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## BREAST CANCER AND OTHER SECOND NEOPLASMS AFTER CHILDHOOD HODGKIN'S DISEASE

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**Abstract Background.** Patients who survive Hodgkin's disease are at increased risk for second neoplasms. As survival times increase, solid tumors are emerging as a serious long-term complication.

**Methods.** The Late Effects Study Group followed a cohort of 1380 children with Hodgkin's disease to determine the incidence of second neoplasms and the risk factors associated with them.

**Results.** In this cohort, there were 88 second neoplasms as compared with 4.4 expected in the general population (standardized incidence ratio, 18.1; 95 percent confidence interval, 14.3 to 22.3). The estimated actuarial incidence of any second neoplasm 15 years after the diagnosis of Hodgkin's disease was 7.0 percent (95 percent confidence interval, 5.2 to 8.8 percent); the incidence of solid tumors was 3.9 percent (95 percent confidence interval, 2.3 to 5.5 percent). Breast cancer was the most common solid tumor (standardized incidence ratio, 75.3; 95 percent confidence interval, 44.9 to 118.4),

with an estimated actuarial incidence in women that approached 35 percent (95 percent confidence interval, 17.4 to 52.6 percent) by 40 years of age. Older age (10 to 16 vs. <10 years) at the time of radiation treatment (relative risk, 1.9) and a higher dose (2000 to 4000 vs. <2000 cGy) of radiation (relative risk, 5.9) were associated with significantly increased risk of breast cancer. The estimated actuarial incidence of leukemia reached a plateau of 2.8 percent (95 percent confidence interval, 0.8 to 4.8 percent) 14 years after diagnosis. Treatment with alkylating agents, older age at the diagnosis of Hodgkin's disease, recurrence of Hodgkin's disease, and a late stage of disease at diagnosis were risk factors for leukemia.

**Conclusions.** The risk of solid tumors, especially breast cancer, is high among women who were treated with radiation for childhood Hodgkin's disease. Systematic screening for breast cancer could be important in the health care of such women. (N Engl J Med 1996;334:745-51.)

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**L**ONG-TERM sequelae of the treatment of Hodgkin's disease are being encountered with increasing frequency because of the marked improvement in survival.<sup>1-4</sup> Second neoplasms, particularly acute myelogenous leukemia, are well-known late complications in patients who have been treated for Hodgkin's disease as adults.<sup>5-15</sup> An increased risk of second neoplasms in patients treated for Hodgkin's disease in childhood has also been reported by the Late Effects Study Group<sup>16</sup> and others.<sup>17,18</sup> In an earlier study, we estimated the cumulative probability of any second neoplasm to be 20 percent (4 percent for leukemia and 16 percent for solid tumors) 20 years after a diagnosis of Hodgkin's disease in childhood.<sup>16</sup> To investigate further the incidence of second neoplasms af-

ter the treatment of childhood Hodgkin's disease and to identify specific factors associated with the risk, we extended the median follow-up for the cohort of the Late Effects Study Group from 7 to 11.4 years and increased the size of the cohort from 979 to 1380.

### METHODS

Fifteen institutions participated in this study (see the Appendix). The cohort consisted of children who were less than 16 years of age when their Hodgkin's disease was diagnosed and who received their primary treatment between 1955 and 1986 at a participating institution.

At each institution, a roster of all patients with Hodgkin's disease was prepared, and data were abstracted from the clinical records. Doses, fields, and equipment used in radiation therapy were noted, as were agents, doses, and durations of chemotherapy. For each patient, the date of last contact was obtained from the clinical records. For patients in whom second neoplasms developed, the date of diagnosis, the histologic characteristics and site of the tumor, and whether the tumor arose in the radiation-therapy field were recorded. If the patient died, the date and cause of death were also reported. Pathological findings were confirmed at the treating institution. The length of time at risk for second neoplasms was computed from the date of the diagnosis of Hodgkin's disease to the date of the diagnosis of the second neoplasm, the date of death, or the date of last contact, whichever came first.

