

Leukemia After Therapy With Alkylating Agents for Childhood Cancer^{1,2}

Margaret A. Tucker, M.D.,^{3,4} Anna T. Meadows, M.D.,⁵ John D. Boice, Jr., Sc.D.,³ Marilyn Stovall, M.P.H.,⁶ Odile Oberlin, M.D.,⁷ Betty J. Stone, Ph.D.,³ Jillian Birch, Ph.D.,⁸ P. A. Voûte, M.D.,⁹ Robert N. Hoover, M.D., Sc.D.,³ and Joseph F. Fraumeni, Jr., M.D.,^{3,10} for the Late Effects Study Group¹¹

ABSTRACT—The risk of leukemia was evaluated in 9,170 2-or-more-year survivors of childhood cancer in the 13 institutions of the Late Effects Study Group. Secondary leukemia occurred in 22 nonreferred individuals compared to 1.52 expected, based on general population rates [relative risk (RR) = 14; 95% confidence interval (CI), 9–22]. The influence of therapy for the first cancer on subsequent leukemia risk was determined by a case-control study conducted on 25 cases and 90 matched controls. Treatment with alkylating agents was associated with a significantly elevated risk of leukemia (RR = 4.8; 95% CI, 1.2–18.9). A strong dose-response relationship was also observed between leukemia risk and total dose of alkylating agents, estimated by an alkylator score. The RR of leukemia reached 23 in the highest dose category. Radiation therapy, however, did not increase risk. Although doxorubicin was also identified as a possible risk factor, the excess risk of leukemia following treatment for childhood cancer appears almost entirely due to alkylating agents.—*JNCI* 1987; 78:459–464.

With the advances in treatment of childhood cancer, more children are surviving long periods of time and are at risk of developing late complications of treatment. An excess of leukemia and other cancers in survivors of childhood cancer has previously been reported by the LESG, a collaborative group of 13 major pediatric oncology centers (1). Because the increased risk of leukemia following Hodgkin's disease (2, 3), ovarian cancer (4), gastrointestinal cancers (5), non-Hodgkin's lymphomas (6), and small-cell carcinoma of the lung (7) has been associated with alkylating agent chemotherapy in adults, with or without radiation therapy, we investigated the role of cancer treatment in the development of leukemia among survivors of childhood cancer.

METHODS

Cohort analysis.—A roster of 9,170 2-or-more-year survivors of childhood cancer from all the centers was

originally constructed to provide a sampling frame from which to select controls for the case-control study. This cohort, however, allowed us to compute an expected number of secondary leukemias based on general population rates (8). Leukemias arising less than 2 years after the initial cancer were excluded from analysis because they were unlikely to be treatment related. Three of 25 patients with secondary leukemia were not treated for their first tumor at an LESG hospital; these "referral" cases were excluded from the cohort analysis. The period of observation for calculating the risk of develop-

¹ Received May 5, 1986; accepted September 16, 1986.

² Supported in part by Public Health Service contract N01CP-91049 from the Division of Cancer Etiology, National Cancer Institute.

³ Epidemiology and Biostatistics Program, Division of Cancer Etiology, National Cancer Institute, National Institutes of Health, Public Health Service, U.S. Department of Health and Human Services, Bethesda, MD 20892.

⁴ Address reprint requests to Dr. Tucker at the Landow Building, Room 3C-29, Bethesda, MD 20892.

⁵ Children's Hospital, Philadelphia, PA.

⁶ Department of Radiation Physics, M.D. Anderson Hospital, Houston, TX.

⁷ Institut Gustave-Roussy, Villejuif, France.

⁸ Manchester Tumor Registry, Manchester, England.

⁹ Emma Kinderziekenhuis, Amsterdam, Holland.

¹⁰ We are indebted to the many physicians and other personnel at the Late Effects Study Group member institutions without whom this study would have been impossible; to Drs. Giulio J. D'Angio, Mark H. Greene, and Leslie Robison for consultation and critical review of the manuscript; and to Millie Jacobus and Louise Oyster for technical assistance.

