EFFECTS OF TREATMENT ON FERTILITY IN LONG-TERM SURVIVORS OF CHILDHOOD OR ADOLESCENT CANCER

JULIANNE BYRNE, PH.D., JOHN J. MULVIHILL, M.D., MAX H. MYERS, PH.D., ROGER R. CONNELLY, M.SC., M. DARLENE NAUGHTON, B.S., MARGOT R. KRAUSS, M.D., M.P.H., SANDRA C. STEINHORN, M.P.H., DAWN D. HASSINGER, M.D., PH.D., DONALD F. AUSTIN, M.D., M.P.H., KAY BRAGG, B.A., GRACE F. HOLMES, M.D., FREDERICK F. HOLMES, M.D., HOWARD B. LATOURETTE, M.D., PETER J. WEYER, M.S., J. WISTER MEIGS, M.D., M. JANE TETA, DR.P.H., JOEANN W. COOK, B.S., AND LOUISE C. STRONG, M.D.

Abstract In a retrospective cohort study of survivors of cancer and of controls, we estimated the risk of infertility after treatment for cancer during childhood or adolescence. We interviewed 2283 long-term survivors of childhood or adolescent cancer diagnosed in the period from 1945 through 1975, who were identified at five cancer centers in the United States. Requirements for admission to the study were diagnosis before the age of 20, survival for at least five years, and attainment of the age of 21. In addition, 3270 controls selected from among the survivors' siblings were interviewed.

Cox regression analysis showed that cancer survivors who married and were presumed to be at risk of pregnancy were less likely than their sibling controls to have ever begun a pregnancy (relative fertility, 0.85; 95 percent confidence interval, 0.78 to 0.92). Radiation therapy directed below the diaphragm depressed fertility in both sexes by about 25 percent. Chemotherapy with alkylating agents, with or without radiation to sites below the diaphragm, was associated with a fertility deficit of about 60 percent in the men. Among the women, there was no apparent effect of alkylating-agent therapy administered alone (relative fertility, 1.02) and only a moderate fertility deficit when alkylating-agent therapy was combined with radiation below the diaphragm (relative fertility, 0.81). Relative fertility in the survivors varied considerably according to sex, site of cancer, and type of treatment; these factors should be taken into consideration in counseling survivors about the long-term consequences of disease. (N Engl J Med 1987; 317:1315-21.)

CONTEMPORARY combined radiotherapy and chemotherapy, the double-edged sword that accounts for the increased survival among children and adolescents with cancer,[1] can also cause severe late complications, such as additional neoplasms, major organ dysfunction, and infertility.[2-4] Early menopause, azoospermia, and germ-cell destruction have all been observed after therapy.[5-7] Although the frequency of these events varies with factors such as the type, dose, and duration of treatment[8-10] and the sex and age of the patient,[11,12] there are no firm estimates of the magnitude of the risk involved and little data on the long-term consequences of treatment of childhood cancer.

At present, the number of survivors of childhood or adolescent cancer is substantial and can be expected to increase. About 45,000 patients in the United States who had childhood cancer diagnosed between 1955 and 1979 were estimated to be alive in 1984.[13] In the future, more types of cancer will be treated by adjuvant chemotherapy with cytotoxic agents.[14,15] Also, cancer drugs are being used more commonly in nonneoplastic conditions, in which the risk of death is lower and the need for safe therapy is greater.

To clarify and quantify the risk of infertility after childhood or adolescent cancer, we conducted a retrospective cohort study of long-term survivors of the disease, using siblings as the comparison group. Fertility among survivors of cancer is the end result of a complex set of choices and circumstances reflecting underlying biologic factors, with an array of psychosocial factors and individual characteristics related to treatment superimposed. In order to evaluate the long-term biologic consequences of treatment, we excluded from the main analyses men and women who did not wish to have children naturally and those who knew that they were sterile. For purposes of comparison and ease in interpretation, the results based on the entire group of eligible subjects are also presented.

