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Analysis of 1380 survivors of childhood Hodgkin's disease (HD) has shown a 75-fold increased risk of breast cancer. The purpose of this proposal is to identify a sub-population among survivors of HD, at an increased risk for developing breast cancer. Construction of pedigrees of patients with secondary breast cancer did not reveal excess cancer among family members. We also planned to identify somatic and/or germline mutations in candidate genes such as p53, BRCA1 & 2, and ATM. Four of the six breast cancer samples examined so far, contained mutations in exons 5-9 of the p53 gene. Three of three blood samples examined for mutations in the ATM gene have shown no mutations. We are recommending a baseline mammogram at 25 years of age, repeated every three years till the age of 40, and then annually. For patients with an increased risk of breast cancer due to other risk factors, we recommend annual mammograms, beginning at age 25 years. We propose to institute these recommendations among a limited number of member institutions of the Children Cancer Group – to address feasibility and compliance issues. In addition, we have initiated the process of updating the LESG cohort to identify new second cancers and associated risk factors.

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1.0 INTRODUCTION

Analysis of a cohort of 1380 survivors of childhood Hodgkin's disease (HD) from the Late Effects Study Group (LESG) has shown a 75-fold increased risk of breast cancer compared with the general population. The cumulative probability of developing breast cancer approaches 35% by 40 years of age among the female survivors of HD. The median age at diagnosis of breast cancer in this cohort was 31.5 years (15.4 to 42 years) and the median latency was 19.3 years (2.4 to 28.5 years). We hypothesized that patients with HD who subsequently develop breast cancer have a genetic susceptibility to develop second cancer, specifically breast cancer. The purpose of this proposal was to identify a sub-population among the survivors of HD that is at an increased risk for developing breast cancer, and to institute intervention in the form of active screening and possibly chemoprevention. We planned to obtain and validate family histories of individuals with secondary breast cancer in order to quantitate the risk of breast cancer in the respective families. We also planned to identify somatic and/or germline mutations in candidate genes known to be associated with breast cancer including p53, BRCA1 and ATM. We planned to make recommendations for mammographic screening of patients identified to be at an increased risk of developing secondary breast cancer (age between 10 and 16 years at time of diagnosis of HD, mantle radiation). In addition, there will be ongoing surveillance and expansion of the original cohort to recruit more patients to the study.

1.1 SPECIFIC AIMS

The goal of this proposal is to identify a sub-population among survivors of HD, that is at an increased risk for developing breast cancer. We will use an established and active cohort of female survivors of HD, diagnosed between 1955 and 1986 at one of the participating institutions of the Late Effects Study Group (LESG) (see Appendix). Thus far, seventeen patients have been identified with secondary breast cancer in this cohort.

1.1.1 Specific Aim 1.

To obtain and validate family histories of individuals with secondary breast cancer following successful treatment of HD, in order to quantify the risk of breast cancer in the respective families.

1.1.2 Specific Aim 2.

To identify somatic and germline mutations in candidate genes known to be associated with both breast cancer and sensitivity to radiation-induced carcinogenesis.

i Tumor tissue (paraffin-embedded or frozen) will be obtained from the 17 patients with post-HD breast cancer. Tissue will be examined, using PCR-SSCP and immunochemistry, for somatic mutations in p53, a gene known to be involved in both radiation sensitivity and in the etiology of breast cancer. Additionally, in frozen samples where RNA is available, tumor will be screened for mutations in the gene ATM which is mutated in ataxia telangiectasia.

ii Samples of peripheral blood will be obtained from those patients with breast cancer who are known to be surviving (n=12), and will be examined using PCR-SSCP for germline mutations in p53, and by RT-PCR and SSCP for germline mutations in the gene ATM.

iii A recurring mutation in exon 20 of the gene BRCA1 has been described in families with breast cancer and HD. PCR-SSCP will be used to screen the study population for germline or somatic mutation of BRCA1 at this site.

iv Samples of peripheral blood will also be obtained from control HD patients who have not developed breast cancer. Controls will be matched with the breast cancer patients for age, length of follow-up and treatment course. These samples will also be studied using PCR-SSCP for germline mutations in p53 and BRCA1, and by RT-PCR and SSCP for mutations in ATM.

1.1.3 Specific Aim 3.
To maintain and expand the cohort of HD survivors under surveillance, in order to incorporate any newly diagnosed patients with breast cancer into the current studies.

2. 0 SIGNIFICANCE OF THE PLANNED RESEARCH

With current therapies, 90% of pediatric HD patients are cured of their cancer.(1) Current data suggest that approximately 35% of the female HD survivors are going to develop secondary breast cancer by the time they are 40 years of age. It is therefore very important to identify risk factors for the development of secondary breast cancer, those related both to HD treatment (age at radiation exposure and dose of radiation) and to genetic susceptibility (p 53, BRCA1, ATM). This information is needed in order to consider instituting measures for early detection (in the form of active screening, specifically mammographies), chemoprevention and modification of therapy for HD.

3.0 RESEARCH DESIGN AND METHODS

3.1 Patient Eligibility:

i) Diagnosis of HD at one of the LESG institutions between 1955 and 1986;
ii) Age less than 16 years at diagnosis of HD;
iii) Diagnosis of breast cancer after successful treatment for Hodgkin's disease.

3.1.1 Control selection

Controls for Specific Aim 2 have been identified from the remaining population of female Hodgkin's disease survivors using the following criteria for matching:

i) Age at diagnosis of Hodgkin's disease (± 1yr)
ii) Length of follow-up following Hodgkin's disease (± 1 yr)
iii) Radiation to mantle area
iv) Primary institution

3.2 Methods - Specific Aim 1

Family Histories

Pedigrees were constructed including all first and second degree relatives of the proband, by using the detailed family history approach.(54). A chronological listing of all first and second degree relatives were obtained and information obtained on demographic factors, vital status of the person (if deceased, the cause of death and age; if alive, inquiry will be made into his or her medical history). If the person had a history of breast and or ovarian cancer, information was obtained about age at diagnosis and the hospital where the diagnosis was made. This information was used to determine the incidence of cancer in the families (data analysis section).

3.3 Methods - Specific Aim 2.

Blood samples from the surviving cases are being collected by the respective institutions and shipped to City of Hope for analysis. Study participants are being informed that results of the analysis will not be available on an individual basis.

3.3.1 Molecular Studies

1. p53 - Sample of tumor tissue (paraffin-embedded or frozen) is being obtained from the 17 patients already identified as having developed breast cancer after treatment for childhood HD. Tumor tissue is being studied for p53 mutation using immunochemistry and PCR-SSCP. Immunochemistry is being performed on paraffin embedded tissue using a purified mouse monoclonal antibody that recognizes wild type and mutant p53 (clone DO-1, Oncogene Science). The presence of detectable p53 protein by immunochemistry has been correlated with the presence of mutation in the gene, and the distribution (nuclear and cytoplasmic) has been suggested to be important in the pathogenesis of breast cancer.(56) The paraffin embedded tissue is dewaxed and then incubated with unlabeled primary monoclonal antibodies.