¹¹ Participating Centers: Children's Hospital of Philadelphia, Philadelphia, PA—Dr. Anna T. Meadows (chairperson) and Dr. G. J. D'Angio; Children's Memorial Hospital, Chicago, IL—Dr. Edward Baum; Columbus Children's Hospital, Columbus, OH—Dr. William Newton; Dana-Farber Cancer Institute, Boston, MA—Dr. Frederick Li, Dr. Stephen Sallan, and Dr. Gordon Vawter; Emma Kinderziekenhuis, Amsterdam, Holland—Dr. P. A. Voûte; Institut Gustave-Roussy, Villejuif, France—Dr. Jean LeMerle and Dr. Odile Oberlin; Istituto Nazionale Tumori, Milano, Italy—Dr. Alberto Banfi, Dr. Marco Gasparini, and Dr. Franca Fossati-Bellani; Los Angeles Children's Hospital, Los Angeles, CA—Dr. Stuart Siegel; M.D. Anderson Hospital, Houston, TX—Dr. Louise C. Strong and Dr. Jan Van Eys; Princess Margaret Hospital, Toronto, Canada—Dr. R. D. T. Jenkin and Dr. A. Zipursky; Roswell Park Memorial Institute, Buffalo, NY—Dr. Daniel Green; Royal Manchester Children's Hospital, Manchester, England—Dr. Patricia Morris-Jones, Dr. Jillian Birch, and Dr. Basil Marsden; University of Minnesota, Minneapolis, MN—Dr. Mark Nesbit, Dr. Leslie Robison, and Dr. William G. Woods (coordinator).

ABBREVIATIONS USED: ALL=acute lymphocytic leukemia; ANLL=acute nonlymphocytic leukemia; CI=confidence interval; CML=chronic myelogenous leukemia; CMOPP=cyclophosphamide (650 mg/m² iv days 1, 8), vincristine (1.4 mg/m² iv days 1, 8), procarbazine (100 mg/m² orally days 2–15), and prednisone (40 mg/m² orally days 2–15); LESG=Late Effects Study Group; MOPP=nitrogen mustard (6 mg/m² iv days 1, 8), vincristine (1.4 mg/m² iv days 1, 8), procarbazine, 100 mg/m² orally days 2–15), and prednisone (40 mg/m² orally days 2–15); RR=relative risk.

ing leukemia began 2 years after diagnosis of the primary tumor and ended with the date of death, date of last follow-up, or date of developing leukemia, whichever came first. Expected values of leukemia were also computed by assuming that all children alive at last follow-up survived and were disease-free at the closing date of the study, January 1980. Person-years of observation were accumulated by means of the computer program of Monson (9). Sex-, age-, and calendar-year-specific rates for both leukemia (all types combined) and ANLL obtained from the Connecticut Tumor Registry were applied to the appropriate person-years of observation to estimate the number of cases expected had this population experienced the same rates prevailing in the Connecticut population (10). Incidence rates from Connecticut were used, since the risk of childhood cancer shows little variation among Western countries (11). Statistical methods for risk estimation were based on the assumption that the observed number of second tumors followed a Poisson distribution. Tests of significance and CIs for the RR (observed/expected cases) were calculated with the use of exact Poisson probabilities. Cumulative probabilities of developing leukemia over time were estimated by the method of Kaplan and Meier (12).

Case-control analysis.—For each of the 25 leukemia cases, 2 patients without subsequent cancer matched on histologic type of the first tumor, duration of follow-up (at least as long as the leukemia latent period), age at first tumor diagnosis (± 2 yr), sex, and race were randomly selected as controls. To gain statistical power, we increased the 50 original matched controls to 90 by including additional controls who met identical matching criteria. These controls were available from the total survey of 222 second cancers matched to 444 controls. The additional controls were thus initially matched to cases who developed second tumors other than leukemia. No second tumor cases were included as controls.

The diagnoses of cases and control subjects were confirmed by pathology reports in the medical records. A panel of LESG pathologists confirmed the histologic type of all first and second tumors of the cases. For the cases and controls, detailed medical and exposure histories were abstracted from medical records. For both radiation therapy and chemotherapy, data were collected on all treatments until the development of leukemia for each case or the corresponding interval for each matched control.