From the Clinical Epidemiology and Biometry Branches, National Cancer Institute, Bethesda, Md.; the California State Department of Health Services, Emeryville; Yale University, New Haven, Conn.; the University of Iowa, Iowa City; the University of Kansas, Kansas City; and the University of Texas–M.D. Anderson Hospital, Houston. Address reprint requests to Dr. Byrne at the Landow Bldg., Rm. 8C41, National Cancer Institute, NIH, Bethesda, MD 20892.

METHODS

Identification of Subjects

In this study, five cancer registries (California Department of Health Services, Yale University for the Connecticut Tumor Registry, the University of Iowa, the University of Kansas, and the University of Texas–M.D. Anderson Hospital) collaborated with the National Cancer Institute. Each center identified all survivors in its records who met the following requirements for eligibility: a first, histologically diagnosed malignant neoplasm or any central nervous system neoplasm in a person less than 20 years old at diagnosis, a diagnosis made any time from 1945 through 1975; survival for at least five years after the date of diagnosis, and attainment of 21 years of age by December 31, 1979. After an interview, survivors were asked to grant us permission to review hospital and physician records and to contact siblings. When possible, up to two controls were selected from among the survivor's siblings. Controls, who had to have been 19 years of age or older by December 31, 1979, were matched to the survivors as closely as possible in regard to full sibship, sex, and date of birth (in that order). Controls were allowed to be eligible at age 19 so that a sibling younger by up to two years could be a control for a 21-year-old survivor. A total of 2498 survivors and 3604 controls were identified.

Data Collection

Interviews were conducted by specially trained interviewers; field work began in August 1980 and ended in April 1983. Subjects or their proxies (spouses, parents, or other family members) were in-

terviewed in person whenever possible. Telephone interviews were done either because subjects lived a long way from a center or for other reasons, such as privacy considerations. The interview lasted for 45 to 60 minutes and dealt with demographic characteristics of subjects and their parents, the medical history (including a history of cancer or benign tumor), exposures to drugs, viruses, and x-rays that may affect pregnancy, and the family medical history. All questions were asked of all subjects, with these exceptions: controls were not asked about family history, and proxies were not queried about the subjects' birth control history or other personal matters. Details regarding the survivors' tumors and treatments were abstracted from tumor-registry and other hospital records.

The interview response rate was 91 percent in both study groups. Reasons for not interviewing a subject included a failure to locate the subject or a refusal by a subject, physician, or subject's next of kin. There were no statistically significant differences between survivors and controls with respect to center, sex, or race. Proxy interviews were obtained for 10 percent of the survivors and 4 percent of the controls. The most frequent reason for a proxy interview was the death of the subject; other reasons included mental incompetence or an inability to locate the subject. Telephone interviews were conducted with 30 percent of the survivors and 41 percent of the controls. Overall, 8 percent of the survivors died between the time they became eligible for the study and the date of the interview, as compared with 1 percent of the controls. At the time of follow-up, the survivors were slightly younger than their sibling controls (32.4 vs. 33.8 years).

Cancer Sites and Treatment

We obtained copies of the original pathology reports when possible; otherwise, we accepted the inclusion of subjects by the tumor registry as evidence of a diagnosis of cancer. Hodgkin's disease was the most common type of cancer in the study (21 percent of cases). Soft-tissue sarcomas, thyroid cancers, and tumors of the brain and central nervous system, in approximately equal numbers, constituted another 37 percent of cases.

Results are presented only for the treatment received within the first 12 months after the diagnosis of cancer. Six categories of treatment were defined: no radiotherapy or chemotherapy (most patients in this group were treated with surgery only) (636 survivors); radiotherapy only (no chemotherapy) (417 survivors), subdivided according to whether the radiation was directed above or below the diaphragm (218 and 153 survivors, respectively, and 46 survivors with an unknown radiation site); alkylating-agent chemotherapy only (55 survivors); and therapy with alkylating agents and radiation (74 survivors), again subdivided according to whether the radiation treatment site was above or below the diaphragm (27 and 45 survivors, respectively, and 2 survivors with an unknown radiation site). Patients who received radiation both above and below the diaphragm were counted in the "below" group. Patients in the last five groups may have received surgical treatment as well. The six categories included all survivors except 50 who were treated with chemotherapy other than alkylating agents (some of whom were also given radiotherapy). Because of their small number they were excluded from the main analyses, but their fertility characteristics are described in this report. The alkylating agents used were chlorambucil, cyclophosphamide, mechlorethamine, procarbazine, triethylenethiophosphoramide, busulfan, and melphalan.