Specifically bound antibody is then visualized by incubation with a biotinylated secondary antibody followed by a preformed avidin-biotinylated horseradish peroxidase macromolecular complex and substrate. Samples are examined by light microscopy and the presence of p53 staining and its distribution recorded and compared with positive and negative controls provided by the manufacturer. PCR-SSCP is then used to identify sites of mutation in the p53 gene, which are then characterized by direct DNA sequencing. DNA is extracted from paraffin-embedded tissue using standard techniques. Briefly, 10 micron slices are prepared from paraffin blocks in a sterile manner. Samples are then chopped into small fragments with a fresh sterile scalpel blade for each sample, deparaffinized with xylene, rehydrated in TEN buffer (10 microm Tris, HCl pH 7.5, 2 mM EDTA and 100 mM NaCl) and digested overnight with proteinase K. Samples are then extracted with phenol-chloroform, ethanol precipated, washed with 70% ethanol, dried and resuspended in TE buffer for amplification. DNA is similarly extracted from frozen tissue by homogenization followed by proteinase K digestion, phenol extraction and ethanol precipitation. PCR amplification of exons 4 to 10 of the p53 gene are performed using six different sets of primers to generate fragments of a suitable size for SSCP, as described by Murakami et al.(57) Briefly, the 5' ends of primers is labeled by the polynucleotide kinase reaction with [^{32}P]ATP. The DNA samples (100 ng) are subjected to PCR using each primer pair. Five microliters of the PCR product are then mixed with formamide dye (95% formamide, 20mm EDTA, 0,05% xylene cyanol and 0.05% bromophenol blue), heated to 80 degrees Centigrade and applied to a 0.5XMDE (mutation detection enhancement, AT Biochem) gel. Samples are then dried on filter paper and exposed to x-ray film for 12 hours. DNA fragments showing mobility shift by PCR-SSCP analysis are subjected to direct sequencing using dideoxy chain termination as previously described to characterize the mutation and distinguish polymorphisms.

2. AT*M* - A cDNA clone representing part of the coding sequence of the gene mutated in ataxia telangiectasia has recently been isolated and the sequence deposited in Genbank.(37) We screen study participants for mutations in this cDNA by extraction of RNA and RT-PCR followed by SSCP, as previously described.(37) Total RNA is extracted from peripheral blood leukocytes or frozen tumor tissue with the Tri-reagent system (Molecular Research Center, Cincinnati, OH) and reverse transcribed with Superscript II reverse transcriptase (Gibco-BRL, Gaithersburg, MD) and an oligo-(dT) primer. The reaction products serve as template for gene-specific primers which is devised from the known sequence of AT*M* and used for PCR amplification and SSCP analysis. Fragments with abnormal migration identified by SSCP are sequenced as described above. It is estimated that approximately 20 primer pairs are needed to cover the 5.9 kb of known sequence. As genomic sequence of the ATM becomes available, genomic primers will be devised and utilized to look for somatic mutations of the ATM gene in paraffin-embedded tumor tissue.

3. BRCA1 - Peripheral leukocytes and tumor tissue from all study participants will be screened for mutations in exon 20 of BRCA1. DNA will be extracted, amplified using specific primers as described by Simard et al,(58) and screened for mutation using SSCP as described above. Fragments with abnormal mobility will be directly sequenced to characterize the mutation. In patients with a high Family History Score (methods for Specific Aim 1), the entire BRCA1 coding sequence will be screened for germline and somatic mutation by PCR-SSCP as described by Simard et al.(58)

3.3.2 Controls Subjects

Samples of peripheral blood are being obtained from control HD patients who have not developed breast cancer. These samples are being used to study germline mutations in p53, BRCA1 and ATM.

3.4 Methods - Specific Aim 3.

All patients who were alive at the time of the last update have been identified, and a survey has been sent to the physician in the respective institutions. The following information is being gathered: 1) date of last contact; 2) vital status of the patients at last contact; 3) development of neoplasm since the last contact; 4) recurrence of HD. Patients newly diagnosed with breast cancer will be incorporated into the study, and consent obtained for construction of pedigrees and procuring blood and tissue samples for identifying somatic and/or germline mutations in the candidate genes.

4.0 DATA ANALYSIS

4.1 Specific aim 1: The expected number of affected family members based on demographic information (age, sex, race, and possibly birth cohort) were calculated for the cases (HD/breast cancer). Estimates of cumulative incidence rates derived from appropriate population surveys (SEER registry, and registries from other countries representing the case-control families) were multiplied by the total person-years at risk for the family to calculate the expected number of cases for a family. Person-years at risk were accumulated from birth until age at interview or age at death for persons without

cancer, or age at diagnosis for persons with breast cancer. Gender, race, age and time-specific incidence rates will be used to compute the expected number of cases. This expected number (E_i) for the ith family is then compared to the observed number (Oi) to give a summary family history (FH) score for this family as $FH_i = O_i - E_i/(E_i)^{1/2}$ (where Oi = $\_O_{ij}$ and Ei = $\_E_{ij}$ for all j members of the ith family).(55) Family history scores directly quantitate the risk of disease in a family, but they can also be categorized into groups of essentially negative family history (FH<0.5), mild positive family history (1.0<FH<2.0), and very strong family history (FH>2.0).(55). Analyses will be performed with the Epilog software.(59)

4.2 Specific Aim 2: Conditional logistic regression will form the basis of most statistical analysis for cases and their matched controls. Three groups of variables will be defined: predominantly hereditary factors (family history, body height), reproductive factors (age at menarche, age at menopause, when applicable, reproductive history) and body measurements. Within these groups, a forward stepwise analysis based on comparison of p-values will be performed to identify risk factors. Relative Risk based on odds ratio will be tested for trend and linearity. In testing a particular variable only those study participants will be excluded, who have missing values for that variable or for those already included in the model.

5.0 PROJECTS COMPLETED AS OF JUNE 1999

5.1 Specific Aim 1

As of June 1999, I have completed the construction of pedigrees for families of patients with secondary breast cancer. Pedigrees were constructed including all first and second-degree relatives of the proband, by using the detailed family history approach. A chronological listing of all first and second degree relatives were obtained and information was obtained on demographic factors, vital status of the person (if deceased, the cause of death and age; if alive, inquiry was made into his or her medical history). If the person had a history of breast and or ovarian cancer, information was obtained about the site and type of cancer, age at diagnosis and the hospital where the diagnosis was made. The expected number of affected family members based on demographic information (age, sex, race, and possibly birth cohort) was calculated for the cases (HD/breast cancer). Estimates of cumulative incidence rates derived from appropriate population surveys (SEER registry) were multiplied by the total person-years at risk for the family to calculate the expected number of cases for a family. Person-years at risk were accumulated from birth until age at interview or age at death for persons without cancer, or age at diagnosis for persons with cancer. This information was used to determine the incidence of cancer in the families (data analysis section). Analysis of the data collected form these families reveals no excess risk compared to the general population. Since the last report, findings from this study have been published in Lancet (Bhatia S, Meadows AT, Robison LL. Family History of Breast Cancer after Treatment of Hodgkin's Disease in Childhood. *Lancet* 1997;350:888-889, see Appendix).

5.2 Specific Aim 2

Mutation in the p53 gene

A total of six patient samples (paraffin embedded tissue) were examined for mutations in exons 5-9 of the p53 gene. One more sample is in the process of being examined at the time of this report. This region contains about 80% or more of all mutations reported for p53. Paraffin sections were treated with proteinase K in buffer containing Tween 20. Each exon was amplified individually, using nested primers, each PCR product was sequenced in both directions by cycle sequencing using thermosequenase 33P radiolabeled terminator sequencing kit from Amersham (#US79750). Mutations were verified by re-amplification and re-sequencing of the affected exon.