Comparisons between cases and matched controls for all variables of interest were made by the conditional logistic regression method; variable matching ratios were taken into account (13). Radiation dose to the active bone marrow and amount of chemotherapy were grouped into categories described below according to the overall distribution of cases and controls, and RRs were calculated between each category and a referent (lowest dose) category. Tests for trend were made by taking the midpoint of each dose category as the representative value or score. For those instances where the matching factors were not correlated with the exposure histories of the cases and controls, or for which the numbers were so

small as to invalidate the conditions necessary for conducting matched logistic regression analyses, unmatched analyses were conducted (14).

Radiation dosimetry.—Most of the radiation therapy was delivered by orthovoltage apparatus, although some megavoltage units were used during the later years. Individual dosimetry determinations were made for all cases and controls by one author (M. S.) incorporating age at exposure and individual body measurements, such as weight, height, and body surface area. Actual exposure conditions were simulated on the basis of machine parameters, field configurations, and treatment conditions, and doses within skeletal components of an anthropomorphic phantom were measured. Collimator head leakage and radiation scatter from the different types of therapy machines were taken into account to the extent possible. The distribution of active bone marrow for children of various ages was taken from Christy (15). For those instances where radiation therapy information was less than adequate (10/115), best estimates of conditions and exposure values were made considering the hospital, calendar year, tumor site, age, and size of the subject at the time of irradiation. These estimates were made in consultation with a pediatric radiation therapist (G. J. D'Angio). The radiation dose was averaged over the total active bone marrow.

Chemotherapy quantification.—An attempt was made to quantify an individual's exposure to all alkylating agents, since this class of therapeutic drugs has been consistently associated with increased rates of leukemia (2-7). For combination of the exposures to multiple drugs into a single parameter, an alkylating agent score was developed that included procarbazine because of its similar mechanism of action (16). For each alkylating agent, we summed the total dose received per body surface area (mg/m^2) for each study subject. Dose distributions for all subjects in the overall case-control study were made for each agent and were divided into thirds. Thus each study subject was assigned a score of 0, 1, 2, or 3 for each separate agent, depending on whether he/she received none or fell into the lower, middle, or upper third of the distribution, respectively. The scores of the individual alkylating agents were then summed for each study subject. The sum was called the "alkylator score" and ranged from 0 to 12. One key assumption is that the relative effectiveness of each alkylating agent in causing leukemia is similar. Similar scores were developed for the vinca alkaloids and doxorubicin, which were the next most commonly used drugs. For doxorubicin, however, the dose levels were split into only two strata, high and low, because few patients had received this drug.

RESULTS

Cohort Study

Among the 9,170 2-or-more-year survivors of childhood cancer, 55% were male; 45% were age 0-4, 25% were age 5-9, and 30% were age 10 or more. The average age

TABLE 1.—Observed (obs) and expected (exp) numbers of secondary leukemia among all children living 2 or more years after diagnosis of a first cancer

Category	Cohort No.	Obs	Exp	Obs/Exp (95% CI)	Absolute excess risk ^a
First cancer total	9,170	22	1.52	14 (9-22)	4.0
Hodgkin's disease	1,036	12	0.14	89 (44-150)	22.6
Wilms' tumor	1,248	4	0.27	15 (4-38)	4.5
Ewing's sarcoma	213	2	0.03	62 (8-241)	16.7

^a Absolute excess risk = [(obs - exp)/person-yr] × 10⁴.

TABLE 2.—RR of leukemia by radiation dose to total active bone marrow

Specification	RR by radiation dose, rad					
	0	<250	250-	1,000-	1,500-	≥2,000
No. of cases	5	5	3	4	5	3
No. of controls	12	11	31	11	13	12
RR	1.0 ^a	1.2	0.1	0.8	0.7	0.4
RR, adjusted for alkylator score	1.0 ^a	1.2	0.2	1.5	1.0	0.1

^a Referent category, matched analysis.