For purposes of analysis, patients were classified in one of three mutually exclusive treatment groups. The first group received radia-

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tion therapy alone, the second group received chemotherapy alone, and the third group received both radiation therapy and chemotherapy (the latter either as part of the primary treatment or as salvage therapy for recurrence).

Patients who were treated with alkylating agents were analyzed separately. The following drugs were included in that class: mechlorethamine hydrochloride, cyclophosphamide, chlorambucil, procarbazine, nitrosoureas, triethylenemelamine, thiotepa, and dacarbazine. A score for the doses of alkylating agents received by each patient<sup>16</sup> was calculated as follows: a single alkylating agent administered for at least six months was assigned a score of 1; two alkylating agents for six months, a score of 2; and so on. All such scores corresponding to the patient's treatment course were added together and rounded to the nearest integer.

To estimate the risk of second neoplasms, the number of person-years of observation was compiled for subgroups of the cohort defined by age and sex. Rates of incidence of cancer (obtained from the registry of the Surveillance, Epidemiology, and End Results Program of the National Institutes of Health<sup>19</sup>) were used to calculate the expected number of cases of cancer. Standardized incidence ratios were calculated as the ratios of observed to expected cases. The 95 percent confidence intervals were estimated by a method described by Vandembroucke.<sup>20</sup> Cumulative probabilities of second neoplasms were calculated with actuarial methods.<sup>21</sup> Cox regression techniques were used to calculate estimates of relative risk. Variables included in the regression model were sex, age at the diagnosis of Hodgkin's disease, clinical stage of the disease, treatment group, whether splenectomy had been performed, the alkylating-agent score, and the dose of radiation. Recurrence was included as a time-dependent covariate in the regression model. Age at the diagnosis of Hodgkin's disease was analyzed both as a categorical variable (less than 10 years or 10 to 16 years) and as a continuous variable. Clinical stages I and II and clinical stages III and IV were grouped because of the strong correlation between treatment and clinical presentation.

## RESULTS

The median duration of follow-up was 11.4 years, and 80 percent of the cohort of 1380 eligible patients with Hodgkin's disease were alive at the time of last contact

Table 1. Characteristics of the Patients.

| CHARACTERISTIC                                      | TOTAL COHORT | PATIENTS WITH SECOND CANCER |          |                        |
|---|--------------|-----------------------------|----------|------------------------|
|   |              | SOLID TUMOR                 | LEUKEMIA | NON-HODGKIN'S LYMPHOMA |
| No. of patients                                     | 1380         | 56                          | 26       | 6                      |
| Male sex — %  | 65           | 43                          | 69       | 50                     |
| Stage of Hodgkin's disease — %                      |              |                             |          |                        |
| I or II   | 65           | 76                          | 31       | 67                     |
| III or IV   | 35           | 24                          | 69       | 33                     |
| Age at diagnosis                                    |              |                             |          |                        |
| Median — yr   | 11           | 12                          | 11       | 11                     |
| Range — yr  | 1–16         | 2–16                        | 3–15     | 7–15                   |
| <10 yr — no. of patients (person-yr of follow-up)   | 504 (6025)   | 17                          | 6        | 2                      |
| 10–16 yr — no. of patients (person-yr of follow-up) | 876 (9635)   | 39                          | 20       | 4                      |
| Time to second cancer — yr                          |              |                             |          |                        |
| Median  | —            | 14                          | 4        | 14                     |
| Range   | —            | 0.8–28                      | 0.8–14   | 0.8–18                 |
| Follow-up — yr                                      |              |                             |          |                        |
| Median  | 11.4         | 19                          | 5        | 13                     |
| Range   | 0.1–37       | 4–36                        | 2–15     | 1–23                   |
| Treatment — % of patients                           |              |                             |          |                        |
| Radiation alone                                     | 23           | 30                          | 0        | 17                     |
| Chemotherapy alone                                  | 8            | 2                           | 19       | 17                     |
| Radiation and chemotherapy                          | 69           | 68                          | 81       | 66                     |
| Death — %   | 20           | 30                          | 96       | 83                     |

