

ORIGINAL ARTICLE

Extended Follow-up of Long-Term Survivors of Childhood Acute Lymphoblastic Leukemia

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ABSTRACT

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BACKGROUND

Children who survive acute lymphoblastic leukemia are at risk for leukemia-related or treatment-related complications, which can adversely affect survival and socioeconomic status. We determined the long-term survival and the rates of health insurance coverage, marriage, and employment among patients who had attained at least 10 years of event-free survival.

METHODS

A total of 856 eligible patients were treated between 1962 and 1992 in 13 consecutive clinical trials. Survival rates, the cumulative risk of a second neoplasm, and selected indicators of socioeconomic status were analyzed for the entire group and for patients who did or did not receive cranial or craniospinal radiation therapy during initial treatment.

RESULTS

Fifty-six patients had major adverse events, including 8 deaths during remission, 4 relapses, and 44 second neoplasms (41 of them radiation-related); most of the second neoplasms were benign or of a low grade of malignant potential. The risk of a second neoplasm was significantly higher in the 597 patients who received radiation therapy (irradiated group) than in the 259 patients who did not receive radiation therapy (nonirradiated group) ($P=0.04$; estimated cumulative risk [\pm SE] at 20 years, 20.9 ± 3.9 percent vs. 0.95 ± 0.9 percent). The death rate for the irradiated group slightly exceeded the expected rate in the general U.S. population (standardized mortality ratio, 1.90; 95 percent confidence interval, 1.12 to 3.00), whereas that for the nonirradiated group did not differ from the population norm (standardized mortality ratio, 1.75; 95 percent confidence interval, 0.34 to 5.00). The rates of health insurance coverage, marriage, and employment in the nonirradiated group were similar to the age- and sex-adjusted national averages. Despite having health insurance rates similar to those in the general population, men and women in the irradiated group had higher-than-average unemployment rates (15.1 percent vs. 5.4 percent and 35.4 percent vs. 5.2 percent, respectively), and women in the irradiated group were less likely to be married (35.2 percent vs. 48.8 percent).

CONCLUSIONS

Children with acute lymphoblastic leukemia who did not receive radiation therapy and who have attained 10 or more years of event-free survival can expect a normal long-term survival. Irradiation is associated with the development of second neoplasms, a slight excess in mortality, and an increased unemployment rate.

ACUTE LYMPHOBLASTIC LEUKEMIA, THE most common childhood cancer, is highly responsive to chemotherapy. Among patients receiving contemporary therapy, the overall five-year survival rate is 80 to 86 percent^{1,2} and the five-year event-free survival rate is 78 to 83 percent.³⁻⁵ Each year in the United States, approximately 2000 patients become five-year survivors of childhood acute lymphoblastic leukemia.⁶ Although most of these patients are likely to be cured, a substantial proportion will die of leukemic relapse, a second cancer, or some other treatment-related complication during the next five years of follow-up.^{7,8} Hence, long-term survivors of childhood acute lymphoblastic leukemia are still perceived by many to have an excessive risk of cancer or other catastrophic disease. This perception can lead to the denial of life insurance or health insurance or an offer of restricted or costly coverage.

Adverse events after treatment of acute lymphoblastic leukemia tend to occur within the first decade after diagnosis.^{7,8} We therefore sought to determine the prospects for normal survival among patients attaining at least 10 years of complete remission.

METHODS

STUDY POPULATION AND TREATMENT PROTOCOLS

From 1962 through 1992, 2069 patients with acute lymphoblastic leukemia under 21 years of age were enrolled in 13 consecutive clinical trials (Table 1)⁹⁻¹³ at St. Jude Children's Research Hospital in Memphis, Tennessee; 1112 patients survived for 10 years or more after the induction of remission. In this cohort of survivors, 856 who had no leukemic recurrence were considered eligible for the follow-up analysis.

FOLLOW-UP PROCEDURES

After the completion of therapy, all patients were examined at least annually at our center. Patients who had remained in remission for at least 10 years and were 18 years of age or older were subsequently monitored by their local physicians. The status of these patients was ascertained by questionnaires sent annually by the hospital's tumor registrar. The records of patients who died or had a second cancer were reviewed. Histopathological samples of second cancers were reviewed by St. Jude pathologists. For deaths outside the institution, death certificates were routinely requested, and the reported cause

was verified by telephone conversations with the local physician, the family, or both. When available, reports of postmortem examinations were also reviewed. At the time of our analysis, only 44 patients (5.1 percent) lacked a documented contact within the previous three years; 599 (70.0 percent) had been contacted within the previous year. The median follow-up for patients attaining at least 10 years of event-free survival was 18.9 years (range, 10.0 to 38.6).