of primary tumor diagnosis was 7.0 years. The average length of follow-up was 5.5 years, ranging from 2 to 42 years; there were no significant differences between males and females. The average year of diagnosis was 1969 and ranged between 1936 and 1979. Twenty-two leukemias occurred versus 1.52 expected (RR=14; 95% CI, 9-22). The excess leukemia incidence rate was 4.0 cases per 10,000 persons per year. Most of the risk was associated with the development of ANLL with 19 cases observed compared to 0.70 expected (RR=27; 95% CI, 16-43). Risk was not found to differ by sex or time since diagnosis, but it appeared to rise with increasing age at initial diagnosis (absolute excess risk in excess cases/10,000/year = 2.6, age 0-4; 4.0, age 5-9; 6.5, age ≥10) and was highest among children treated for Hodgkin's disease and Ewing's sarcoma (table 1). The absolute excess risks for ANLL were not significantly different from total leukemias, but the RRs of ANLL after Hodgkin's disease and Ewing's sarcoma were 138 and 112, respectively. The cumulative mean probability (±SE) of developing leukemia rose to 0.8% (±0.2%) 20 years after initial diagnosis for the entire cohort and to 4.2% (±1.9%) for patients treated for Hodgkin's disease (text-fig. 1). Making the conservative assumption that subjects alive at last follow-up survived and were disease-free until the study closing date had little effect on the

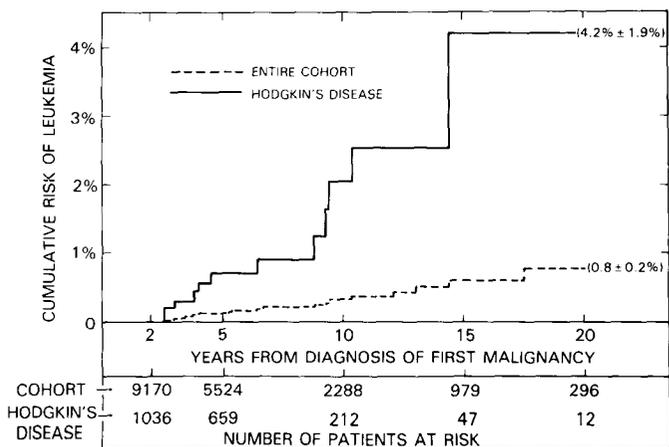
risk estimates: RR=11.2 and absolute risk=2.9 excess cases/10,000/year.

Case-control study.—Of the 25 cases of leukemia, 20 had ANLL, 3 had ALL, and 2 had CML. The initial tumors were Hodgkin's disease-12 (11 ANLL; 1 CML); Wilms' tumor-5 (4 ANLL, 1 CML); Ewing's sarcoma-3 (2 ANLL, 1 ALL); medulloblastoma-2 (1 ANLL, 1 ALL); neuroblastoma-1 (ALL); rhabdomyosarcoma-1 (ANLL); and glioblastoma-1 (ANLL). The 3 referral cases excluded from the cohort study were Wilms' tumor followed by CML, Ewing's sarcoma followed by ALL, and medulloblastoma followed by ALL.

All persons who developed leukemia were treated with radiation therapy and/or alkylating agent chemotherapy. The average radiation dose to active bone marrow ranged from 0 to 3,800 rad (mean = 1,000 rad). There was no significant difference in risk of leukemia by radiation dose between the cases and controls (table 2), even after adjustment was made for alkylating agent treatment. No dose response was seen among the subjects treated only with radiation.

Procarbazine and nitrogen mustard were the alkylating agents most commonly used in the cases (48 and 36%) and the controls (13.3 and 14.4%). Nitrosoureas were used in 24% of the cases and 5% of the controls. Chlorambucil and cyclophosphamide were also more common in the cases. Overall, 61% of the study subjects received no alkylating agents, 10% received one drug, 7% received two drugs, 10% received three drugs, 7% received four drugs, and 5% received five or more drugs. Sixty-four percent of the cases and 32% of the controls were treated with alkylating agents (RR=4.8; 95% CI, 1.2-18.9). The small number of cases precluded detailed analysis of the risks of individual drugs, particularly since they were usually given in combination with other alkylating agents. The interval between initial treatment with alkylating agents and leukemia ranged between 2.6 and 12 years (median 3.5; mean 5.1). The interval between last treatment with alkylating agents and leukemia ranged between 0 and 5.7 years (median 1.7; mean 1.8).