Data Analysis

Two groups of study subjects were defined with use of a series of exclusions (Table 1). Only 3 percent of pregnancies occurred among unmarried or non-cohabiting subjects; therefore, only married or cohabiting survivors were included in the analysis. Nine controls who had had a childhood or adolescent cancer were excluded; 113 survivors who married before their cancer was diagnosed were also excluded because of the inverted sequence of events. A number of women who became pregnant or men who fathered a child before their first marriage were excluded because their interval between marriage and pregnancy was "negative" and therefore they could not be included in the proportional-hazards analysis.

Finally, we excluded other subjects because of known sterility or voluntary infertility. Among the 62 who were known to be sterile before their first marriage were 7 women who had never menstruated, 21 women with secondary amenorrhea, and 34 people who had had sterilizing surgery. The results presented in Tables 2, 3, and 4 and in Figures 1 to 3 apply to the subjects remaining after all the exclusions — i.e., those presumed to be at risk of pregnancy. Table 4 also shows the relative fertility associated with treatment before the exclusion of subjects who were at little or no risk of pregnancy.

Table 1. Exclusion of Subjects from Study Analysis.

	No. of Survivors	No. of Controls
Subjects eligible for study	2498	3604
Not interviewed	215	334
Unknown length of time from marriage to first pregnancy	22	43
Control's cancer diagnosed before age 20	—	9
Subject never married	568	581
Survivor married before diagnosis of cancer	113	—
Subject pregnant before first marriage	152	252
Subtotal	1428	2385
Subjects presumed not to be at risk of pregnancy		
Subjects known to be sterile before first marriage	60	2
Subjects reporting no pregnancies who said they did not want to have children	102	115
Subjects reporting no pregnancies who said they wanted to adopt children	34	15
Subjects available for analysis	1232	2253

Other analyses of the entire group of female survivors indicated a considerable risk of early menopause among those treated with radiation below the diaphragm in combination with alkylating agents.[16] Although most of the excess risk of early menopause (for all reasons, including surgery) in the analysis was lost as a result of the exclusions (the proportion of survivors who were postmenopausal at the interview was 15 percent, as compared with 17 percent of controls), the average age at menopause of the survivors was still lower than that of the controls (31 vs. 36 years). Therefore, we censored the data on year of menopause.

The age at diagnosis was dichotomized at 15 years because of small numbers of subjects; for instance, of 27 males treated with alkylating agents, only 6 received their treatment before they were 10 years old. The numbers of male subjects treated before 10 years of age in the other treatment groups were also small.

"Pregnancy status" refers to a first pregnancy, regardless of the age of the subject at the time, and was dichotomized as "ever or never pregnant." The measure of association between survivor and control status and fertility is called "relative fertility" and is equivalent to a relative risk. "Pregnancy rate" refers to the proportion of subjects who had ever been pregnant or who had fathered a child. Data analysis was done with crude and multiple contingency tables, using the Mantel–Haenszel method.[17] Proportional-hazards models[18] were used to estimate the fertility of survivors relative to that of their siblings while controlling for the effects of covariates. We obtained estimates and 95 percent confidence limits for relative fertility after adjustment for age and calendar year of marriage (as continuous variables), sex, and varying duration of the risk of pregnancy after first marriage in the presence of censoring due to death, end of follow-up, or menopause. Survival curves were calculated with the Kaplan–Meier method.[19]

The analyses reported here used quasi-matched controls — i.e., survivors in each treatment and site category were compared with their own sibling controls. Results obtained from exactly matched analyses — i.e., proportional-hazards analysis stratified according to family — were closely similar but were not reported because of the 80 percent loss of subjects, due partly to the number of survivors who had no siblings and partly to the lack of sibling controls of the same sex.