With the approval of the institutional review board, a questionnaire was mailed to all eligible patients who were at least 18 years of age to ascertain health insurance coverage and other socioeconomic characteristics. The results were compared with findings in the general population of the United States in 2000 and 2001.¹⁴⁻¹⁶

STATISTICAL ANALYSIS

Survival and event-free survival from the 10th anniversary date of event-free survival (base line) were estimated by the method of Kaplan and Meier, and the associated standard errors were calculated by the method of Peto and Pike.¹⁷ Survival estimates for different groups of patients were compared by a Cox proportional-hazards regression model adjusted for age at the diagnosis of leukemia, sex, race, and treatment era (studies 1 to 10 vs. studies 11 to 13). The duration of event-free survival was measured from base line to the date of the first treatment failure of any kind (relapse, second cancer, or death) or to the date of the last follow-up. Cumulative incidence functions for second cancers, relapses, and deaths during remission were analyzed by Gray's method¹⁸ and with use of a proportional-hazards model adjusted for age and leukocyte count at diagnosis.¹⁹

Standardized mortality ratios (the observed number of deaths divided by the expected number) and their 95 percent confidence intervals were calculated by the method of Breslow and Day.²⁰ The expected number of deaths was calculated with the Epilog Plus Program²¹ by multiplying the number of person-years of follow-up by the corresponding mortality rate in the general population matched for age, sex, race, and calendar year (1973 to 2000) in which our patients achieved their first 10 years of event-free survival. Confidence intervals were calculated by Byar's approximation.²⁰ The survival curve of the U.S. population was constructed as a linear interpolation of the expected survival for each year from 1973 to 2000. The expected survival in a cal-

Table 1. General Characteristics of Treatment Protocols.

Study No.	Reference	Years	Concept of Therapy	Central Nervous System Irradiation
1, 2, 3, 4	Simone et al. ⁹	1962–1966	Combination chemotherapy is superior to sequential administration of single agents; full-dose is superior to half-dose chemotherapy	None
5, 6, 7	Simone et al. ⁹	1967–1971	Adequate central nervous system-directed therapy will increase event-free survival	All patients received 24 Gy of cranial irradiation* in study 5; patients were randomly assigned to receive or not to receive 24 Gy of craniospinal irradiation in study 6; patients were randomly assigned to 24 Gy of cranial irradiation or 24 Gy of craniospinal irradiation* in study 7
8, 9	Pui et al. ¹⁰	1972–1979	Intensive induction of remission or post-remission therapy will improve outcome	All patients received 24 Gy of cranial irradiation*
10	Pui et al. ¹⁰	1979–1983	High-dose methotrexate and teniposide–cytarabine combination will improve outcome	Patients with standard-risk leukemia were randomly assigned to high-dose methotrexate or 18 Gy of cranial irradiation*; patients at high risk received 24 Gy of cranial irradiation*
11	Rivera et al. ¹¹	1984–1988	Early intensification therapy and alternating use of non-cross-resistant drug pairs will improve end results	Cranial irradiation† was given to patients at high risk (18 Gy) or those with central nervous system leukemia (24 Gy)
12	Evans et al. ¹²	1988–1991	Individualized dosage of chemotherapy will improve clinical outcome	Same as Study 11
13	Pui et al. ¹³	1991–1994	Early intensification of intrathecal therapy will decrease central nervous system relapse and improve overall event-free survival	Same as Study 11

* Irradiation was given together with intrathecal methotrexate.

† Irradiation was given together with intrathecal methotrexate, hydrocortisone, and cytarabine.

endar year was calculated as 1 minus the expected risk of death in that year, which was defined as the expected number of deaths in that year divided by the total number of patients at risk. The expected number of deaths in a calendar year was calculated by multiplying the number of patients at risk in that year by the average death rate in the U.S. population from 1973 to 2000, after adjustment for age, sex, and race.

The standardized incidence ratio, or the number of observed cases divided by the number of expected cases, for second cancers was calculated on the basis of data from the Surveillance, Epidemiology, and End Results (SEER) program, adjusted for age and sex. Confidence intervals were calculated by Byar's approximation or, in cases with two or

fewer observed events, by the exact Poisson distribution.

The summary statistics and national average rates of marriage, employment, and health insurance coverage were stratified according to sex and age categories identical to those of the Medical Expenditure Panel Survey¹⁴ or the Current Population Surveys of the U.S. Census Bureau.^{15,16} Confidence intervals were calculated by exact multinomial statistics. The age-adjusted national average was calculated as the sum of the fraction of participants in each age category multiplied by the sex-specific rate of employment or marital status (Current Population Surveys) or by the insurance rate for that age category (Medical Expenditure Panel Survey). Multiple logistic-regression analysis was used to com-

pare the rates of marriage, employment, and health insurance coverage between the patients who received cranial or craniospinal radiation therapy as part of their initial treatment (irradiated group) and those who did not receive such therapy (nonirradiated group), with adjustment for age and leukocyte count at the diagnosis of acute lymphoblastic leukemia, age at the time of survey, sex, and race. All reported P values are two-sided.

RESULTS

PATIENT CHARACTERISTICS

Of the 856 patients studied, 419 (48.9 percent) were male and 788 (92.1 percent) were white. Their ages ranged from 0.2 to 20 years (median, 4.5) at the time of diagnosis and from 10.3 to 30.2 years (median, 14.6) when they attained 10 years of event-free survival. The median leukocyte count at diagnosis was 8600 per cubic millimeter (range, 800 to 999,000). Of the 549 cases with successful immunophenotyping, 475 (86.5 percent) were classified as B-lineage acute lymphoblastic leukemia. Hyperdiploid karyotypes (more than 50 chromosomes) were identified in 195 of the 499 cases analyzed (39.1 percent).

ADVERSE EVENTS

Fifty-six patients had adverse events after the 10th anniversary date of event-free survival (Table 2). The cumulative incidence (\pm SE) of any adverse event was 5.1 ± 0.9 percent at 10 years after base line (20 years after the induction of remission) and 22.0 ± 3.8 percent at 20 years after base line (30 years after the induction of remission). When basal-cell carcinoma was excluded, these rates were 4.7 ± 0.9 percent and 14.7 ± 2.9 percent, respectively (Fig. 1). With three exceptions, the second neoplasms occurred within or adjacent to the field of cranial or craniospinal irradiation. Only one second neoplasm (Hodgkin's disease) was found among the 259 patients in the nonirradiated group.