Table 2. Observed and Expected Rates of Second Cancers in the Entire Cohort, According to Type and Site.

| TYPE OR SITE               | OBSERVED CASES | EXPECTED CASES | STANDARDIZED INCIDENCE RATIO (95% CI)* |
|----------------------------|----------------|----------------|--|
| All cancers†               | 79             | 4.4            | 18.1 (14.3–22.3)                       |
| Leukemia                   | 26             | 0.3            | 78.8 (56.6–123.2)                      |
| Acute myelogenous leukemia | 24             | 0.1            | 321.3 (207.5–467.1)                    |
| Non-Hodgkin's lymphoma     | 6              | 0.3            | 20.9 (7.7–42.0)                        |
| Solid tumors‡              | 47             | 3.9            | 11.8 (8.7–15.4)                        |
| Breast§                    | 17             | 0.2            | 75.3 (44.9–118.4)                      |
| Thyroid                    | 10             | 0.3            | 32.7 (15.3–55.3)                       |
| Bone                       | 4              | 0.2            | 24.6 (6.4–54.5)                        |
| Brain                      | 4              | 0.4            | 10.5 (2.7–23.4)                        |
| Colorectal                 | 3              | 0.1            | 38.9 (7.3–95.3)                        |
| Gastric                    | 2              | 0.02           | 121.3 (11.4–145.2)                     |

\*CI denotes confidence interval.

†This category excludes the nine cases of nonmelanoma skin cancer.

‡This category excludes lymphatic and hematopoietic tumors. The sum of the solid tumors listed does not equal the total number given because only types for which the risk was significantly elevated are included.

§The cohort for this analysis included only women.

(Table 1). At the time data were abstracted, there had been documented contact with approximately 71 percent of the patients within the previous five years and with 54 percent of the patients within the previous two years. Treatment for Hodgkin's disease consisted of radiation and chemotherapy in 69 percent of the patients, radiation alone in 23 percent, and chemotherapy alone in 8 percent. Among the patients who received radiation therapy, orthovoltage techniques were used for treatment in only 2 percent.

Second neoplasms developed in 109 patients: 56 had solid cancers, 26 had leukemia, 6 had non-Hodgkin's lymphoma, and 21 had benign tumors. The benign tumors included 12 thyroid adenomas, 4 osteochondromas, 3 fibroadenomas of the breast, and 2 dysplastic nevi.

The numbers of observed and expected second cancers are shown in Table 2. There were significantly elevated relative risks for all cancers combined, for leukemia, for non-Hodgkin's lymphoma, and for breast, thyroid, bone, central nervous system, colorectal, and gastric cancers.

Figure 1 shows the actuarial risks of all second cancers, solid tumors, leukemia, and non-Hodgkin's lymphoma. The mean cumulative incidence of any second cancer was 7.0 percent (95 percent confidence interval, 5.2 to 8.8 percent) at 15 years. Most of this risk was due to solid tumors; the steep increase in the cumulative incidence of solid tumors began 12 years after the diagnosis of Hodgkin's disease, and the risk rose to 3.9 percent (95 percent confidence interval, 2.3 to 5.5 percent) at 15 years. In contrast, the risk of leukemia reached a plateau at 2.8 percent (95 percent confidence interval, 0.8 to 4.8 percent), and the risk of non-Hodgkin's lymphoma plateaued at 1.1 percent (95 percent confidence interval, 0 to 3.1 percent).

We also estimated the standardized incidence ratio for cancer according to the period of observation (i.e., the interval from first treatment to the diagnosis of a

second cancer) (Table 3). The standardized incidence ratio was highest during the first five years of follow-up and gradually declined thereafter. This phenomenon is consistent with the increase in the expected incidence of cancer with increasing age. For leukemia, the excess risk appeared within the first 5 years of treatment and declined over the next 10 years of follow-up. No cases of leukemia were observed beyond 15 years after the diagnosis of Hodgkin's disease.

