has been shown in numerous randomized trials to increase survival in a significant number of patients with breast cancer (4). Thus, for many women the small cumulative risk of leukemia demonstrated in the present series and in other analytic studies is outweighed by the benefits of these therapies in prolonging life. Nonetheless, it is essential to continue the effort to quantify the potential risks for various treatments and to find therapies that minimize late effects while providing equivalent survival benefits.

ACKNOWLEDGMENTS

We are grateful to the staffs of the SEER cancer registries, in particular the Connecticut Tumor Registry, Connecticut Hospital As-

Table 6  Adjusted relative risks of ANLL and preleukemia by type of therapy for breast cancer (18 cases and 54 controls)

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Status</th>
<th>Cases</th>
<th>Controls</th>
<th>Adjusted RR*</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alkylating agents</td>
<td>No</td>
<td>5</td>
<td>42</td>
<td>1.0 (R)</td>
<td>20.0*</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>13</td>
<td>12</td>
<td>20.0*</td>
<td>3.2-124</td>
</tr>
<tr>
<td>Adjuvant radiotherapy</td>
<td>No</td>
<td>13</td>
<td>39</td>
<td>1.0 (R)</td>
<td>3.6*</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>5</td>
<td>15</td>
<td>3.6*</td>
<td>0.6-22</td>
</tr>
<tr>
<td>Melphalan</td>
<td>No</td>
<td>10</td>
<td>53</td>
<td>1.0 (R)</td>
<td>44.6*</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>8</td>
<td>1</td>
<td>44.6*</td>
<td>4.9-409</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>No</td>
<td>13</td>
<td>43</td>
<td>1.0 (R)</td>
<td>1.3*</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>5</td>
<td>11</td>
<td>1.3*</td>
<td>0.3-6.6</td>
</tr>
</tbody>
</table>

* RR are from matched analyses using conditional logistic regression models for all therapies with the exception of melphalan. R, referent group.

* Adjusted for radiotherapy.

* Adjusted for alkylating agent exposure.

* RR shown in table for melphalan is from unmatched analysis using unconditional logistic regression model. RR from matched analysis = ∞, 95% CI = 4.9 - ∞.

* Adjusted for exposure to other alkylating agents.
sociation, and the participating Connecticut oncology clinics and medical facilities that made this study possible; to Diane Fuchs for field support; to Bonnie Johnson for abstracting and review of chemotheraphy dose data; and to Charlene Hartsock for computer support.

REFERENCES


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