In a proportional-hazards regression model adjusted for age and leukocyte count at diagnosis, the 597 patients in the irradiated group had a significantly higher cumulative risk of second neoplasms than did the 259 patients in the nonirradiated group ($P=0.04$; estimated cumulative incidence rate at 20 years after base line, 20.9 ± 3.9 percent vs. 0.95 ± 0.9 percent) (Fig. 2). By comparison with data from the SEER program, we determined that the risk of a second neoplasm was increased only in the irradiated group (Table 3). The irradiated group also ap-

Table 2. Timing and Cumulative Risk of Adverse Events after the 10th Anniversary of Event-free Survival.

Type of Event	No. of Cases	Time to Development years	Mean (\pm SE) Cumulative Risk at 20 Yr percent
Death during remission*	8		1.94 \pm 0.78
Median		6.5	
Range		2.1–16.2	
Leukemic relapse†	4		0.63 \pm 0.32
Median		4.1	
Range		0.7–7.4	
Basal-cell carcinoma	10		7.54 \pm 2.74
Median		17.9	
Range		4.4–20.0	
Meningioma	10		3.68 \pm 1.41
Median		10.6	
Range		2.6–19.0	
Malignant brain tumor	5		0.65 \pm 0.29
Median		1.1	
Range		1.0–4.1	
Myeloid neoplasm	2		0.24 \pm 0.17
Median		0.8	
Range		0.7–1.0	
Soft-tissue sarcoma	2		1.50 \pm 1.36
Median		12.1	
Range		4.7–19.6	
Hodgkin's disease	1		0.20 \pm 0.20
Median		7.0	
Other carcinomas‡	14		5.57 \pm 1.85
Median		8.8	
Range		1.4–19.2	

* Five deaths (three from car accidents, one from obstetrical complications, and one from unknown causes) occurred in the irradiated group and three (two from suicide and one from a car accident) in the nonirradiated group.

† Two relapses occurred in Study 10 and one each in Study 9 and Study 11.

‡ Other carcinomas included four thyroid carcinomas, two hepatocellular carcinomas, two squamous-cell carcinomas, two parotid-gland carcinomas, and one each of breast cancer, ovarian adenocarcinoma, papillary carcinoma of the bladder, and pancreatic neuroendocrine carcinoma.

peared to be at greater risk for any adverse event ($P=0.08$; estimated cumulative risk rate at 20 years from base line, 23.0 ± 3.8 percent vs. 2.7 ± 1.4 percent) (Fig. 2).

SURVIVAL

At 20 years from base line (30 years from achievement of the first complete remission), the estimated survival rates for the entire group and the irradiated and nonirradiated groups were 95.3 ± 2.2 , 95.1 ± 2.3 , and 98.3 ± 7.4 percent, respectively, as compared with 99.7 percent for the general U.S. population (Fig. 3). Twenty-one patients, of whom 18 were in the irradiated group, died at 1.0 to 17.6

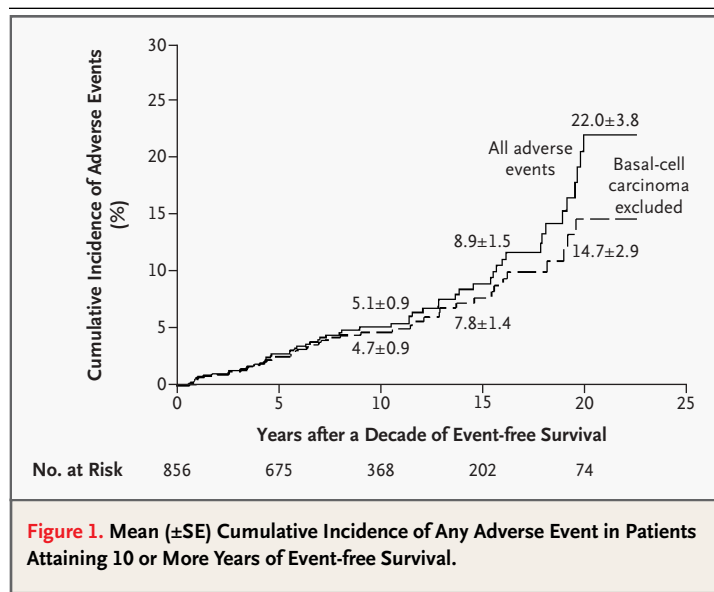


Figure 1. Mean (\pm SE) Cumulative Incidence of Any Adverse Event in Patients Attaining 10 or More Years of Event-free Survival.

years (median, 5.5) from base line. Of the 18 deaths in the irradiated group, 12 were due to a second cancer and 1 was due to a relapse of leukemia. Of the three deaths in the nonirradiated group, two were due to suicide and one to a car accident. According to multivariate analysis adjusted for age at the diagnosis of acute lymphoblastic leukemia, sex, race, and treatment era, the probability of survival did not differ significantly between the irradiated and nonirradiated groups (hazard ratio for death in the irradiated group, 1.27; 95 percent confidence interval, 0.36 to 4.47; $P=0.71$). Comparison of survival data between patients and the general population revealed a higher standardized mortality ratio in the irradiated group (1.90; 95 percent confidence interval, 1.12 to 3.00) but not in the nonirradiated group (1.75; 95 percent confidence interval, 0.34 to 5.00).