Results

Married survivors of childhood or adolescent cancer who were at least potentially fertile were significantly less likely than their sibling controls to report a

pregnancy (77 vs. 86 percent; $P<0.001$). Therefore, the overall crude relative fertility of survivors of cancer as compared with their sibling controls was 0.88. The male survivors had a greater fertility deficit than the female survivors (relative fertility, 0.83 vs. 0.94, respectively; Table 2).

In preliminary analyses, age at diagnosis seemed to be associated inversely with fertility, but the effects failed to reach statistical significance. For instance, among the men who had been treated with alkylating-agent chemotherapy before they were 15 years old, 50 percent became fathers, as compared with only 41 percent treated when they were 15 or older ($\chi^2 = 0.22$). Among men who had been treated with both radiation and alkylating agents, the proportion with proved fertility dropped from 50 percent among those who had been younger than 15 at diagnosis to 22 percent among those who had been 15 or older ($\chi^2 = 3.6$). Among all survivors, the relative fertility shifted only slightly, from 0.90 among those under 15 at diagnosis to 0.85 among those 15 and older. In an early proportional-hazards analysis that included age at diagnosis, this factor did not contribute significantly. Therefore, age at diagnosis was not included in the final analysis.

Lower pregnancy rates among survivors persisted when we considered only those who married once and stayed married. However, both the age at marriage and the decade of marriage, which were strongly associated with pregnancy rates among both survivors and controls, were also related to relative fertility in survivors. Relative fertility in survivors who married when they were 25 or older was 0.80, as compared with 0.90 in survivors who married before they were 25. Survivors who married before 1970 had higher relative fertility than those who married after 1970 (relative fertility, 0.95 vs. 0.85). Consequently, age at marriage and calendar year of marriage were controlled for in the analysis.

Relative fertility was not significantly affected by income, educational attainment, race, center, self-reported health status, vital status, or other potentially confounding variables such as the frequency of intercourse, the number of marriages or current marital status, the use of intrauterine devices, the presence of endometriosis or pelvic inflammatory disease, the year of birth, whether the interview was conducted by telephone or in person, whether the subject or proxy was interviewed, difficulty in becoming pregnant, or seeking medical help because of infertility — regardless of whether the variables were examined in the aggregate or separately for each sex.

Table 2. Crude and Adjusted Relative Fertility of Survivors of Cancer.*

	No. of Survivors	Relative Fertility (95% Confidence Interval)	
		Crude†	Adjusted‡
Total	1232	0.88 (0.86–0.92)	0.85 (0.78–0.92)
Men	595	0.83 (0.74–0.93)	0.76 (0.68–0.86)
Women	637	0.94 (0.85–1.05)	0.93 (0.83–1.04)

*Excludes subjects presumed not to be at risk of pregnancy.

†Relative fertility indicates the rate of first pregnancies in the survivors as compared with that in the controls.

‡Derived from Cox regression models after adjustment for age at marriage and year of marriage.

After adjustment with Cox regression models for age at marriage and calendar year of marriage and stratification according to sex, the overall fertility of survivors was 15 percent less than that of controls (0.85; Table 2) — very similar to the crude estimate of relative fertility. After adjustment, the relative fertility in the male survivors was slightly lower than the crude estimate and remained statistically significant. In the female survivors, the adjusted relative fertility was not significantly different from that in the controls. Seen as unadjusted cumulative-time-to-pregnancy curves through 12 years after marriage (Fig. 1), the differences in pregnancy rates among spouses of male survivors as compared with those among controls were apparent even after only one year of marriage; the differences between female survivors and controls were slight and diminished over time.

Separate analyses according to the site or type of cancer were carried out for sites with at least 25 survivors; adjusted relative fertility values significantly less than 1 were observed only among survivors of Hodgkin's disease and tumors of the male genital system (Table 3).

Two different sets of treatment effects are shown in Table 4. The final analysis presented in the upper portion of the table attempts to quantify the unsuspected infertility in cancer survivors by excluding those known to be sterile and those who chose not to become natural parents (the numbers excluded by these criteria are listed in Table 1, according to the reason for exclusion). For comparison, the lower portion of Table 4 shows the same analysis before exclusion of these survivors.