Four of the six samples contained mutations, although one was a silent mutation that would not change the protein sequence and another sample contained two intron mutations (not in the splice site region) that probably do not affect the protein structure or splicing. Only two samples contained mutations that would affect the protein structure; one of these contained two mutations. The summary of these mutations is as follows:

Tumor #	Exon	Codon	Nucleotide change	Codon change	AA change
1	7	260	C>G	TCC>TGC	ser>cys
	8	281	G>A	GAC>AAC	asp>asn
2	7	233	C>T	CAC>TAC	his>tyr
3	8	300	C>A	GCC>CCA	pro>pro (silent)
4	int 7 (E7+40bp)	___	g>a	___	___
	int 6	___	t>c	___	___
5	no mutations found				
6	no mutations found				

Mutations in the ATM gene, BRCA1 & 2 genes

Peripheral blood was obtained from four patients with secondary breast cancer following Hodgkin's Disease. To screen for the *Alw* I polymorphism in Exon 24 of the *ATM* gene, 50 ng of genomic DNA was amplified in a 20 □l PCR reaction. The primers were ATME23F (5'-TCTTTGTTTGTTAATGAGTA-3') and ATME23R (5'-CAGCATTCCAAATACTTCAT-3'), and were used at 1 □M each. The PCR amplification was performed in a Perkin Elmer 9600 Gene Amp. The reaction contained 1x Perkin Elmer PCR II Buffer (50 mM KCl, 10mM Tris-HCl [pH 8.3], and 1.5 mM MgCl2), and also contained 0.2 □M dNTPs, and 1U of AmpliTaq Gold DNA Polymerase. There was a 10-minute incubation at 95° C to activate the polymerase. Then, 35 rounds of cycling were performed as follows: denaturation at 94° C for 30 sec; annealing at 52° C for 45 sec, and extension at 72° C for 30 sec. The reactions were then held at 4° C. The PCR products were then digested with 1 U of *Alw* I restriction endonuclease for at least 2 hours at 37 ° C. The digestion products were then resolved on native 6% polyacrylamide gels. In addition to patient samples, genomic DNA from a known homozygous wild type individual and a known heterozygous individual were always run as digestion controls.

Using the methodology outlined above, we examined three of the four samples for mutations in the ATM gene. No mutations were identified.

We are in the process of examining these samples for mutations in the BRCA1 gene.

Because this study is a multi-institutional study, the investigators are dependent upon the responsible investigators at the primary institutions for a timely delivery of the specimens. Multiple reminders have been sent to the various institutions, and have been assured of eight additional peripheral blood samples and five additional tissue samples shortly from France and Italy, which will be analyzed as soon as they arrive.

RECOMMENDATIONS FOR SCREENING OF SURVIVORS OF HODGKIN'S DISEASE AT INCREASED RISK FOR BREAST CANCER

After an extensive review of the literature, we have formulated recommendations for screening female survivors of Hodgkin's Disease for early detection of secondary breast cancer. This manuscript has been submitted for publication to Annals of Internal Medicine (manuscript is provided in Appendix). In this manuscript we conclude that there exists an increased risk of breast cancer among women treated with radiation to the chest for Hodgkin's disease in early puberty, with the excess cancers typically developing after a latent period of 10 or more years. Since the increased risk of cancer may persist for decades after irradiation, survivors of childhood Hodgkin's disease should be monitored carefully throughout their lives. We recommend a baseline mammogram at 25 years of age, repeated every three years till the age

of 40, and then annually. For patients with an increased risk of breast cancer due to other risk factors, we recommend annual mammograms, beginning at age 25 years. Self-breast examination every month and clinical breast examination every six months, beginning at age 15 years (or later for those diagnosed and treated after 15 years of age), are also recommended. We propose to institute these recommendations among a limited number of member institutions of the Children Cancer Group – to address feasibility and compliance issues.

Specific Aim 3:

The Late Effects Study Group was last updated approximately eight years ago. Since this cohort is the largest and best-followed group of adolescent Hodgkin's disease patients followed for the longest period of time, every additional year comes closer to estimating the total life-time risk of adult-onset cancers in this population. All the members of the Late Effects Study Group have been contacted to get their commitment for updating the LESG cohort. A roster of all surviving patients has been generated. The following information is being requested from the 15 member institutions: 1) date of last contact; 2) vital status of the patients at last contact; 3) development of neoplasm since the last contact (pathology report of the second neoplasm); 4) recurrence of HD; 5) details of treatment for recurrence; 6) cause of death, if the patient has died (autopsy report, if available). Over the next year, we plan to collect, code and enter this information – thus updating the previous database – and analyze the data for the incidence and identification of risk factors.

7.0 CONCLUSION

Analysis of a cohort of 1380 survivors of childhood Hodgkin's disease has shown a 75-fold increased risk of breast cancer, with the cumulative probability of developing breast cancer approaching 35% by 40 years of age among the female survivors of HD. We hypothesized that patients with Hodgkin's disease who develop breast cancer have a genetic susceptibility to do so. The purpose of this proposal was to identify a subpopulation among the survivors of Hodgkin's disease, at an increased risk for developing breast cancer, and to institute intervention in the form of active screening and possibly chemoprevention. Construction of pedigrees of patients with secondary breast cancer has failed to reveal excess cancer among family members. We also planned to identify somatic and/or germline mutations in candidate genes known to be associated with breast cancer, including p53, BRCA1 & , and ATM. Four of the six breast cancer samples examined so far, contained mutations in exons 5-9 of the p53 gene. Three of three peripheral blood samples from patients with secondary breast cancer examined for mutations in the ATM gene have shown no mutations. We are recommending a baseline mammogram at 25 years of age, repeated every three years till the age of 40, and then annually. For patients with an increased risk of breast cancer due to other risk factors, we recommend annual mammograms, beginning at age 25 years. We propose to institute these recommendations among a limited number of member institutions of the Children Cancer Group – to address feasibility and compliance issues. In addition, we have initiated the process of updating the LESG cohort to identify new second cancers and associated risk factors..

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Table 1. Characteristics of the 17 patients with secondary breast cancer

LESGNO*	Age at HD**	Age at BC#	Years to BC	Status
252	6 yrs	34.5 yrs	28.5 yrs	Alive
256	12 yrs	16.3 yrs	4.3 yrs	Alive
257	14 yrs	22.3 yrs	8.2 yrs	Alive
448	15 yrs	28.7 yrs	13.7 yrs	Dead
454	11 yrs	32.1 yrs	21.1 yrs	Alive
596	13 yrs	15.4 yrs	2.4 yrs	Alive
606	15 yrs	37.3 yrs	22.3 yrs	Alive
629	14 yrs	39.0 yrs	25.0 yrs	Alive
642	15 yrs	37.1 yrs	22.1 yrs	Alive
674	14 yrs	27.1 yrs	13.1 yrs	Alive
701	12 yrs	38.4 yrs	26.4 yrs	Alive
756	12 yrs	36.2 yrs	24.2 yrs	Alive
914	15 yrs	25.0 yrs	10 yrs	Alive
2174	14 yrs	29.8 yrs	15.8 yrs	Dead
2175	14 yrs	42.0 yrs	28.0 yrs	Unknown
2176	12 yrs	36.3 yrs	24.3 yrs	Dead
2253	13 yrs	30.8 yrs	17.8 yrs	Unknown

*LESGNO denotes Late Effects Study Group Number # BC denotes breast cancer

** Age at HD dnotes age at diagnosis of Hodgkin's disease

Late Effects Study Group

The Late Effects Study Group (LESG) consists of 15 institutions from the United States, Canada and Western Europe, and is involved in studying Long-Term Complications following childhood cancer. The following institutions are included in the LESG:

Dana-Farber Cancer Institute, Boston
Columbus Children's Hospital, Columbus
Children's Hospital of Philadelphia
Children's Memorial Hospital, Chicago
Roswell Park Memorial Institute, Buffalo
University of Minnesota, Minneapolis
Children's Hospital of Los Angeles, LA
Institut Gustave-Roussy, Villejuif, France
Children's Hospital Medical Center, Cincinnati
Children's NationalMedical Center, Washington DC
Children's Hospital of Pittsburgh
Hospital for Sick Children, Toronto
Emma KinderZiekenhuis, Amsterdam
Royal Manchester Children's Hospital, England
Istituto Nazionale Tumori, Milan, Italy

KEY RESEARCH ACCOMPLISHMENTS

- Specific Aim 1: Obtained pedigree information on all patients with secondary breast cancer. Analyzed data for excess risk in the family members and published results in Lancet. (Bhatia S, Meadows AT,Robison LL. Family History of Breast Cancer after Treatment of Hodgkin's Disease in Childhood. *Lancet* 1997;350:888-889, see Appendix).

- Specific Aim 2: Efforts are ongoing to obtain all relevant tissue and blood samples for examining mutations in the candidate genes.