The risk of leukemia rose with increasing alkylator score (P=.003) (table 3). There was no apparent increased risk with low-dose alkylating agents, but with multidrug therapy (score >3) the RR rose to 23.2 in the highest dose category. To differentiate between duration of exposure to alkylating agents and total amount of



TEXT-FIGURE 1.—Cumulative risk of leukemia after childhood cancer. ---, cumulative risks of leukemia after all childhood cancers. —, risks of leukemia after Hodgkin's disease.

TABLE 3.—Matched RR of leukemia according to alkylator score, adjusted for radiation dose

Specification	RR for alkylator score:				
	0	1-2	3-4	5-6	≥7
No. of cases	9	1	3	7	5
No. of controls	61	12	7	7	3
RR	1.0 ^a	0.7	8.4	16.0	24.2 ^b
RR, adjusted for radiation	1.0 ^a	0.7	7.9	18.3	23.2 ^c

^a Referent category.^b Risks for alkylator score >3 statistically significant.^c Trend significant $P=.003$.

drugs received, we totaled the actual number of days that each subject received alkylating agents. Within each duration of treatment interval (<100 days, 101-300, ≥301), there was a clear dose response with increasing alkylating agent score. Within each alkylating agent score stratum, however, there was no consistent effect with increasing days of treatment. The risk of leukemia was higher in the patients who had received the last alkylating agent within 2 years of developing leukemia (RR = 6.2; 95% CI, 2.2-17.2) than in those who received the last alkylating agent more than 2 years prior to leukemia (RR = 2.0; 95% CI, 0.6-6.7). This effect did not vary when risks were stratified by alkylator score, duration of treatment, or time from initiation of alkylating agent. The major determinant of risk remained the alkylator score. Only those individuals who had an alkylator score greater than 3 were at risk of leukemia more than 2 years after the last alkylating agent, and those who received the highest doses were at risk for the longest period of time.

Other chemotherapy given to study subjects included vinca alkaloids, prednisone, dactinomycin, and doxorubicin. No meaningful evaluation of the vinca dose level was possible because vinca alkaloids were so highly correlated with alkylating agents (e.g., combined therapy with the use of MOPP, CMOPP, and their variations). Among the 33 patients with Wilms' tumor, none of the cases received alkylating agents, and there was no case-control difference in the use of dactinomycin.

The risk of leukemia appeared to increase with higher doses of doxorubicin ($P=.13$) even after adjustment for alkylator score (table 4). The mean latencies between start and end of doxorubicin treatment and diagnosis of leukemia were 2.6 years (range 1.5-3.5) and 2.1 years

TABLE 4.—RR of leukemia according to doxorubicin dose adjusted for alkylator score

Specification	RR at doxorubicin dose		
	None	Low	High
No. of cases	18	2	5
No. of controls	84	3	3
RR	1.0 ^a	2.3	4.9
Trend $P=.13$			

^a Referent category, matched analysis.TABLE 5.—Effects of alkylator score and doxorubicin on the RR of leukemia^a

Alkylator score	Specification	Doxorubicin	
		No	Yes
≤4	No. of cases	12	1
	No. of controls	75	5
	RR	1.0 ^b	2.5
≥5	No. of cases	6	6
	No. of controls	9	1
	RR	5.4 ^c	46.2 ^c

^a Age-stratified analysis performed since matched analysis prohibited due to small numbers.^b Referent category.^c Risk significantly elevated ($P<.05$).

(range 0.8-2.7). Subsequently, the alkylator score was reexamined; adjustment was made for doxorubicin, with no significant change in the risks (RR = 19.5 in the highest dose category). The combined effect of doxorubicin and alkylating agent therapy on leukemia risk was examined, and the risk appeared more than multiplicative; i.e., the combined effect exceeded that anticipated based on the product of the individual effects (table 5). Although the analysis was limited by small numbers, we found no evidence to suggest positive interaction between alkylating agents and radiation therapy or between doxorubicin and radiation therapy.