When both sexes were combined, each cancer treatment was associated with impaired fertility. The least damaging was surgery alone (Table 4 and Fig. 2), for which there was a 9 percent reduction in fertility. Radiation below the diaphragm had a more severe effect than radiation above the diaphragm, and treatment with alkylating agents was more harmful than radiation. Combined treatment with infradiaphragmatic radiation and alkylating agents had the most severe effect on fertility in the survivors, reducing it to almost half that in the controls (relative fertility, 0.57). Treatment with non-alkylating agents (data not shown) induced no apparent fertility deficit (crude relative fertility, 0.98); the 24 survivors who received radiotherapy combined with non-alkylating agents had a 20 percent deficit (crude relative fertility, 0.80; 95 percent confidence interval, 0.59 to 1.04).

These treatment effects were noted principally among the men (Table 4 and Fig. 3), in whom the effect of alkylating agents alone was greater than the effect of radiation alone, whether administered above or below the diaphragm (relative fertility, 0.42 vs. 0.89 and 0.74, respectively). Radiation above the dia-

Table 4. Adjusted Relative Fertility and 95 Percent Confidence Intervals of Survivors of Cancer, According to Type of Treatment Received.*

TREATMENT†	ALL SUBJECTS	MEN	WOMEN
Subjects presumed to be at risk of pregnancy			
No rad or chemotherapy	0.91 (0.82–1.00)	0.81 (0.70–0.94)	0.98 (0.86–1.11)
Rad above diaphragm	0.88 (0.75–1.02)	0.89 (0.71–1.12)	0.85 (0.69–1.05)
Rad below diaphragm	0.76 (0.63–0.92)	0.74 (0.57–0.96)	0.78 (0.59–1.03)
AA	0.67 (0.52–0.87)	0.42 (0.27–0.62)	1.02 (0.74–1.42)
Rad above diaphragm + AA	0.65 (0.49–0.86)	0.46 (0.30–0.71)	0.89 (0.62–1.28)
Rad below diaphragm + AA	0.57 (0.43–0.75)	0.38 (0.25–0.58)	0.81 (0.57–1.17)
All survivors, including subjects not at risk of pregnancy			
Total	0.80 (0.74–0.87)	0.71 (0.63–0.80)	0.89 (0.79–0.99)
No rad or chemotherapy	0.91 (0.84–1.01)	0.82 (0.71–0.96)	1.01 (0.89–1.14)
Rad above diaphragm	0.81 (0.70–0.95)	0.84 (0.67–1.05)	0.78 (0.63–0.96)
Rad below diaphragm	0.59 (0.49–0.71)	0.61 (0.47–0.78)	0.56 (0.42–0.74)
AA	0.62 (0.48–0.79)	0.35 (0.23–0.51)	1.13 (0.82–1.56)
Rad above diaphragm + AA	0.54 (0.41–0.72)	0.35 (0.23–0.55)	0.87 (0.61–1.25)
Rad below diaphragm + AA	0.39 (0.30–0.52)	0.26 (0.17–0.39)	0.63 (0.43–0.91)

*Adjusted values were derived from Cox regression models after adjustment for year of marriage and age at marriage.
†AA denotes alkylating agent, and rad radiation.

disease and male genital cancer (Table 3). In survivors of many other types of malignant disease, an effect of cancer on fertility, if present, was too small to detect, despite adequate statistical power. For instance, the relative fertility of 0.73 in survivors of retinoblastoma failed to reach statistical significance, despite a power above 80 percent.

Fertility estimates were quite different in men and women. For all forms of therapy combined, fertility in women seemed little affected (relative fertility, 0.93; Table 2), whereas fertility in men decreased markedly (Fig. 1). Women treated with surgery only had almost no fertility deficit, in contrast to a 20 percent deficit in men treated with surgery (Fig. 3). It would seem that subfertility or unsuspected infertility is not a large problem for female survivors of cancer. Radiotherapy, regardless of whether it was given to sites above or below the diaphragm, seemed to affect women and men similarly. In contrast, the effect of treatment with alkylating agents on the women was quite different from that on the men; the women had unimpaired fertility, but male survivors had only half the fertility of male controls. The combination of radiation and alkylating agents, which depressed male fertility more than either treatment alone, did not affect female fertility any more than did infradiaphragmatic radiation alone.