### Leukemia

Leukemia developed in 26 patients. Twenty-four of them had acute myeloid leukemia, one had acute lymphoblastic leukemia, and one had chronic myeloid leukemia. There were no cases of leukemia in the group treated only with radiotherapy. The cumulative risks of leukemia (at 15 years) were higher in the group of patients who received chemotherapy alone (7.9 percent; 95 percent confidence interval, 1.0 to 14.8 percent) than among the patients who were treated with both radiation and chemotherapy (3.4 percent; 95 percent confidence interval, 1.8 to 4.9 percent) (Table 4).

The risk of leukemia rose with an increase in the alkylating-agent score (relative risk of leukemia per unit increase in the score, 1.5; 95 percent confidence interval, 1.2 to 1.8). Among the 340 patients who received a combination of mechlorethamine, vincristine, procarbazine, and prednisone, the cumulative probability of leukemia 15 years after the diagnosis of Hodgkin's disease was 2.9 percent (95 percent confidence interval, 0.7 to 5.1 percent), as compared with 0.9 percent (95 percent confidence interval, 0 to 9.5 percent) among the 103 patients who received a combination of doxorubicin, bleomycin, vinblastine, and dacarbazine. Univariate analysis revealed that patients were at increased risk for leukemia if they had had one or more recurrences of Hodgkin's disease (relative risk, 2.3; 95 percent confidence interval, 1.2 to 5.2), a later stage (III or IV) at diagnosis (relative risk, 4.2; 1.7 to 10.3), or an older age (10 to 16) at the diagnosis of Hodgkin's disease (relative risk, 3.6; 1.1 to 12.2). The risk of leukemia was not significantly increased in the subjects who had undergone splenectomy (relative risk, 1.4; 95 percent confidence interval, 0.6 to 3.4). Of the 572 patients who underwent splenectomy, 13 had leukemia, as compared with 9 of the 637 patients who did not undergo splenectomy.

Multivariate analysis revealed that a late stage of Hodgkin's disease at diagnosis and recurrent disease independently predicted the risk of secondary leukemia. However, patients presenting with late-stage disease had a significantly higher mean ( $\pm$ SE) alkylating-agent score than those presenting with early-stage disease ( $2.4 \pm 0.06$  vs.  $1.2 \pm 0.04$ ,  $P < 0.001$ ). Similarly, patients with recurrent Hodgkin's disease had received significantly higher cumulative doses of alkylating agents than patients with no recurrence (mean score,  $2.5 \pm 0.08$  vs.  $1.2 \pm 0.03$ ;  $P < 0.001$ ). In addition, patients who presented with late-stage disease and had also had a recurrence had significantly higher alkylating-agent scores than patients who present-

ed with early-stage disease and had no subsequent recurrence (mean score,  $3.4 \pm 0.1$  vs.  $0.9 \pm 0.04$ ;  $P < 0.001$ ).

Of the 26 patients with leukemia, 25 died; the median survival was 2.5 months after the diagnosis of leukemia. Twenty-three patients died of secondary leukemia, one in an accident, and one of progressive Hodgkin's disease.

### Lymphomas

Non-Hodgkin's lymphoma developed in six patients. The alkylating-agent score was the only significant independent risk factor for non-Hodgkin's lymphoma (relative risk, 1.7; 95 percent confidence interval, 1.2 to 2.6). Five patients with non-Hodgkin's lymphoma died; the median survival was 2.5 months. Four died of the non-Hodgkin's lymphoma, and one of progressive Hodgkin's disease.

### Solid Cancers

Solid cancers developed in 56 patients. Breast cancer was the most common solid tumor, occurring in 17 patients. Ten patients had thyroid cancer, nine had basal-cell carcinomas, four had bone tumors, four had brain tumors, and three had colorectal carcinomas. Gastric carcinomas, tumors of the female genitourinary tract, parotid-gland tumors, soft-tissue sarcomas, and neuroblastoma occurred in one or two patients each. Risk factors were analyzed both with and without the inclusion of basal-cell carcinomas. There was no difference between the results of the two analyses, and so those of the latter are reported.