- Specific Aim 3: Have made recommendations for screening Hodgkin's disease survivors at high risk for development of breast cancer (submitted for publication to Annals of Internal Medicine: Manuscript provided in the Appendix). We propose to institute these recommendations as a limited institution study – to assess the feasibility and compliance.

- Specific Aim 4: Have initiated the process of updating the cohort.

REPORTABLE OUTCOMES

Publications

1) Bhatia S, Meadows AT, Robison LL. Family History of Breast Cancer after Treatment of Hodgkin's Disease in Childhood. *Lancet* 1997;350:888-889.

2) Bhatia S, Hudson M, Meadows, AT, Robison LL: Screening for Breast Cancer in Survivors of Childhood Hodgkin's Disease (Submitted, 1999).

3) Bhatia S, Meadows AT, Robison LL. Second Cancers after Pediatric Hodgkin's Disease. (*J Clin Oncol* 1998;16:2570-1).

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.)

LONG-TERM sequelae of the treatment of Hodgkin's disease are being encountered with increasing frequency because of the marked improvement in survival.[1-4] Second neoplasms, particularly acute myelogenous leukemia, are well-known late complications in patients who have been treated for Hodgkin's disease as adults.[5-15] 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[16] and others.[17,18] 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.[16] To investigate further the incidence of second neoplasms after 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.

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Supported by the University of Minnesota Children's Cancer Research Fund and a Public Health Service Training Grant (T32 CA09607) from the National Cancer Institute.

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-

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[16] 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[19]) 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 Vandenbroucke.[20] Cumulative probabilities of second neoplasms were calculated with actuarial methods.[21] 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). 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.

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.

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 (±SE) alkylating-agent score than those presenting with early-stage disease (2.4±0.06 vs. 1.2±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±0.08 vs. 1.2±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 presented with early-stage disease and had no subsequent recurrence (mean score, 3.4±0.1 vs. 0.9±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

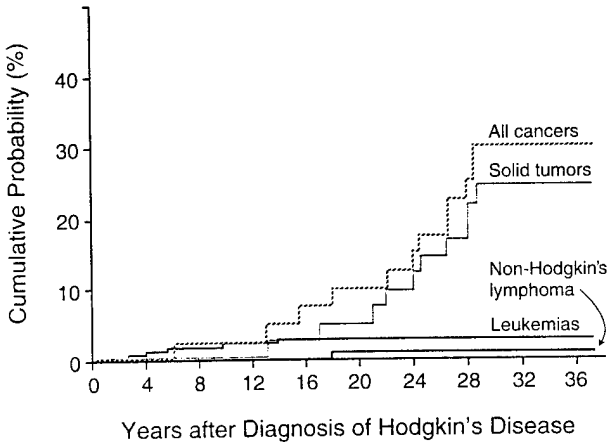

Figure 1. Cumulative Probability of Second Cancers in 1380 Patients with Hodgkin's Disease in Childhood.

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 (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 (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 (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 (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 (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 (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 disease (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)
			%
Leukemia			
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)
Non-Hodgkin's lymphoma			
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)
Solid tumors			
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.[17]

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[19] 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).[22]

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.[23-28] 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.[17,18,29-33] 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.[34] 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.[35] 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.[35] 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.[27] 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.[13] The dose-dependent association of alkylating agents with secondary leukemia and non-Hodgkin's lymphoma has been reported by others.[15,16] 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.[17,36-44] 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 ($P=0.09$),[16] 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-

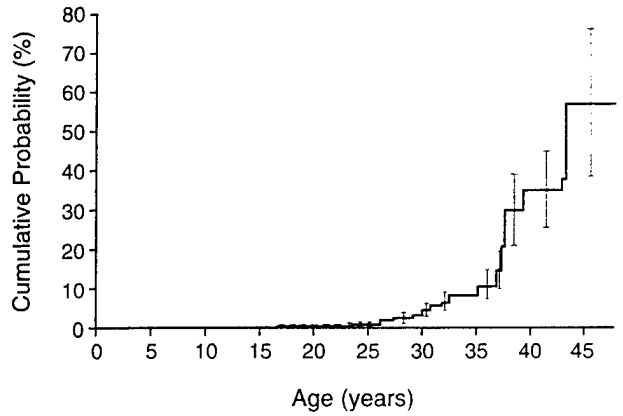

Figure 2. Cumulative Probability of Breast Cancer as a Function of Age in the Cohort of Female Survivors of Hodgkin's Disease in Childhood.

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

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Continuous hyperfractionated accelerated therapy in non-small-cell lung cancer

SIR—Michele Saunders and colleagues (July 19, p 161)[1] describe the treatment of inoperable non-small-cell lung cancer (NSCLC) irradiated with one of the most inventive radiation therapy regimens currently under investigation. The design, data management, and results of this randomised trial are impressive and clearcut; it shows a significant increase in survival of patients irradiated with 54 Gy in the continuous hyperfractionated accelerated radiotherapy (CHART) group.

A major obstacle to tumour clearance in the treatment of NSCLC is local failure. Two different treatment strategies can be adopted to overcome this obstacle. The first is to reduce the overall treatment time of radiation therapy, assuming that repopulation of tumour cells during therapy contributes significantly to treatment failures. CHART addresses this hypothesis by reducing the overall treatment time from about 6 weeks to 12 days. The results indicate that repopulation does indeed have a negative role in radiotherapy of human cancers. The second strategy is to increase the total dose to about 70 Gy either conventionally fractionated or with hyperfractionated radiotherapy. After 60 Gy, 2-year survival of 13–20% can be expected, which is supported by the results for the control group in the CHART trial.[1–3] Increasing the total dose to about 70 Gy can increase 2-year survival to 25–29%,[2–4] which compares favourably with CHART. Perhaps an increase in the total dose with CHART might further improve the results. However, normal tissue toxicity might limit a substantial increase in dose. 54 Gy with CHART produced severe dysphagia and paraesthesia in the lower limbs, which did not occur in the control group. Such paraesthesia suggests a decreased radiation tolerance of the spinal cord if three fractions daily are given with interfraction time intervals of 6–8 h. The spinal cord dose should probably be limited to 30–35 Gy in CHART.

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Chemotherapy for lung cancer

SIR—In his July 19 commentary on the CHART trial Everett Vokes[1] suggests that induction chemotherapy for stage III non-small-cell lung cancer has been validated by two important randomised trials and a meta-analysis, and is currently standard therapy.

One of the randomised trials cited showed an increased 5-year survival rate of 7% versus 17%;[2] the actual numbers of patients alive at 5 years were four in the radiotherapy arm and 12 in the combined treatment arm, which may be regarded as too few patients on which to base definitive conclusions. Interestingly, the disease-free survival at 5 years was identical—ie, four patients in each category—and was subsequently better in the radiotherapy arm, but there were fewer than four patients in each arm. Moreover, the response rate, though higher in the combined treatment arm, was not significantly different in the two arms of the study ($p<0·092$). So if there were a survival advantage with induction chemotherapy it must be unrelated to antitumour treatment. A reasonable interpretation is that the differences in outcome probably reflect biological differences in the disease or in the supportive measures used.

The second randomised trial cited was larger and included some stage II cases. It also emphasised the importance of careful preselection criteria for these treatments.[3] Although a survival difference was detected, it was 2·4 months rather than 4·1 months, as reported by Dillman and colleagues.[2] In fact the difference in median survival between the hyperfractionated radiation therapy and combined treatment groups was only 1·5 months. In a 3-year follow-up of the second study,[3] the differences between the groups decreased slightly and the survival difference between hyperfrationated radiation therapy and combined therapy was 1%.[4]

The meta-analysis suggests a benefit for chemotherapy of early-stage surgical patients but no demonstrable advantage for stage III surgical patients.[5] For surgery and radiotherapy in stage III cases an advantage was present. In all instances of benefit the effect was modest. We do not regard induction chemotherapy as the standard treatment for non-small-cell lung cancer stage III, but as an option to be considered for carefully selected patients and those included in clinical trials.