Treatment effects in the survivors who never married but had a pregnancy were also assessed, and the results generally confirmed our studies in married survivors. Relative fertility in the unmarried men was considerably depressed after treatment with radiation or alkylating agents, given either alone or together. Relative fertility in the unmarried women was depressed only in the group of survivors who were treated with radiation. When the entire group of survivors and controls was studied, the unadjusted treatment effects were similar — i.e., male fertility was more severely depressed by all treatments than female fertility (relative fertility, 0.69 and 0.86, respectively), women were more affected by radiation (relative fertility, 0.70), and men were more susceptible to the effects of alkylating agents (relative fertility, 0.34).

Our findings are generally consistent with previous studies in other patients. One study of 18 girls treated with an alkylating agent (cyclophosphamide) for the nephrotic syndrome between 6 and 15 years of age indicated that all except one had normal menstrual function and normal fertility at follow-up.[21] Studies of fertility in older patients given mechlorethamine, vincristine, prednisone, and procarbazine for Hodgkin's disease indicated that half the women retained fertility, as compared with almost none of the men.[11,22] Another study of women treated for Hodgkin's disease[23] found that chemotherapy was less likely than radiotherapy to result in loss of menstrual function.

However, our finding of similar impairment of fertility after radiotherapy in men and women diverges from the widely held view[24] that the ovary is more radioresistant than the testis. Even when radiation was administered above the diaphragm, fertility was reduced in both men and women — slightly more in the women. It is likely that these patients received shielding that was considered to be adequate when

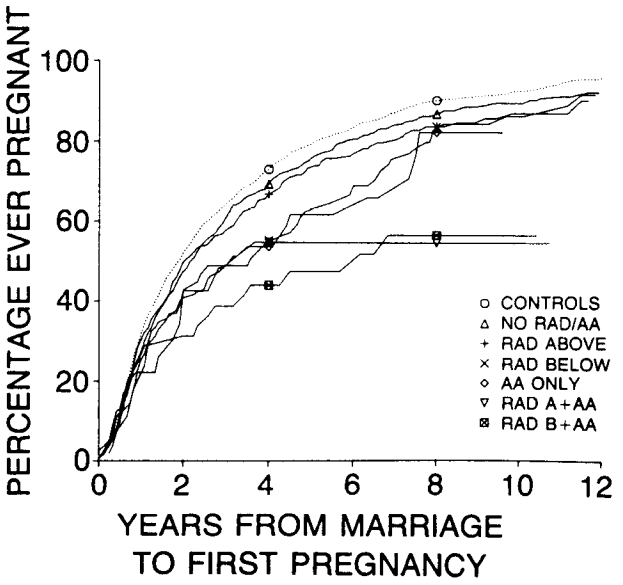

Figure 2. Effects of Different Cancer Treatments on the Cumulative Unadjusted Time to First Pregnancy of Survivors of Cancer and Controls (Both Sexes Combined).

No RAD/AA denotes treatment with neither radiation nor alkylating-agent chemotherapy, RAD ABOVE denotes radiation only, above the diaphragm, RAD BELOW radiation only, below the diaphragm, AA ONLY alkylating agent only, RAD A+AA radiation above the diaphragm and alkylating agent, and RAD B+AA radiation below the diaphragm and alkylating agent.