To clarify the effects of age and the first tumor diagnosis on the risk of leukemia as shown in the cohort analysis, we examined the use of alkylating agents among the controls, who were representative of the cohort. Among the controls, 13.5% received alkylating agents at age 0-4 years, 37.5% received them at age 5-9 years, and 56% received them over age 10. After adjustment for dose, there was no difference in leukemia risk associated with alkylating agents between those younger or older than 10 years. Similarly, alkylating agents were received by only 4% of the Wilms' tumor controls, compared to 60% of Hodgkin's disease, 75% of Ewing's sarcoma, and 30% of the other controls. The number of Hodgkin's disease patients was sufficient to examine by collapsed dose categories, but the risks in each category were not greater than those seen in other cancers. Nine of the 12 cases with Hodgkin's disease had an alkylator score of 6 or more.

DISCUSSION

Our findings indicate that the increased risk of leukemia following treatment for childhood cancer is almost entirely due to the use of alkylating agents. This conclusion is supported by the strong dose-response relationship observed between leukemia risk and the total dose of alkylating agents, estimated by an alkylator score with the RR reaching 23.2 in the highest dose category. The risk was primarily associated with ANLL, consistent with the experience of various adult cancers treated with alkylating agents (2-7).

In the cohort analyses, the elevated risk of leukemia at

older ages can be explained by the higher doses of alkylating agents received. Similarly, the excess leukemia after Hodgkin's disease and Ewing's sarcoma can be explained by treatment with alkylating agents. The cumulative risk of leukemia following Hodgkin's disease was about 1.5% at 10 years and 4% at 20 years; the risk at 10 years resembles that of the Stanford series of cases treated under age 20 (2).

To obtain an index of the total amount of alkylating agents received, we developed an alkylator score as a method for combining different drugs. We recognize that this artificial score may not be appropriate in different circumstances when large proportions of a homogeneous patient population receive single-agent chemotherapy. In this case, direct analysis of drug dose in mg/m^2 would be preferable. This unique score is based on the actual amount of drugs received (mg/m^2), not a summation of the number of cycles or the number of drugs as used by previous investigators (3). The construct of the score, however, requires a major assumption: that dose levels of different drugs in the same third of their respective dose distributions are equally leukemogenic. Despite this assumption, the model appears to be useful in quantitatively evaluating the risk of leukemia following exposure to combination drug therapy; dose-response relationships were evident and interactive analyses were facilitated. Summing the individual drug scores produced a measure of exposure for which risk increased in proportion to the increment in score. There was no evidence that risk was concentrated only among those who received the highest quantities of individual drugs. For example, within the limits of the data, it appeared that an individual with a score of 6, because of receiving 2 drug scores of 3 had the same or similar risk as an individual with a score of 6, because of 3 drug scores of 2, etc. Total dose seemed to be a more important parameter of risk than duration of treatment. To evaluate whether bias was inadvertently introduced by expanding the control group, we reanalyzed the data using only the original controls. There was no significant difference in the leukemia risk estimates.

An attempt was made to evaluate the separate effects of individual alkylating agents, but this was not possible because of small numbers and because drugs were frequently given in combination. Empirically, procarbazine seems important, since over half of the cases received it, usually in high doses. Procarbazine, however, is present in MOPP, CMOPP, and similar combinations of drugs, and it is difficult to disentangle its effects from exposure to nitrogen mustard derivatives or nitrosoureas. One potential concern was classifying procarbazine with the alkylating agents and adding its effects to those of the alkylating agents. Excluding procarbazine from the analysis lowered the alkylator score, range 0-9, but the risks of leukemia and dose response were essentially unchanged (RR=19.9 in the highest dose category adjusted for radiation).

Despite the small numbers of cases, there was an excess of leukemia following the use of doxorubicin and a suggestive dose-response relationship after controlling

for alkylator score. The more than multiplicative interaction with alkylating agents suggests that combined treatment with doxorubicin and alkylating agents is more leukemogenic than one would expect based on their independent risks. Since doxorubicin was usually given after alkylating agent therapy in this survey, its effect, if real, could result from a second mutational event that promotes the development of the leukemia after the initial DNA damage to stem cells by alkylating agents.