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Family history of patients with breast cancer after treatment of Hodgkin's disease in childhood

SIR—Sabine Kony and colleagues (July 12, 91–95)[1] report that both genetic factors and exposure to ionising radiation have independent effects on the risk of second malignant neoplasms after a first cancer in childhood. Compared with patients who had no family history of early-onset cancer, those with one or more affected family members had a 4·7-fold increased risk of developing a second malignant neoplasm. The role of genetic predisposition in the development of a second malignant neoplasm has been explored by Strong and colleagues, who showed that p53 germline mutation carriers among relatives of patients with soft tissue sarcomas are at increased risk for second malignant neoplasms.[2]

In a recent study of the Late Effects Study Group (LESG),[3] we found an increased risk of breast cancer among female survivors of Hodgkin's disease diagnosed in childhood (standardised incidence ratio [SIR] 75·3), with the estimated actuarial incidence approaching 35% by age 40. Age at time

History of cancer in family members	Observed	Expected	SIR (95% CI)
All relatives	19	30·9	0·6 (0·4–0·9)
Relatives of probands ≤13 years at diagnosis of HD	10	12·3	0·8 (0·4–1·4)
Relatives of probands >13 years at diagnosis of HD	9	18·6	0·5 (0·2–0·9)
Relatives of probands ≤34 years at diagnosis of BC	13	12·7	1·0 (0·5–1·7)
Relatives of probands >34 years at diagnosis of BC	6	18·2	0·3 (0·1–0·6)
First-degree relatives	3	5·8	0·5 (0·1–1·3)
Maternal relatives	13	13·2	1·0 (0·5–1·6)
Paternal relatives	6	17·1	0·4 (0·1–0·7)

BC=breast carcinoma. HD=Hodgkin's disease.

Risk of cancer in relatives of patients (in LESG cohort[2]) with secondary breast cancer according to age of proband and relationship to proband

of radiation (10–16 years: relative risk 1·7) and radiation dose (relative risk 5·9) were associated with significantly increased risk. This finding suggests that pubertal breast tissue is especially sensitive to the carcinogenic effects of ionising radiation. Others have reported an increased risk of breast cancer after radiation therapy for Hodgkin's in this age group.[4] However, the influence of well established risk factors for breast cancer (eg, a family history) on the development of radiation-associated tumours have not been explored yet.

We studied the role of genetic predisposition (as measured by family history of cancer) in the development of breast cancer among the LESG cohort of survivors of Hodgkin's disease in childhood. Of 17 women with breast cancer identified in this cohort,[3] 13 probands (76%) or their surviving next of kin were available for construction of pedigrees. The median age at diagnosis of Hodgkin's disease for these patients was 13 years (range 7–15 years), and that for breast cancer was 34 years (range, 24–40 years). 19 family members among the 180 first-degree and second-degree relatives (total follow-up of 9351 person-years) were reported to have had cancer. Observed and expected cases (with cancer incidence rates from the Surveillance, Epidemiology, and End Results Registry[5]), standardised incidence ratios (SIR), and 95% CI were calculated.

Overall, there was a significantly decreased risk of cancer among the family members (SIR 0·6, 95% CI, 0·4–0·9) (table). Breast cancer was reported in three family members (median age at diagnosis, 59·5 years; range 46–70 years). There was no excess of breast cancer overall or in any of the subgroup of relatives examined.

Thus in an expanded assessment of the 13 cases with breast cancer developing at a young age after treatment for Hodgkin's disease, we did not find any evidence of familial aggregation of cancer (breast or otherwise) among family members. However, the influence of other well established risk factors for the development of breast cancer, and biomarkers of genetic susceptibility (mutations in candidate genes), need to be explored in future studies, in order to identify high-risk populations.

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Stress, bottlefeeding, and diabetes

SIR—David J Pettitt and colleagues (July 19, p 166)[1] report a two-fold higher rate of type 2 diabetes in bottlefed Pima Indians. Their interpretation of this important observation, based on a nutritional thrifty hypothesis, is debatable. A limitation of the thrifty hypothesis is that it addresses only overnutrition and physical inactivity as contributing factors, and overlooks stress associated with urbanisation, as an important secular change. Although type 2 diabetes has been proposed as a civilization disease,[2] or one of the stress disorders,[3] the role of stress in the pathogenesis of type 2 diabetes has been hard to prove.

Studies in non-human primates by Harry Harlow[4] and others have shown that early mother–child separation or lack of contact comfort from the mother in early infanthood are among the most potent stressors to infants, contributing to abnormal behaviour, immune dysfunction, and raised concentrations of cortisol, which may have longlasting consequences later in life. The mother-child bond formed by breastfeeding has a positive effect on a child's physical and emotional development and health.[5] So, an alternative explanation for Pettitt and co-workers' observation of a link between bottlefeeding and type 2 diabetes could be that bottlefeeding may not involve the type of close contact with the mother that is associated with breastfeeding. This difference could be a psychological stressor superimposed on to other genetic and environmental risk factors for diabetes in the Pima Indians at this susceptible time of life. Bottlefeeding may lack not only a satiety signal, but also the kind of intimate interaction between mother and child provided uniquely by breastfeeding.

It would also be interesting to compare the life stress events for Pima mothers during pregnancy and postpartum in the two feeding groups, and to identify underlying causes of bottlefeeding, since psychological stress can affect lactation. Bottlefeeding is often chosen because of lack of milk production, lack of interest in breastfeeding, little time or energy for breastfeeding at home or work, physical or mental illnesses, or absence of the mother. All these factors may be associated with psychological stress for both mother and infant.

If bottlefeeding is a marker of psychological stress for the mother and child, the mysterious links between type 1 diabetes and cow's milk, as well as between type 2 diabetes and bottle-feeding, might be partly explained by a cascade of stress-activated hypothalamic-pituitary-adrenal-axis events.[3] For an individual or ethnic group with genetic defects involving the processes of insulin secretion or insulin action, an additional stressor, such as bottlefeeding in the neonatal period, could hypothetically trigger the pathogenesis of diabetes, by alterations in the immune system targeted on β-cell destruction (in type 1 diabetes) or in glucose metabolism, insulin secretion, or insulin sensitivity (in type 2 diabetes).

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Recommendations for Screening Survivors of Childhood Hodgkin's Disease for Breast Cancer

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ABSTRACT

There has been a marked improvement in survival following Hodgkin's disease in childhood, with five-year survival rates now approaching 90%. With this improvement in survival, increasing attention is being focused on long-term sequelae, including second neoplasms. Women with Hodgkin's disease who receive mantle irradiation have been observed to be at an increased risk of breast cancer. Results from several studies show that 10 or more years after radiation, the overall breast cancer risk is increased approximately four-fold and can be as high as 75-fold in girls exposed to radiation at puberty, thus indicating that the risk of breast cancer after irradiation for Hodgkin's disease is influenced by the age at radiation exposure, with the highest risk seen among women irradiated at puberty. Since the increased risk of breast cancer may persist for decades after irradiation, survivors of childhood Hodgkin's disease should be monitored carefully throughout their lives. We recommend a baseline mammogram at 25 years of age, repeated every three years until the age of 40, and then annually. For patients with an increased risk of breast cancer due to other risk factors (family history of breast cancer, younger age at menarche, nulliparity or older age at first live birth), we recommend annual mammograms, beginning at age 25 years. Self-breast examination every month and clinical breast examination every six months, beginning at age 15 years (or later for those diagnosed and treated after 15 years of age), are also recommended.

Hodgkin's disease is the fourth most common neoplasm in children less than 20 years of age, with an annual incidence of 1.2 per 100,000.[1] Over the last three decades there has been a marked improvement in survival, with five-year rates now approaching 90%.[2,3] Because of this improvement in survival, long-term sequelae of Hodgkin's disease and its treatment such as second neoplasms are now being encountered.[4-12] In contrast to the risk of treatment-related leukemia, which does not appear to extend beyond 10 years,[11] the risk of developing a solid tumor continues beyond 15 years (Figure 1).[9,12,13] This is the most important problem facing Hodgkin's disease patients and their physicians today.