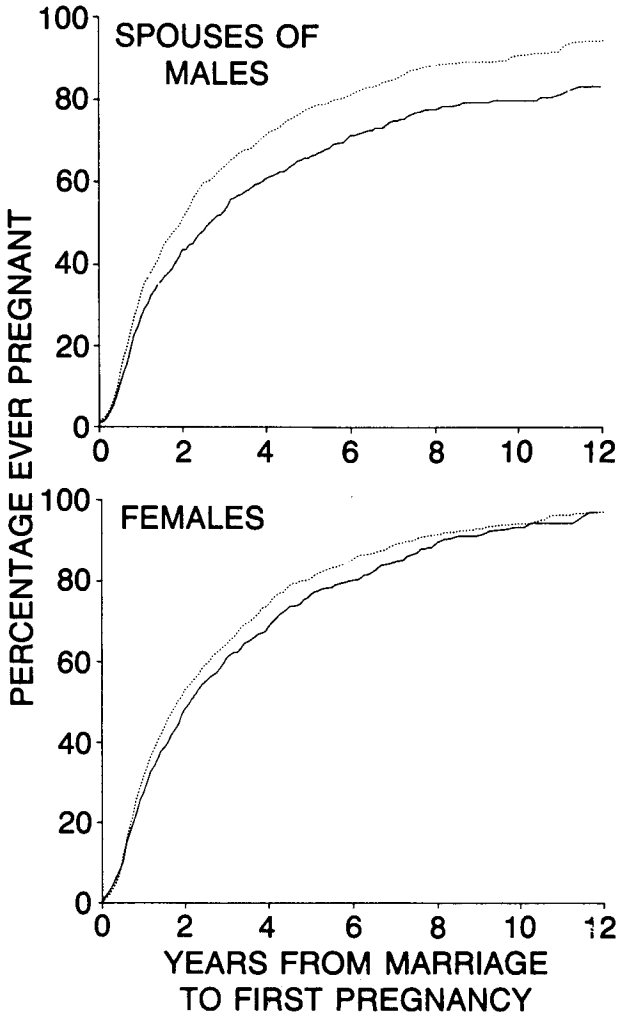

Figure 1. Cumulative Unadjusted Probability of First Pregnancy in Survivors of Cancer (Solid Lines) and Controls (Dotted Lines), as a Function of Years since First Marriage, among Female Subjects and Spouses of Male Subjects.

phragm did not seem to add significantly to the risk associated with alkylating-agent treatment in men, but therapy with a combination of alkylating agents and radiation to the vicinity of the testes seemed to reduce relative fertility (0.38).

In the women, the effects of radiation were similar in magnitude and direction to those in the men (Fig. 3). However, alkylating agents had no detectable effect on fertility in the women (relative fertility, 1.02). Combined radiotherapy and chemotherapy in the women did not alter the relative fertility as compared with radiotherapy alone. In neither sex did the combined treatments have a multiplicative effect greater than that due to the separate effects of radiation and alkylating agents.

In analyses in which subjects not at risk for pregnancy were included, the drop in overall fertility from 0.85 (Table 2) to 0.80 (Table 4) was mirrored at each treatment level and reflected the effect of aggressive forms of therapy, which were more likely to produce sterility. Again, radiotherapy had the strongest effect on fertility in the women, especially when it was administered below the diaphragm. Treatment with alkylating agents affected male fertility adversely, but had no discernible effect on female fertility. Radiotherapy, particularly that given below the diaphragm, was harmful to both men and women, and the combination of radiotherapy given below the diaphragm and treatment with alkylating agents was most damaging to fertility in men.

Discussion

This study has shown that married female survivors of childhood or adolescent cancer and the wives of male survivors were 85 percent as likely as their sibling controls to have begun a pregnancy. This estimate applied to survivors who married after the diagnosis of cancer, who survived for at least five years after diagnosis, and who had reached 21 years of age by the time they entered the study. Furthermore, it applied to persons who had no obvious cause of infertility, and the analysis included some pregnancies that occurred before the subject reached the age of 21 or had survived for five years after diagnosis. Sixteen percent of the male controls and 12 percent of the female controls had reported no pregnancies by the end of the study.

The only national data known to us that express fertility in terms of "ever pregnant" and "never pregnant" are from a representative sample of U.S. women aged 15 to 44 years who were interviewed in 1982.[20] We applied the same exclusions as in Table 1 to these data and found that 14 percent of married women in the United States who were potentially fertile had never reported a pregnancy.