Sixty-six percent of the solid cancers developed in the group of patients who had received both radiation and chemotherapy (Table 4). The estimated cumulative probability of a solid tumor 20 years after the diagnosis of Hodgkin's disease was significantly higher among women (12.6 percent; 95 percent confidence interval, 6.8 to 18.4 percent) than men (3.9 percent; 1.5 to 6.3 percent). When the 17 women with breast cancer were excluded, the cumulative probability of solid tumors among the women in the group (8.8 percent; 95 percent

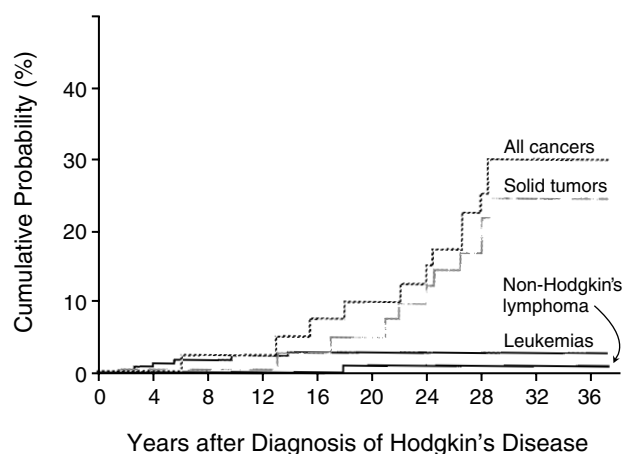


Figure 1. Cumulative Probability of Second Cancers in 1380 Patients with Hodgkin's Disease in Childhood.

Table 3. Standardized Risk Ratios for Second Cancers, According to the Length of the Follow-up Interval.

| TYPE OF CANCER*               | LENGTH OF FOLLOW-UP     |                    |                   |                 |                    |
|-------------------------------|-------------------------|--------------------|-------------------|-----------------|--------------------|
|                               | 0-5 YR                  | 6-10 YR            | 11-15 YR          | 16-20 YR        | >20 YR             |
| All cancers                   |                         |                    |                   |                 |                    |
| Observed                      | 29                      | 15                 | 17                | 8               | 10                 |
| Observed:expected<br>(95% CI) | 28.0 (18.8-39.2)        | 17.9 (10-28.5)     | 15.3 (8.9-23.5)   | 6.7 (2.9-12.2)  | 35.9 (17.1-61.7)   |
| Leukemia                      |                         |                    |                   |                 |                    |
| Observed                      | 18                      | 6                  | 2                 | 0               | 0                  |
| Observed:expected<br>(95% CI) | 99.6 (58.9-150.9)       | 83.3 (29.9-163.3)  | 37.3 (3.5-106.9)  | 0               | 0                  |
| Non-Hodgkin's lymphoma        |                         |                    |                   |                 |                    |
| Observed                      | 2                       | 2                  | 1                 | 1               | 0                  |
| Observed:expected<br>(95% CI) | 24.6 (2.3-70.6)         | 33.1 (3.1-94.7)    | 13.3 (0-52.3)     | 12.6 (0-49.5)   | 0                  |
| Solid tumors                  |                         |                    |                   |                 |                    |
| All                           |                         |                    |                   |                 |                    |
| Observed                      | 9                       | 7                  | 14                | 7               | 10                 |
| Observed:expected<br>(95% CI) | 11.6 (5.2-20.5)         | 10 (3.9-18.7)      | 14.3 (7.8-22.2)   | 6.5 (2.6-12.2)  | 39.7 (18.9-68.1)   |
| Breast                        |                         |                    |                   |                 |                    |
| Observed                      | 2                       | 2                  | 4                 | 1               | 8                  |
| Observed:expected<br>(95% CI) | 4950.5 (466.7-14,188.8) | 231.8 (21.8-664.3) | 76.2 (19.8-169.2) | 7.5 (0-29.6)    | 141.5 (60.4-256.5) |
| Thyroid                       |                         |                    |                   |                 |                    |
| Observed                      | 1                       | 3                  | 4                 | 2               | 0                  |
| Observed:expected<br>(95% CI) | 18.7 (0-73.2)           | 41.1 (7.7-100.7)   | 40.9 (10.6-90.8)  | 21.5 (2.0-61.7) | 0                  |