Women with Hodgkin's disease who receive mantle irradiation are at an increased risk of breast cancer.[13,14,15] Results from several registries show that 10 or more years after radiation, the overall breast cancer risk is increased approximately four-fold,[16-25] and can be as high as 33- to 75-fold, in girls exposed to radiation at puberty.[13] The risk of developing breast cancer remains elevated through the entire follow-up period.[13] Moreover, follow-up of a cohort of female Hodgkin's disease survivors diagnosed and treated for Hodgkin's disease before 16 years of age, showed that the actuarial estimated cumulative probability of developing breast cancer approached 35±9% at 40 years of age (Figure 2).[13] Table 1 shows the risk of breast cancer as a second neoplasm following Hodgkin's disease, according to age at diagnosis of Hodgkin's disease, and latency from treatment for Hodgkin's disease.[6,13,16-27]

The high risk of breast cancer in women exposed to radiation for the treatment of Hodgkin's disease during adolescence raises important issues about cooperative efforts among institutions to mount prospective screening programs including breast physical examination, sonography, mammography or quantitative magnetic resonance imaging for these patients.

Although breast cancer is a heterogeneous disease, with a wide range of growth patterns, most breast cancer has a long preclinical phase. The median doubling time for breast cancer may be 100 to 200 days,[28,29] and the preclinical lead time gained by screening is two to four years compared to clinical detection.[30-32] Moreover, treatment of early stage disease is more effective than treatment of late-stage disease. There is convincing and unequivocal evidence that breast cancer screening with mammography reduces the breast cancer mortality rate for screened compared to control-group women by approximately one third.[33] The most conservative recommendation for average risk women is annual or biannual screening mammography for ages 50 to 69[34], or perhaps ages 50 to 74[32]. The American Cancer Society (ACS) and the National Cancer Institute (NCI) now recommend regular mammograms for average-risk women in their 40s, although the recommended intervals differ (yearly for the ACS and every 1 or 2 years for the NCI).[35,36]

When screening mammography is performed in asymptomatic average-risk women younger than 35 years old, it is reported to be of little value.[37,38] These findings are not surprising if one considers the low prevalence of breast cancer in women less than 35 years old and the possibly diminished sensitivity of mammography in these

women (increased density of glandular breast tissue in younger women).[39] However, it seems that early-onset breast cancers are readily evident on mammography. Meyer et al reported 28 out of 31 (90%) cancers in women younger than 35 were visible on mammography.[40] Morrow reported that 34 of 42 (81%) cancers in women aged 40 years and younger had mammographic abnormalities.[41] Yahalom et al reported mammographic abnormalities in 81% of the patients diagnosed with secondary breast cancer diagnosed at a median age of 27 years.[26] Dershaw et al identified a subpopulation of 27 women with 29 breast carcinomas who had previously undergone treatment for Hodgkin's disease and for whom mammograms were available.[42] Nine patients were younger than 40 years at diagnosis of breast cancer. Mammography demonstrated 26 of the 29 cancers (90%); *11 of the 29 cancers (38%) were detected only with mammography.*

If the prevalence of breast cancer is higher, as in high risk populations, then screening at a young age may be justified. Mammographic screening for breast cancer beginning at age 25 has been advocated for women from families with multiple first-degree relatives affected with breast cancer, particularly when the disease had been diagnosed premenopausally and was bilateral.[43] Recommendations for breast cancer surveillance for carriers of BRCA1 and BRCA2 mutations include monthly breast self-examination beginning early in adult life (e.g. by age 18-21 years), annual or semiannual clinician examination beginning at age 25 to 35 years, and annual mammography, beginning at age 25 to 35 years.[44]

A prospective program of breast physical examination with screening mammography conducted within large institutional settings will help define rational screening recommendations for patients with Hodgkin's disease, who are at an increased risk for secondary breast cancer. The issues that need to be addressed include the following:

i) defining a high risk population

ii) minimum age to initiate screening, and frequency of screening

iii) evaluation of sensitivity, specificity and predictive value for screening in younger women.

I) Defining a High Risk Population

Review of reports from the literature identify three important risk factors for the development of secondary breast cancer following treatment for Hodgkin's disease: a) irradiation; b) age at irradiation; and c) genetic predisposition.

a) Irradiation

A dose-dependent relationship between irradiation and risk of subsequent breast cancer has been reported frequently. Results of the Late Effects Study Group[13] showed that 16 of the 17 patients had developed breast cancer within or at the margin of the radiation field. Moreover, patients with breast cancer received a higher dose of radiation to the mantle (median 4000 cGy) as compared to those who did not develop breast cancer (median 2000 cGy, $p=0.05$). Multivariate analysis revealed radiation to be associated with an increased risk in a dose-dependent fashion (as compared with a

radiation dose of < 2000 cGy, the relative risk for a dose between 2000 and 4000 cGy was 5.9 [95% CI, 1.2 to 30.3], and the relative risk for a dose exceeding 4000 cGy was 23.7 [95% CI, 3.7 to 152.3]. Twenty-three of the 25 breast cancers in the Hancock study[15] developed in patients who had received > 4000 cGy to the mantle region (SIR=4.3, 95% CI, 2.6 to 6.1). One patient had received 3000-3900 cGy, and one had not received any radiation. Thus a higher dose of radiation to the mantle region was associated with an increased risk of secondary breast cancer.

b) Age at diagnosis and treatment of Hodgkin's Disease

Table 1 summarizes the reports in the literature on risk of secondary breast cancer by age and latency. Multivariate analysis of the LESG Hodgkin's disease cohort[13] showed that age between 10 and 16 years (as compared to less than 10 years) at diagnosis of Hodgkin's disease was independently associated with an increased risk of developing secondary breast cancer (RR=1.9; 95% CI, 1.1 to 3.2). Hancock's study[15] showed age at irradiation strongly influenced risk (22 of the 25 breast cancers developed in patients who were less than 30 years of age at diagnosis of Hodgkin's disease): RR was 136 for women treated before 15 years of age, declined with age at irradiation, but the elevation remained statistically significant for subjects less than 30 years old at the time of irradiation (for those 15-24 years, RR=19; for those 24-29 years, RR=7). In women above 30 years of age, the risk was not elevated (RR=0.7).

Using the results of these two studies, it would seem that the risk for developing secondary breast cancer is increased for patients diagnosed and treated for Hodgkin's

disease between 10 and 30 years of age, and is greatest for patients in the second decade at diagnosis and treatment of Hodgkin's disease.

c) Genetic predisposition

Primary breast cancer has been attributed to a genetic predisposition associated with the BRCA1 and BRCA2 genes in 5% to 10% of patients. In addition to these two genetic loci, other germ-line mutations may confer some susceptibility to radiation-associated breast cancer. These mutations include the tumor-suppressor gene p53 and the ataxia telangiectasia (AT) gene. In vitro data indicate that the p53 tumor-suppressor gene is an important participant in the cellular response to ionizing radiation. Cells lacking in p53 are unable to arrest the cell cycle to repair DNA damage or enter into apoptotic cell death following irradiation.[45] Heterozygotes for the AT gene are five times more likely to develop breast cancer than are non-carriers. People with this genetic background appear to be particularly sensitive to the effects of ionizing radiation.[46] In a study to evaluate the role of genetic predisposition (as measured by family history of cancer) in the development of breast cancer among the LESG cohort of survivors of Hodgkin's disease in childhood,[13] the authors failed to demonstrate any evidence of familial aggregation of cancer (breast or otherwise) among family members.[47] The role of genetic predispostion, and its interaction with radiation, and other risk factors in the development of breast cancer after Hodgkin's disease is unclear and needs to be explored further.