MARITAL, EMPLOYMENT, AND HEALTH INSURANCE STATUS AND ACCESS TO HEALTH CARE

Of the 694 eligible patients, 584 (84.1 percent) responded to the study questionnaire. Only 44 patients (6.3 percent) declined to participate; current addresses and telephone numbers were not available for the remaining 66 patients. The median age of the respondents was 27 years (range, 18 to 50), and the median time from the diagnosis of leukemia to the date of response to the survey was 20 years (range, 10 to 37). Forty-seven percent of the respondents were men.

The marital rate (the proportion of patients currently married) was similar to that in the age- and

sex-matched general population, with the exception of women in the irradiated group, whose marital rate (35.2 percent; 95 percent confidence interval, 27.6 to 43.3 percent) was lower than in the corresponding general population (48.8 percent) (Table 4). Most respondents were employed full time (51.7 percent) or part time (7.8 percent); 22.0 percent were students. The rate of full-time employment for nonirradiated patients was similar to that of the age- and sex-matched general population (Table 4). However, in the irradiated group the unemployment rates for both women (35.4 percent; 95 percent confidence interval, 27.0 to 44.1 percent) and men (15.1 percent; 95 percent confidence interval, 9.2 to 22.7 percent) were higher than those in the corresponding general population (5.2 and 5.4 percent, respectively); women in the irradiated group were also less likely to be employed full time.

Health insurance was provided through the employer, spouse, or parent in 59.2 percent of cases; federal or state-supported health plans in 15.1 percent; and self-purchase in 6.9 percent. Only 19.7 percent of the respondents lacked health insurance. A history of leukemia had resulted in the denial of health insurance to 28.4 percent of the respondents, prohibitive premiums for 18.6 percent, and restrictions on health care plans for 7.0 percent. As compared with those with private insurance, respondents with public insurance were more likely to report some difficulty in obtaining health care (13.9 percent vs. 6.6 percent) or not receiving needed care (20.9 percent vs. 4 percent). Not surprisingly, an even greater proportion of uninsured survivors reported difficulties in obtaining health care (19.6 percent) or not receiving needed care (27.7 percent). Although 89.3 percent of the long-term survivors reported using a community physician for their health care needs, only 53.2 percent had seen a physician in the preceding 12 months.

Multiple logistic-regression analysis, adjusted for potentially confounding factors, indicated similar rates of health insurance coverage and marriage for irradiated and nonirradiated patients of the same sex. However, the unemployment rate was higher among female survivors in the irradiated group than in the nonirradiated group (odds ratio, 2.15; 95 percent confidence interval, 1.10 to 4.20).

DISCUSSION

Among survivors of childhood acute lymphoblastic leukemia who were event-free for 10 years after

the induction of remission, the cumulative risk of relapse was only 0.63 ± 0.32 percent at 20 years (30 years after the induction of an initial complete remission). Another research group reported an actuarial risk of relapse of 1 percent at 20 years of follow-up among 1134 survivors who were event-free for 10 years and who had been treated between 1970 and 1984, but the investigators did not determine the incidence of other adverse events in their cohort.²² The risk of late relapse is likely to be even less in survivors who are event-free for 10 years and who have been treated according to contemporary protocols.²³ Our results suggest a new working definition of cure: 10 or more years of continuous complete remission, a standard that could be used to gauge the effectiveness of current and future treatment plans.

The cumulative risk of second neoplasms in children treated for acute lymphoblastic leukemia is less than 4 percent 15 to 20 years after the diagnosis.^{3,6,24-27} Our study showed that the cumulative incidence of second neoplasms in patients who received cranial or craniospinal irradiation rose sharply 20 years after the diagnosis of acute lymphoblastic leukemia, a finding not previously appreciated because of shorter follow-up in other studies. Most of these late-onset second neoplasms were benign tumors or low-grade cancers, and only 12 of 44 patients with second neoplasms died, in contrast to the high mortality rate among patients whose second neoplasms developed within 10 years after the diagnosis of acute lymphoblastic leukemia.^{3,6-8,24-29} Consequently, the long-term survival in the irradiated group in our study was only slightly less than that in sex- and age-matched persons in the general population (Fig. 3). Survival in the non-irradiated group was virtually identical to that in the general population.

Any assessment of the long-term survival of persons cured of cancer must consider the quality of life.³⁰ Young adult survivors of childhood cancer have lower marital rates than the general population,³¹⁻³⁶ and survivors of brain tumors are especially vulnerable.^{32,36} This finding has been attributed to the sequelae of the treatment, including neuroendocrine dysfunction that affects height and body build and neurocognitive deficits that influence social and emotional development.³² Cranial irradiation is a risk factor for learning deficits in survivors of brain tumors or acute lymphoblastic leukemia, especially in young patients treated with high doses of radiation.^{35,37}