Although the impact of chemotherapy may have masked a much smaller radiation risk, it appears that radiation therapy for childhood cancer is not as an important a factor in the development of subsequent leukemias. However, our ability to evaluate the effect of radiation in those who did not receive alkylating agents was hampered by small numbers and the fact that all these cases received substantial radiation. Although no radiation dose response was evident, all four ANLLs following Wilms' tumor received radiation (<1,000 rad average marrow dose) but no alkylating agent, and the population expectation was only 0.3 for all leukemia.

The identified leukemia risks must be put in perspective. Over the last 30 years, when the patients in this study were treated, significant therapeutic advances were made which resulted in thousands of children surviving for extended periods of time. Much of this success is due to the use of alkylating agents in combination therapy. Until less toxic but equally effective therapy is found, the small risk of leukemia of approximately 1% at 20 years should not discourage the use of established forms of treatment for advanced cancer. In the setting of adjuvant therapy or therapy for nonneoplastic disease, however, this risk should be considered and balanced with the anticipated benefit from such treatment.

REFERENCES

- (1) MIKÉ V, MEADOWS AT, D'ANGIO GJ. Incidence of second malignant neoplasms in children: Results of an international study. *Lancet* 1982; 2:1326-1331.
- (2) COLEMAN CN, KAPLAN HS, COX R, et al. Leukemias, non-Hodgkin's lymphomas and solid tumors in patients treated for Hodgkin's disease. *Cancer Surveys* 1982; 1:733-744.
- (3) BOIVIN J-F, HUTCHISON GB, LYDEN M, et al. Second primary cancers following treatment of Hodgkin's disease. *JNCI* 1984; 72:233-241.
- (4) GREENE MH, BOICE JD JR, GREER BE, et al. Acute nonlymphocytic leukemia after therapy with alkylating agents for ovarian cancer: A study of five randomized clinical trials. *N Engl J Med* 1982; 307:1416-1421.
- (5) BOICE JD JR, GREENE MH, KILLEN JY JR, et al. Leukemia and preleukemia after adjuvant treatment of gastrointestinal cancer with semustine (*methyl-CCNU*). *N Engl J Med* 1983; 309:1079-1084.
- (6) GREENE MH, YOUNG RC, MERRILL JM, et al. Evidence of a treatment dose response in acute nonlymphocytic leukemias which occur after therapy of non-Hodgkin's lymphoma. *Cancer Res* 1983; 43:1891-1898.
- (7) CHAK LY, SIKIC BI, TUCKER MA, et al. Increased incidence of acute lymphocytic leukemia following therapy in patients with small cell carcinoma of the lung. *J Clin Oncol* 1984; 2:385-390.
- (8) TUCKER MA, MEADOWS AT, BOICE JD JR, et al. Cancer risk following treatment of childhood cancer. In: Boice JD Jr, Fraumeni JF Jr, eds. *Radiation carcinogenesis: Epidemiology*

- and biological significance. New York: Raven Press, 1984:211-224.
- (9) MONSON RR. Analysis of relative survival and proportional mortality. *Comput Biomed Res* 1974; 7:325-332.
- (10) HESTON J, MEIGS JW, KELLY J, et al. Forty-five years of cancer in Connecticut: 1935-79. *Natl Cancer Inst Monogr* 1986; 70:506-617.
- (11) WATERHOUSE J, MUIR C, CORREA P, eds. Cancer incidence in five continents. Vol III. Lyon, France: IARC, 1976.
- (12) KAPLAN EL, MEIER P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 1958; 53:457-481.
- (13) LUBIN JH. A computer program for the analysis of matched case-control studies. *Comp Biomed Res* 1981; 14:138-143.
- (14) ROTHMAN KJ, BOICE JD JR. *Epidemiologic analysis with a programmable calculator*. Boston: Epidemiology Resources, Inc., 1982.
- (15) CHRISTY M. Active bone marrow distribution as a function of age in humans. *Phys Med Biol* 1981; 26:389-400.
- (16) CHABNER BA, MYERS CE. Clinical pharmacology of cancer chemotherapy. In: DeVita VT Jr, Hellman S, Rosenberg SA, eds. *Cancer: Principles and practice of oncology*. Philadelphia: Lippincott, 1982:156-197.