II) MINIMUM AGE TO INITIATE SCREENING AND FREQUENCY OF SCREENING

a) Routine self breast examinations /clinical breast examinations

Breast self-exams and clinical breast exams are probably equally important as mammography in this population, but neither has been properly evaluated. There is indirect evidence from the HIP study (Health Insurance Plan of Greater New York) in favor of a benefit from clinical breast exam, by skilled examiners, especially in women aged 40 to 49.[48] The American Cancer Society recommends clinical breast examination (every three years for women between the ages of 20 and 40 and then annually) and breast self-examination (monthly, beginning at age 20).[49]

In the absence of additional data, screening guidelines to perform monthly breast self-exams beginning at age 15 or at end of therapy for Hodgkin's disease (if age at diagnosis is greater than 15 years) are appropriate. In this high-risk population it is critical that patients be properly instructed, with confidence in and accuracy of breast self-examination increasing with training. A clinical breast exam should be performed by a physician or other health care professional on a regular basis (at least twice per year), beginning with each follow-up visit at age 15 years or, for patients older than 15 years at diagnosis of Hodgkin's disease, beginning as soon as they finish therapy.

b) Mammography

We recommend that survivors of childhood Hodgkin's disease treated with thoracic irradiation have their first mammogram at 25 years of age. This is based on prior studies that have shown that the pubertal breast tissue (10 to 16 years of age) is

especially sensitive to the carcinogenic effects of ionizing radiation, with excess cancers typically developing after a latent period of 10 or more years.[13,16-27,50] Moreover, secondary breast cancers were detected at a median age of 28 to 32 years, for patients diagnosed and treated for their primary Hodgkin's disease in puberty.[13,27] We recommend screening mammograms every 3 years after the baseline mammogram (unless clinical findings or the presence of other known risk factors such as a mother, sister or daughter with breast cancer history, younger age at menarche, nulliparity or older age at first live birth, dictate a more frequent evaluation), and annual screening beginning at 40 years of age. Mammograms should be done at a consistent location when possible, with prior films for comparison. Individuals should be counseled that the risks and benefits of mammography before age 50 years are not established and that benefits for women aged 50 years and older are based on studies of average-risk women.

The stated "risks" from mammography (i.e. false positive results, false negative results, anxiety, and a potential increased cancer risk associated with early and repeated radiation exposure) should be quantified and efforts made to minimize adverse consequences associated with the limitations of mammography. All of these problems have been reported to be more frequent in younger women: screening misses up to a quarter of cancers in younger women (compared with a tenth in older women), and the false positive rate is higher in younger women, leading to more benign biopsies, increased costs, and greater anxieties.[51] Diagnostic radiation exposure has been estimated to account for fewer than 1% of all breast cancer cases, with

mammography accounting for only 10% of diagnostic exposure.[52] The risk of radiation-induced cancer may be regarded as an adverse side effect of mammography, but must be balanced against the likelihood of a cancer being present and detected, and hence the adverse effect of any such cancer remaining undetected if mammography is not performed.

In a recent report, Joseph et al[53] suggest that survivors of childhood cancer be screened for breast cancer with a clinical breast exam every six months, and yearly mammography, beginning 10 years after the diagnosis of childhood cancer. Van Leeuwen et al[7] also strongly recommend breast palpation and yearly mammography beginning 10 years after the initial treatment of the primary cancer, as do Goss and Sierra[54], who recommend initiating mammography eight years post-radiation. Our recommendations are to initiate monthly self-breast exam and biannual clinical breast exam at age 15 years or after completion of treatment for Hodgkin's disease (for patients diagnosed with Hodgkin's disease after the age of 15). Baseline mammography is recommended for this group of survivors at age 25, with screening mammograms every three years after the first one, followed by annual mammography after age 40 years. Our recommendations appear to be slightly more conservative than the above authors,[7,53] but are similar to those proposed by Kaste et al,[27] who recommend initiation of screening mammography at age 25 years, repeated every 3 years till age 40, followed by annual mammographic exams thereafter. They also recommend breast self-exam and annual clinical breast exam starting at puberty.

These are, however, suggested guidelines, and the primary oncologists need to assess each survivor on an individual basis, when making the decisions.

III) Evaluation of sensitivity, specificity, predictive value for screening in younger women.

The ultimate goal of screening for a progressive disease is a reduction in mortality from that disease. The ideal way to assess the efficacy of screening is to conduct a randomized trial with cancer-specific mortality as the endpoint of interest. Unfortunately, an extended period of time may be required to observe any impact on mortality in this group of patients. Early indicators of the effectiveness of a screening test are the length of time the diagnosis is advanced by screening (lead time), and the sensitivity of the screening test. Using a model described by Straatman et al[55], it is possible to simultaneously estimate the mean lead time and the sensitivity when only the number of cancers detected at the successive screenings and the number of cancers occurring in the time interval between screening examinations are known. This model would be particularly useful in assessing the effect of screening when the underlying cancer incidence in the screened group (such as the survivors of Hodgkin's disease) is unknown.

Conclusions

There exists an increased risk of breast cancer among women treated with radiation to the chest for Hodgkin's disease in childhood, with the excess cancers

typically developing after a latent period of 10 or more years. Since the increased risk of cancer may persist for decades after irradiation, survivors of childhood Hodgkin's disease should be monitored carefully throughout their lives. We recommend a baseline mammogram at 25 years of age, repeated every three years till the age of 40, and then annually. For patients with an increased risk of breast cancer due to other risk factors, we recommend annual mammograms, beginning at age 25 years. Self-breast examination every month and clinical breast examination every six months, beginning at age 15 years (or later for those diagnosed and treated after 15 years of age), are also recommended.

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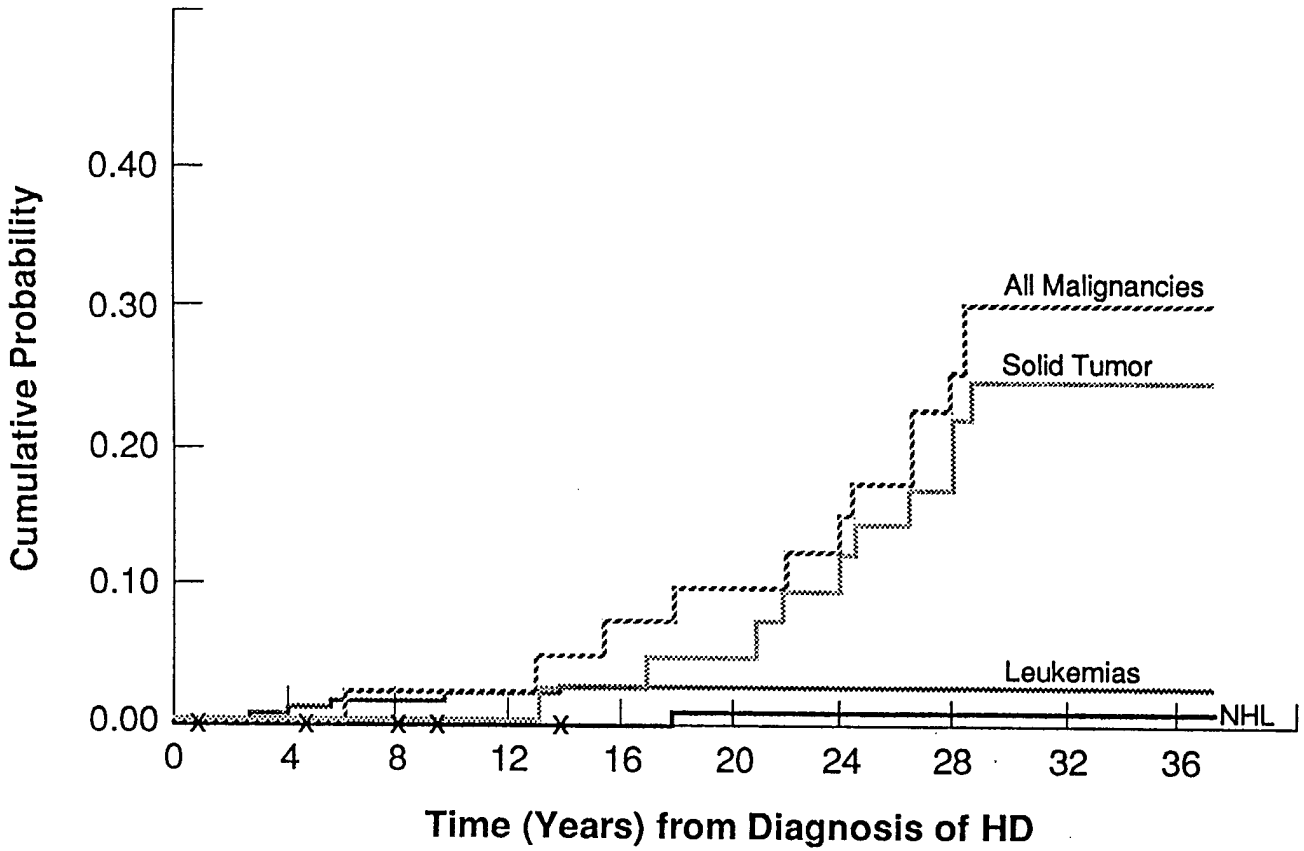
Table 1. Risk of Breast Cancer by Age and Latency