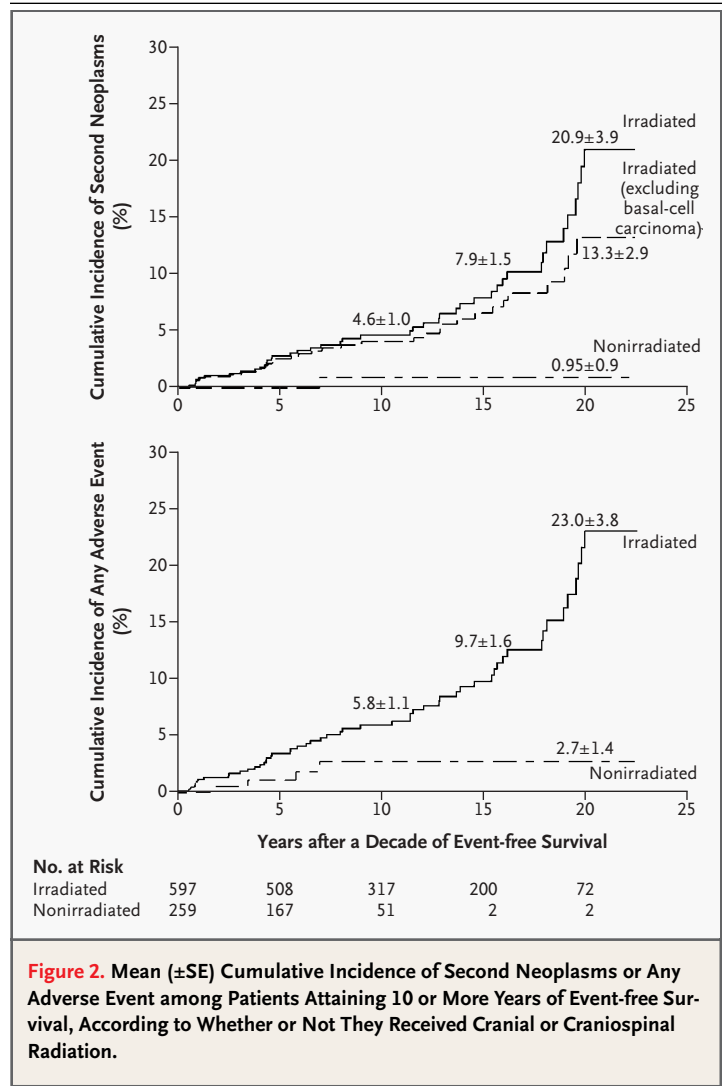


Figure 2. Mean (\pm SE) Cumulative Incidence of Second Neoplasms or Any Adverse Event among Patients Attaining 10 or More Years of Event-free Survival, According to Whether or Not They Received Cranial or Craniospinal Radiation.

Although the doses of cranial radiation delivered to our patients were relatively low (18 to 24 Gy), we found higher unemployment rates and lower marital rates among the women in the irradiated group than in the age- and sex-matched general population, a result consistent with the greater vulnerability of female patients to the adverse effects of cranial irradiation on the central nervous system.³⁸⁻⁴⁰ These results support current efforts to limit the use of cranial irradiation in initial therapy for acute lymphoblastic leukemia.^{3,41,42} In two recently published clinical trials, cranial irradiation was omitted altogether, without an undue increase in the rate of central nervous system relapse.^{43,44}

Previous investigations of the insurance cover-

Table 3. Comparison of the Incidence of Cancer in the Study Group with That in the General Population.

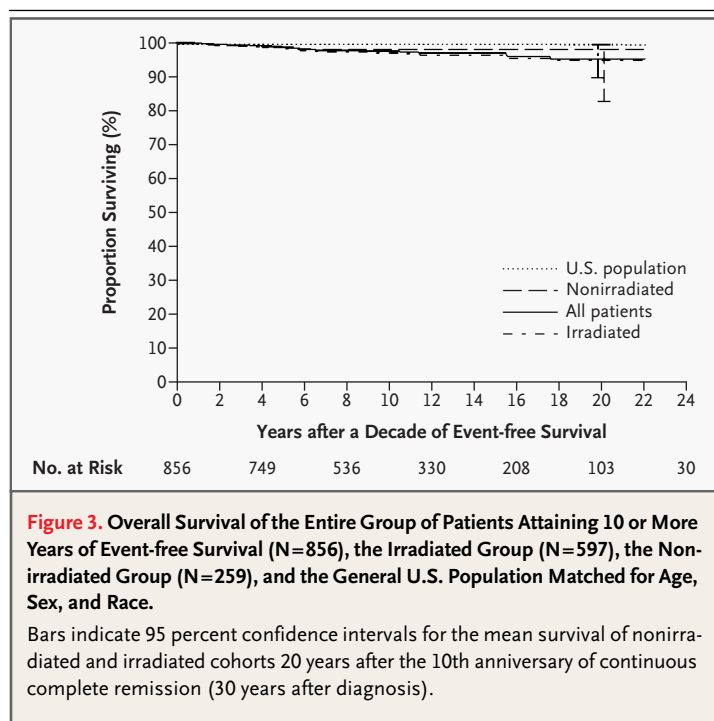
Type or Site of Cancer	Group	No. of Observed Events	No. of Expected Events	Standardized Incidence Ratio	95% Confidence Interval
All sites*	All patients	23	3.79	6.07	3.85–9.11
	Irradiated	22	3.31	6.65	4.16–10.06
	Nonirradiated	1	0.48	2.08	0.02–11.59
Brain tumor†	Irradiated	5	0.18	27.74	8.94–64.75
Thyroid cancer	Irradiated	4	0.34	11.73	3.15–30.0
Oral cavity and pharyngeal cancer	Irradiated	3	0.07	45.08	9.06–131.65
Liver cancer‡	Irradiated	2	0.01	362.97	40.76–1310.50
Myeloid neoplasm§	Irradiated	2	0.18	11.15	5.26–156.96
Pancreatic cancer	Irradiated	1	0.01	166.94	2.18–928.85
Urinary-bladder cancer	Irradiated	1	0.03	35.97	0.47–200.14
Ovarian cancer	Irradiated	1	0.14	7.16	0.09–39.85
Breast cancer	Irradiated	1	0.38	2.61	0.03–14.55
Hodgkin's disease	Nonirradiated	1	0.06	17.41	0.23–96.86

* Basal-cell carcinoma, squamous-cell carcinoma of the skin, and meningioma are excluded; two cases of soft-tissue sarcoma are included.