\*Observed denotes the number of cases observed, observed:expected the ratio of observed to expected cases, and CI confidence interval.

confidence interval, 3.4 to 14.2 percent) approached that among the men (3.9 percent; 1.5 to 6.3 percent). Multivariate analysis revealed that female sex was associated with an increased risk of solid tumors (relative risk, 2.9; 95 percent confidence interval, 1.5 to 5.4). Older patients (those 10 to 16 years of age at the diagnosis of Hodgkin's disease) also appeared to be at increased risk for solid tumors (relative risk as compared with those <10 years at diagnosis, 1.8; 95 percent confidence interval, 0.96 to 4.0). Exclusion of the nine patients with basal-cell carcinoma made this association nonsignificant (relative risk, 1.6; 95 percent confidence interval, 0.8 to 3.1).

Seventeen of the 56 patients with solid tumors died. The median survival was 12.5 months after the diagnosis of the second neoplasm; 10 deaths were due to the second neoplasm and 7 to accidents.

### Breast Cancer

Of the 17 women in whom breast cancer developed, 7 had received radiation therapy alone and 10 had received radiation and chemotherapy. Of the 17 cancers, 16 appeared within or at the margin of the radiation field. In one patient, the tumor (a multifocal infiltrating ductal carcinoma) occurred outside the radiation field (the patient had received radiation to the neck). Five patients had bilateral breast tumors. The majority of the tumors were infiltrating ductal or lobular carcinomas. The median age at the time of diagnosis of breast cancer was 31.5 years (range, 16 to 42). Three patients died of their breast cancer (median survival, 3 years), eight were alive with disease at this writing (median length of follow-up after diagnosis, 10 months), four were alive without dis-

ease (median length of follow-up, 4.5 years), and the status of two was unknown.

The women in our cohort of survivors of Hodgkin's disease had a risk of breast cancer that was 75 times the risk in the general population (Table 2). The risk of breast cancer was elevated throughout the follow-up period, and the interval from the diagnosis of Hodgkin's disease to the diagnosis of breast cancer was less than five years in two cases (Table 3). Figure 2 shows the estimated cumulative probability of breast cancer as a function of the age of the cohort of female survivors of Hodgkin's disease. The estimated actuarial cumulative probability of breast cancer was 35 percent (95 percent confidence interval, 17.4 to 52.6 percent) at 40 years of age.

Univariate analysis revealed that patients who were 10 to 16 years of age when Hodgkin's disease was diagnosed and treated were at increased risk for breast cancer as compared with those who were younger than 10 at diagnosis (relative risk, 6.7; 95 percent confidence interval, 1.2 to 28.6). In addition, patients who underwent splenectomy appeared to be at increased risk for breast cancer (relative risk, 2.6; 95 percent confidence interval, 0.96 to 5.0). Patients with breast cancer received a higher dose of radiation to the mantle region (median, 4000 cGy; range, 0 to 4750) than those in whom breast cancer did not develop (median, 2000 cGy; range, 0 to 5200). Seventy-six percent of the patients who had breast cancer had received at least 2000 cGy of radiation to the mantle region, as compared with 48 percent of the patients who did not have breast cancer.