Study	Size of cohort	Length of follow-up	No. with BC‡	Median age at Dx of HD*/BC‡	Years to BC median)	Risk Factors	Outcome (% alive)
Yahalom et al[26] U.S. (1969-1991)	___**	___**	37	27/43 yrs	15 yrs	all received XRT¶	78%
Hancock et al[16] U.S. (1961-1989)	885	10 yrs	26	28/40 yrs all BC within XRT¶	15 yrs	age < 30 yrs	73%
Bhatia et al[13] LESG (1955-1986)	483	11 yrs	17	11/32 yrs 16/17 BC within XRT fields¶	19 yrs	10-16 yrs at HD	82%
Aisenberg et al[20] U.S. (1964-1984)	111	18 yrs	14	24/38 yrs all received XRT¶	18 yrs	age < 19 yrs	93%
Chung et al[18] U.S. (1962-1985)	136	___**	11	31/44 yrs	15 yrs	splenectomy	73%
Tinger et al[19] U.S. (1966-1985)	314	> 5 yrs	10	29/40 yrs	14 yrs	axillary dose > 36 Gy	50%
Kaste et al[27] U.S. (1962-1995)	257	10 yrs	6	14/28 yrs	14 yrs	all BC within XRT fields¶	___**
Sankila et al[6] Nordic countries (1943-1987)	670	10 yrs	16	16/__** yrs	> 10 yrs	all BC within XRTfields¶	___**
Travis et al[17] U.S. (1935-1992)	3869	___**	55	All ages/__**yrs	> 10 yrs	age < 16 yrs at Dx of HD	___**
Carey et al[22] U.S. (1964-1970)	164	___**	4	__**/37 yrs	11-17 yrs	all within XRT fields	___**
Tester et al[24] U.S. (1964-1981)	473	12 yrs	1	26/30 yrs	11 yrs	____**	100%
Kaldor et al[25] (1945-1984)	11,491	___**	62	__**/__**	10-15 yrs	____**	___**
Prior et al[21] U.K. (1950-1979)	2,999	6.7 yrs	9	__**/__**	10-19 yrs	all received XRT	___**
Cook et al[23] U.S. ((1936-1989)	133	___**	6	< 40/33.5 yrs	17.5 yrs	all received XRT	___**

* Dx of HD denotes diagnosis of Hodgkin's disease ; ‡Age at Dx of BC denotes age at diagnosis of breast cancer ; ** Information not available; ¶ XRT denotes radiation therapy


Cumulative Probability
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Solid Tumor
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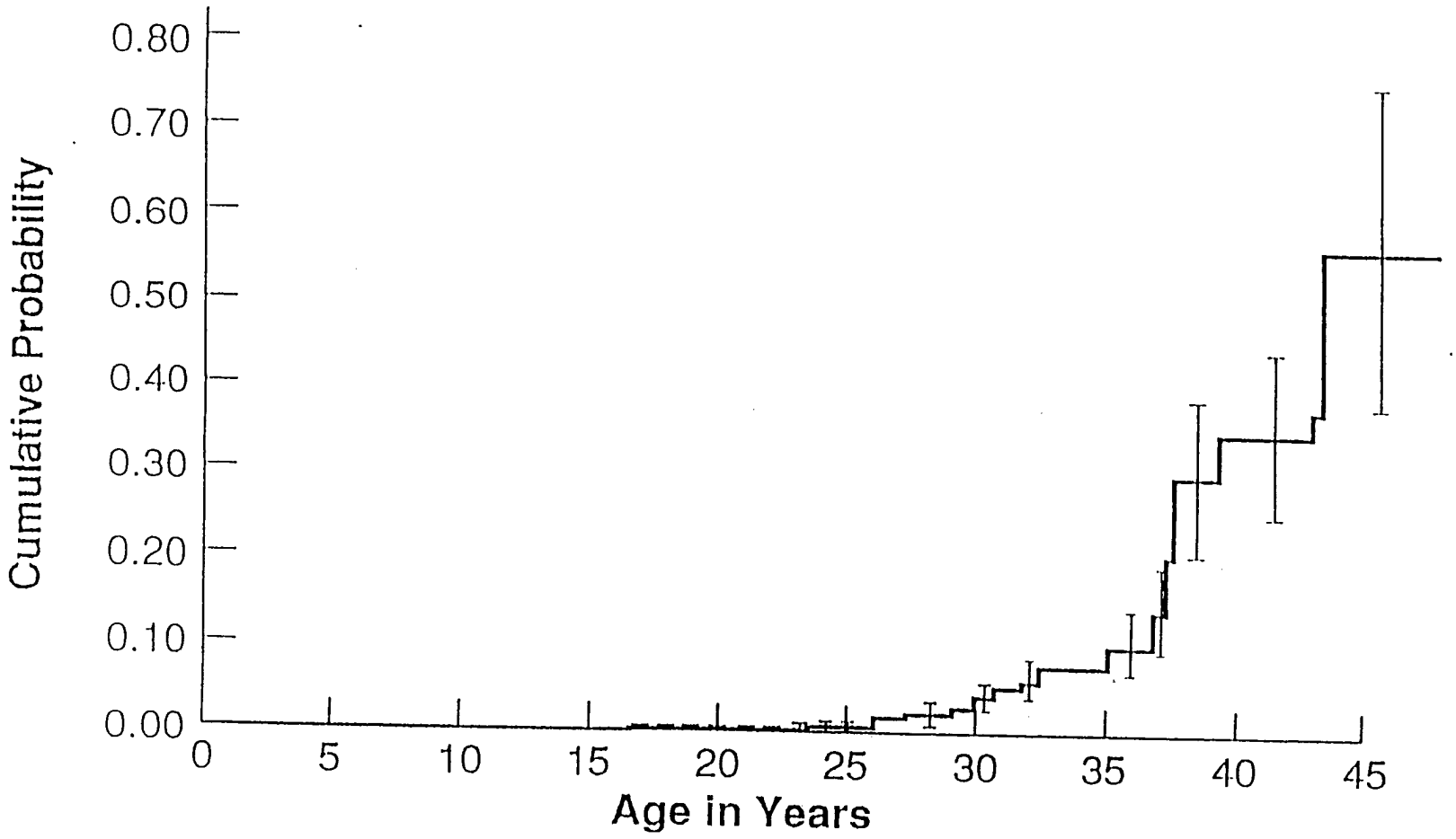
Time (Years) from Diagnosis of HD


Cumulative Probability
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