† Meningioma is not included; four patients received 18 Gy of cranial irradiation, and the remaining patient received 24 Gy.

‡ Hepatitis B was diagnosed in one patient, and hepatitis C in the other (therapy for acute lymphoblastic leukemia began in 1964 and 1971, respectively).

§ Both patients had received teniposide, but neither had an 11q23 rearrangement in the myeloid blasts.



age of survivors of childhood cancer found clear evidence of discrimination, particularly in employment-related health insurance.^{34,35,45-49} Survivors were also more likely than sibling controls to have policies with clauses excluding coverage of preexisting health conditions.^{34,35,48} More recent studies of older survivors treated according to contemporary protocols indicate improved access to insurance and less economic discrimination,^{34,35} probably because of the public's awareness of the favorable prognosis for most survivors of childhood cancer and because of legislation prohibiting discrimination in employment and promoting insurance portability.⁵⁰⁻⁵² Our data indicate that the rate of insurance coverage for long-term survivors of acute lymphoblastic leukemia is at least similar to or, in the case of female survivors, higher than that in the general population.

Adult survivors of childhood cancer are at risk for health problems that may adversely affect their quality of life and long-term survival.^{7,8,53,54} Because these risks may be exacerbated by the physiologic changes associated with normal aging, lifelong

Table 4. Marital, Employment, and Health Insurance Status According to Sex and History of Irradiation.*

Sex and History of Irradiation	No. of Patients	National Average	Rate in Patients (95% CI)		National Average	Rate in Patients (95% CI)	
			Married	Separated or Divorced		Never Married	
Female							
Irradiated	219	48.8	35.2 (27.6–43.3)†	8.5	13.7 (8.8–20.0)†	40.4	51.1 (43.0–59.4)†
Not irradiated	86	27.0	36.1 (24.5–49.4)	3.0	9.3 (3.8–19.0)†	68.1	54.7 (41.6–67.3)†
Male							
Irradiated	208	43.5	43.3 (35.3–51.8)	7.5	7.7 (3.9–13.1)	49.0	49.0 (40.8–57.5)
Not irradiated	62	22.5	22.6 (11.9–37.5)	3.6	1.6 (0.0–10.1)	73.9	75.8 (61.0–87.5)
Employed Full Time							
Employed Part Time							
Unemployed							
Female							
Irradiated	181	71.8	51.4 (42.3–60.4)†	22.9	13.3 (7.9–20.1)†	5.2	35.4 (27.0–44.1)†
Not irradiated	58	61.6	63.8 (47.3–77.8)	30.8	13.8 (5.7–27.7)†	7.6	22.4 (10.9–37.2)†
Male							
Irradiated	172	85.1	78.5 (70.4–85.4)	9.5	6.4 (2.8–12.1)	5.4	15.1 (9.2–22.7)†
Not irradiated	37	72.5	86.5 (68.8–95.9)	19.1	5.4 (0.5–20.0)	8.3	8.1 (1.5–24.2)
Private Health Insurance							
Public Health Insurance							
No Health Insurance							
Female							
Irradiated	213	66.9	63.4 (55.4–71.2)	7.3	18.8 (12.8–25.8)†	25.7	17.8 (12.1–24.9)†
Not irradiated	86	59.9	65.1 (51.8–76.8)	8.4	16.3 (8.4–27.4)	31.7	18.6 (9.9–30.3)†
Male							
Irradiated	202	66.9	71.8 (63.9–79.1)	7.3	6.9 (3.3–12.3)	25.8	21.3 (14.8–28.7)
Not irradiated	65	60.7	70.8 (55.6–83.3)	8.3	1.5 (0.0–9.6)	31.0	27.7 (16.1–42.7)

* Students were not included in the employment analysis; some questions were not answered by all participants. CI denotes confidence interval. National averages were calculated with adjustment for age and sex.

† The national average was not within the 95 percent confidence interval.

medical monitoring is recommended for all survivors of childhood cancer. Although 89 percent of the survivors of acute lymphoblastic leukemia who were discharged from follow-up at our institution reported having a usual place to obtain health care, only 53 percent had had a medical evaluation within the previous year. This rate appears to be lower than that in the general population (approximately 80 percent),⁵⁵ underscoring the need for further investigation of the patterns of health care use among long-term survivors of acute lymphoblastic leukemia.