Multivariate analysis revealed that an age of more than 10 years at the time of diagnosis of Hodgkin's dis-

Table 4. Risks of Second Cancers According to the Type of Treatment for Hodgkin's Disease.\*

| TYPE OF CANCER AND TREATMENT  | OBSERVED CASES | OBSERVED:EXPECTED CASES (95% CI) | CUMULATIVE PROBABILITY AT 15 YR (95% CI)<br>% |
|-------------------------------|----------------|----------------------------------|---|
| <b>Leukemia</b>               |                |                                  |   |
| Radiation                     | 0              | 0                                | 0   |
| Chemotherapy                  | 5              | 1091 (344-2256)                  | 7.9 (1.0-14.8)                                |
| Radiation and chemotherapy    | 21             | 439 (270-645)                    | 3.4 (1.8-4.9)                                 |
| <b>Non-Hodgkin's lymphoma</b> |                |                                  |   |
| Radiation                     | 1              | 11 (0.01-44)                     | 0.4 (0-1.2)                                   |
| Chemotherapy                  | 1              | 60 (0.02-235)                    | 0.0   |
| Radiation and chemotherapy    | 4              | 23 (6-50)                        | 0.9 (0-1.9)                                   |
| <b>Solid tumors</b>           |                |                                  |   |
| Radiation                     | 15             | 11 (6-17)                        | 3.3 (2.9-3.7)                                 |
| Chemotherapy                  | 1              | 5 (0.01-18)                      | 2.9 (2.3-3.5)                                 |
| Radiation and chemotherapy    | 31             | 13 (9-18)                        | 4.6 (4.4-4.8)                                 |

\*CI denotes confidence interval.

ease was independently associated with increased risk (relative risk, 1.9; 95 percent confidence interval, 1.1 to 3.2), as was a higher dose of radiation (as compared with a radiation dose of <2000 cGy, the relative risk for a dose between 2000 and 4000 cGy was 5.9 [1.2 to 30.3], and the relative risk for a dose exceeding 4000 cGy was 23.7 [3.7 to 152.3]).

## DISCUSSION

Among the 1380 patients who were treated for childhood Hodgkin's disease between 1955 and 1986 at 15 institutions, we found the estimated cumulative risk of a second cancer to be 7.0 percent 15 years after the initial diagnosis. This report provides evidence that the risk of a second neoplasm is increased about 18 times in long-term survivors of childhood Hodgkin's disease. The risk was highest in patients who were older when they had Hodgkin's disease, with 74 percent of the cancers occurring in those who received diagnoses between 10 and 16 years of age. This finding is similar to that reported by Beaty et al.<sup>17</sup>

Breast cancer was the most common solid tumor in this group of patients. The women in our cohort had a risk of breast cancer 75 times greater than that in the general population. Moreover, the estimated cumulative probability of breast cancer among women in our cohort who survived childhood Hodgkin's disease approached 35 percent at 40 years of age. For our multinational investigation, we used the rates of the U.S. Surveillance, Epidemiology, and End Results Program for the incidence of breast cancer in the general population<sup>19</sup> because the age-standardized rates for France (66.2 per 100,000), Italy (65.4 per 100,000), and the United Kingdom (63.4 per 100,000) are roughly similar to that in the United States (89.2 per 100,000).<sup>22</sup>

An increased risk of breast cancer has been observed among women exposed to radiation from atomic-bomb explosions, repeated chest fluoroscopy, or treatment of postpartum mastitis.<sup>23-28</sup> Most previous studies of large

populations of patients who were treated for Hodgkin's disease did not detect a significantly elevated risk of breast cancer.<sup>17,18,29-33</sup> This may be because of the long interval between the occurrence of Hodgkin's disease and the appearance of breast cancer. The paucity of young patients in most reported series must also be taken into account because of the association of the risk of breast cancer with younger age at the time of treatment for Hodgkin's disease.<sup>34</sup> One study of 885 women who were treated for Hodgkin's disease with radiation before 30 years of age found a fourfold increase in the risk of breast cancer.<sup>35</sup> However, only 76 patients in this report were less than 15 years old when Hodgkin's disease was diagnosed; 3 of those 76 patients had breast cancer.

In our study, breast cancer occurred exclusively in women. The majority of breast cancers arose within the field of radiation. We found that the risk of breast cancer increased with the dose of radiation; most breast cancers occurred in patients who had received at least 2000 cGy in the mantle region.

The increased risk of breast cancer after treatment for Hodgkin's disease was related to age at the time of radiation exposure. Sixteen of the 17 breast cancers occurred in patients who were between 10 and 16 years of age when Hodgkin's disease was diagnosed. Hancock et al. reported an increased risk of breast cancer among women who were less than 30 years old when Hodgkin's disease was diagnosed.<sup>35</sup> In atomic-bomb survivors, an increased risk of breast cancer was found in the group of women who were in the first three decades of life when they were exposed to the radiation.<sup>27</sup> The high incidence of breast cancer in women who are exposed to high doses of radiation between 10 and 16 years of age suggests that the tumorigenic influence of radiation mainly affects proliferating breast tissue.

We found that after a relatively short period of latency (4.4 years), the cumulative incidence of leukemia rose sharply, but it appeared to reach a plateau after 14 years, which is consistent with data from other studies.<sup>13</sup> The dose-dependent association of alkylating agents with secondary leukemia and non-Hodgkin's lymphoma has been reported by others.<sup>15,16</sup> The combination of doxorubicin, bleomycin, vinblastine, and dacarbazine appeared to be less leukemogenic than the combination of mechlorethamine, vincristine, procarbazine, and prednisone, but the difference was not statistically significant.

It has not been established that splenectomy is a risk factor for secondary leukemia.<sup>17,36-44</sup> In the original cohort of 979 survivors of Hodgkin's disease in the Late Effects Study Group, splenectomy had borderline significance as a risk factor ( $P=0.09$ ),<sup>16</sup> and in the present study, we did not find any independent relation between splenectomy and the risk of secondary leukemia or solid tumors.

In contrast to the risk of treatment-related leukemia, which plateaued after 14 years, the risk of solid tumors continued to increase beyond 15 years and approached 30 percent at 30 years. This is an important problem in survivors of Hodgkin's disease and underscores the ne-

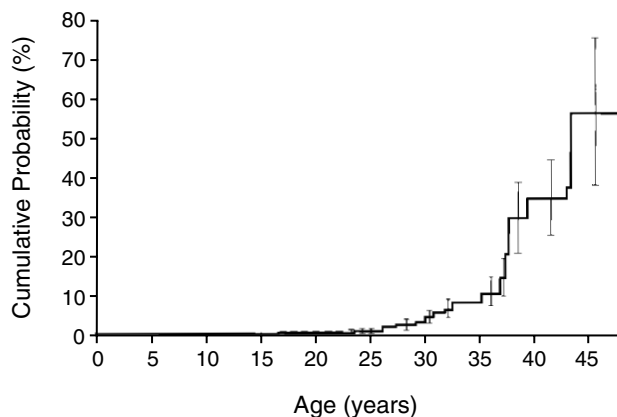


Figure 2. Cumulative Probability of Breast Cancer as a Function of Age in the Cohort of Female Survivors of Hodgkin's Disease in Childhood.

Bars indicate standard errors.

cessity of medical monitoring. The high risk of breast cancer in women exposed to radiation at a young age raises important issues regarding screening programs (such as physical examination of the breast, sonography, mammography, and quantitative magnetic resonance imaging). We must also consider chemoprevention (tamoxifen and retinoids) for survivors of Hodgkin's disease who are at high risk for breast cancer. Efforts to develop treatments for Hodgkin's disease that are curative but less carcinogenic should continue.

#### APPENDIX

In addition to the authors, the Late Effects Study Group included the following: Dana-Farber Cancer Institute, Boston — S. Sallen and F. Li; Columbus Children's Hospital, Columbus, Ohio — R. Ruyman and W. Newton; Children's Memorial Hospital, Chicago — E. Morgan; Royal Manchester Children's Hospital, Manchester, England — P. Morris-Jones and J. Birch; Emma Kinderziekenhuis, Amsterdam — P.A. Voute; Children's Hospital, Los Angeles — S. Siegel; Children's Hospital Medical Center, Cincinnati — C. DeLaat; Children's National Medical Center, Washington, D.C. — H.S. Nicholson; and Children's Hospital, Pittsburgh — J. Blatt.

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