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REFERENCES

- Reis LAG, Eisner MP, Kosary CL, et al, eds. SEER cancer statistics review, 1973-1998. Bethesda, Md.: National Cancer Institute, 2001.
- Brenner H, Kaatsch P, Burkhardt-Hammer T, Harms DO, Schrappe M, Michaelis J. Long-term survival of children with leukemia achieved by the end of the second millennium. *Cancer* 2001;92:1977-83.
- Schrappe M, Reiter A, Ludwig WD, et al. Improved outcome in childhood acute lymphoblastic leukemia despite reduced use of anthracyclines and cranial radiotherapy: results of trial ALL-BFM 90. *Blood* 2000;95:3310-22.
- Silverman LB, Gelber RD, Dalton VK, et al. Improved outcome for children with acute lymphoblastic leukemia: results of Dana-Farber Consortium Protocol 91-01. *Blood* 2001;97:1211-8.
- Pui C-H, Evans WE. Acute lymphoblastic leukemia. *N Engl J Med* 1998;339:605-15.
- Bhatia S, Sather HN, Pabustan OB, Trigg ME, Gaynon PS, Robison LL. Low incidence of second neoplasms among children diagnosed with acute lymphoblastic leukemia after 1983. *Blood* 2002;99:4257-64.
- Hudson MM, Jones D, Boyett J, Sharp GB, Pui CH. Late mortality of long-term survivors of childhood cancer. *J Clin Oncol* 1997;15:2205-13.
- Mertens AC, Yasui Y, Neglia JP, et al. Late mortality experience in five-year survivors of childhood and adolescent cancer: the Childhood Cancer Survivor Study. *J Clin Oncol* 2001;19:3163-72.
- Simone J, Aur RJA, Hustu HO, Pinkel D. "Total therapy" studies of acute lymphocytic leukemia in children: current results and prospects for care. *Cancer* 1972;30:1488-94.
- Pui C-H, Dodge RK, Look AT, et al. Risk of adverse events in children completing treatment for acute lymphoblastic leukemia: St. Jude Total Therapy studies VIII, IX, and X. *J Clin Oncol* 1991;9:1341-7.
- Rivera GK, Raimondi SC, Hancock ML, et al. Improved outcome in childhood acute lymphoblastic leukaemia with reinforced early treatment and rotational combination chemotherapy. *Lancet* 1991;337:61-6.
- Evans WE, Relling MV, Rodman JH, Crom WR, Boyett JM, Pui C-H. Conventional compared with individualized chemotherapy for childhood acute lymphoblastic leukemia. *N Engl J Med* 1998;338:499-505.
- Pui C-H, Mahmoud HH, Rivera GK, et al. Early intensification of intrathecal chemotherapy virtually eliminates central nervous system relapse in children with acute lymphoblastic leukemia. *Blood* 1998;92:411-5.
- Center for Cost Financing Studies. Medical Expenditure Panel Survey: household component. Rockville, Md.: Agency for Healthcare Research and Quality, 2000.
- America's families and living arrangements: March 2000. Current population survey reports. Washington, D.C.: Census Bureau, June 2001.
- Employment status: annual averages 2001. Current population survey report. Washington, D.C.: Bureau of Labor Statistics, 2002.
- Peto R, Pike MC, Armitage P, et al. Design and analysis of randomized clinical trials requiring prolonged observation of each patient. II. Analysis and examples. *Br J Cancer* 1977;35:1-39.
- Gray RJ. A class of K-sample tests for comparing the cumulative incidence of a competing risk. *Ann Stat* 1988;16:1141-54.
- Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc* 1999;94:496-509.
- Breslow NE, Day NE. Statistical methods in cancer research. Vol. 2. The design and analysis of cohort studies. Lyons, France: International Agency for Research on Cancer, 1987:1-406. (IARC scientific publications no. 82.)
- Epilog Plus: statistical package for epidemiology and clinical trials, version 3. Pasadena, Calif.: Epicenter Software, 1993.
- Vora A, Frost L, Goodeve A, et al. Late relapsing childhood lymphoblastic leukemia. *Blood* 1998;92:2334-7.
- Rivera GK, Pinkel D, Simone JV, Hancock ML, Crist WM. Treatment of acute lymphoblastic leukemia: 30 years' experience at St. Jude Children's Research Hospital. *N Engl J Med* 1993;329:1289-95.
- Neglia JP, Meadows AT, Robison LL, et al. Second neoplasms after acute lymphoblastic leukemia in childhood. *N Engl J Med* 1991;325:1330-6.
- Loning L, Zimmermann M, Reiter A, et al. Secondary neoplasms subsequent to Berlin-Frankfurt-Münster therapy of acute lymphoblastic leukemia in childhood: significantly lower risk without cranial radiotherapy. *Blood* 2000;95:2770-5.
- Kimball Dalton VM, Gelber RD, Li F, Donnelly MJ, Tarbell NJ, Sallan SE. Second malignancies in patients treated for childhood acute lymphoblastic leukemia. *J Clin Oncol* 1998;16:2848-53.
- Nygaard R, Garwicz S, Haldorsen T, et al. Second malignant neoplasms in patients treated for childhood leukemia: a population-based cohort study from the Nordic countries. *Acta Paediatr Scand* 1991;80:1220-8.
- Walter AW, Hancock ML, Pui C-H, et al. Secondary brain tumors in children treated for acute lymphoblastic leukemia at St. Jude Children's Research Hospital. *J Clin Oncol* 1998;16:3761-7.
- Relling MV, Rubnitz JE, Rivera GK, et al. High incidence of secondary brain tumours after radiotherapy and antimetabolites. *Lancet* 1999;354:34-9.
- Pinkel D. Cure of the child with cancer: definition and prospective. In: American Cancer Society proceedings of the National Conference on the Care of the Child with Cancer. Washington, D.C.: American Cancer Society, 1979:191-200.
- Teeter MA, Holmes GE, Holmes FF, Baker AB. Decisions about marriage and family among survivors of childhood cancer. *J Psychosoc Oncol* 1987;5:59-68.
- Byrne J, Fears TR, Steinhorn SC, et al. Marriage and divorce after childhood and adolescent cancer. *JAMA* 1989;262:2693-9.
- Zevon MA, Neubauer NA, Green DM. Adjustment and vocational satisfaction of patients treated during childhood or adolescence for acute lymphoblastic leukemia. *Am J Pediatr Hematol Oncol* 1990;12:454-61.
- Green DM, Zevon MA, Hall B. Achievement of life goals by adult survivors of modern treatment for childhood cancer. *Cancer* 1991;67:206-13.
- Hays DM, Landsverk J, Sallan SE, et al. Educational, occupational, and insurance status of childhood cancer survivors in their fourth and fifth decades of life. *J Clin Oncol* 1992;10:1397-406.
- Rauck AM, Green DM, Yasui Y, Mertens A, Robison LL. Marriage in the survivors of childhood cancer: a preliminary description from the Childhood Cancer Survivor Study. *Med Pediatr Oncol* 1999;33:60-3.
- Haupt R, Fears TR, Robison LL, et al. Educational attainment in long-term survivors of childhood acute lymphoblastic leukemia. *JAMA* 1994;272:1427-32.
- Christie D, Leiper AD, Chessells JM, Vargha-Khadem F. Intellectual performance after presymptomatic cranial radiotherapy for leukaemia: effects of age and sex. *Arch Dis Child* 1995;73:136-40.
- Waber DP, Tarbell NJ. Toxicity of CNS prophylaxis for childhood leukemia. *Oncology (Huntingt)* 1997;11:259-65.
- von der Weid N, Mosimann I, Hirt A, et al. Intellectual outcome in children and adolescents with acute lymphoblastic leukaemia treated with chemotherapy alone: age- and sex-related differences. *Eur J Cancer* 2003;39:359-65.
- Kamps WA, Bökkerink JPM, Hakvoort-Cammel FGAJ, et al. BFM-oriented treatment for children with acute lymphoblastic leukemia without cranial irradiation and treatment reduction for standard risk patients: results of DCLSG protocol ALL-8 (1991-1996). *Leukemia* 2002;16:1099-111.
- Pui CH. Toward optimal central nervous system-directed treatment in childhood acute lymphoblastic leukemia. *J Clin Oncol* 2003;21:179-81.
- Manera R, Ramirez I, Mullins J, Pinkel D. Pilot studies of species-specific chemotherapy of childhood acute lymphoblastic leukemia using genotype and immunophenotype. *Leukemia* 2000;14:1354-61.
- Vilmer E, Suciu S, Ferster A, et al. Long-term results of three randomized trials (58831, 58832, 58881) in childhood acute lymphoblastic leukemia: a CLCG-EORTC report. *Leukemia* 2000;14:2257-66.
- Holmes GE, Baker A, Hassanein RS, et al. The availability of insurance to long-term survivors of childhood cancer. *Cancer* 1986;57:190-3.

46. Teta MJ, Del Po MC, Kasl SV, Meigs JW, Myers MH, Mulvihill J. Psychosocial consequences of childhood and adolescent cancer survival. *J Chronic Dis* 1986;39:751-9.
47. Tebbi CK, Bromberg C, Piedmonte M. Long-term vocational adjustment of cancer patients diagnosed during adolescence. *Cancer* 1989;63:213-8.
48. Vann JC, Biddle AK, Daeschner CW, Chaffee S, Gold SH. Health insurance access to young adult survivors of childhood cancer in North Carolina. *Med Pediatr Oncol* 1995; 25:389-95.
49. Novakovic B, Fears TR, Horowitz ME, Tucker MA, Wexler LH. Late effects of therapy in survivors of Ewing's sarcoma family tumors. *J Pediatr Hematol Oncol* 1997;19: 220-5.
50. Hoffman B. Cancer survivors' employment and insurance rights: a primer for oncologists. *Oncology (Huntingt)* 1999;13:841-6.
51. Equal employment opportunity for individuals with disabilities, final rules. *Fed Regist* 1991;56:35725-55.
52. Health Insurance Portability and Accountability Act of 1996, Pub. L. No. 104-191.
53. Marina N. Long-term survivors of childhood cancer: the medical consequences of cure. *Pediatr Clin North Am* 1997;44:1021-42.
54. Green DM, Hyland A, Chung CS, Zevon MA, Hall BC. Cancer and cardiac mortality among 15-year survivors of cancer diagnosed during childhood or adolescence. *J Clin Oncol* 1999;17:3207-15.
55. Blackwell DL, Collins JG, Coles R. Summary health statistics for U.S. adults: National Health Interview Survey, 1997. Vital and health statistics. Series 10. No. 205. Hyattsville, Md.: National Center for Health Statistics, May 2002. (DHHS publication no. (PHS) 2002-1533.)

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CORRECTION

Extended Follow-up of Long-Term Survivors of Childhood Acute Lymphoblastic Leukemia

Extended Follow-up of Long-Term Survivors of Childhood Acute Lymphoblastic Leukemia . On page 642, in the last column of the first row of Table 1, the summary of central nervous system irradiation should have read, "Patients received 5 or 12 Gy of craniospinal irradiation in studies 1, 2, and 3; patients received no irradiation in study 4," rather than "None," as printed.