This risk estimate is a composite of many factors and conceals considerable variability due to the type of cancer and the sex of the survivor. For instance, a significant depression of fertility was seen in married survivors of only two types of cancer — Hodgkin's

Table 3. Adjusted Relative Fertility of Survivors of Cancer, According to Type of Cancer.*

Type of Cancer	No. of Survivors	Adjusted Relative Fertility† (95% Confidence Interval)
Hodgkin's disease	253	0.77 (0.64–0.92)
Soft-tissue sarcoma	177	0.82 (0.66–1.02)
Brain and central nervous system tumor	142	0.90 (0.72–1.11)
Thyroid carcinoma	140	0.85 (0.68–1.07)
Bone cancer	90	0.85 (0.63–1.15)
Non-Hodgkin's lymphoma	71	0.81 (0.56–1.16)
Melanoma	64	0.98 (0.70–1.38)
Male genital cancer	37	0.45 (0.26–0.78)
Retinoblastoma	31	0.73 (0.43–1.25)
Wilms' tumor	29	1.47 (0.81–2.65)
Female genital cancer	26	1.04 (0.62–1.76)

*Includes pregnancies of wives of male subjects and excludes subjects presumed not to be at risk of pregnancy. Values were derived from Cox regression models after adjustment for age at marriage and year of marriage and stratification according to sex.

†The relative fertility indicates the probability of pregnancy among survivors as compared with that among the controls.

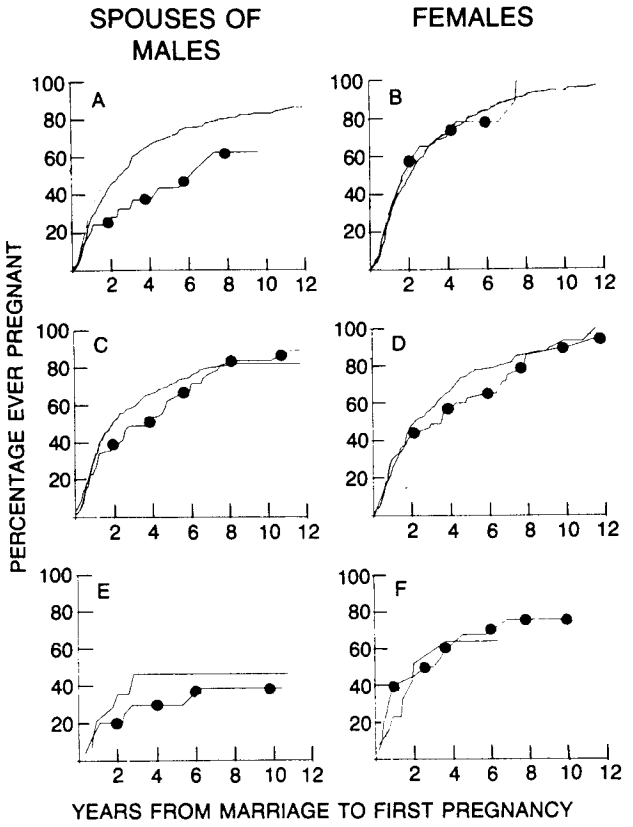

Figure 3. Pregnancy among Survivors (Dark Lines) and Controls (Light Lines), According to the Sex of All Subjects and the Type of Cancer Treatment in the Survivors.

Panels A and B show the results in survivors who had received no radiation or alkylating-agent therapy (dark lines, no circles) or alkylating agent only (dark lines and circles); C and D the results in those who had received radiation above the diaphragm only (dark lines, no circles) or radiation below the diaphragm (dark lines and circles); and E and F the results in those who had received radiation above the diaphragm and alkylating-agent chemotherapy (dark lines; no circles) or radiation below the diaphragm plus alkylating-agent chemotherapy (dark lines and circles).

distant ports were involved, yet the scatter dose was biologically detectable. At least one other (smaller) study of adult patients showed no effect on fertility of mantle radiation for Hodgkin's disease.[11] Many of the survivors in our study were treated when they were children, and their shorter trunk lengths put them at greater risk of exposure to radiation scatter.

Other investigations of reproductive function after treatment of cancer during childhood have been hampered by the enrollment of small numbers of patients and by short follow-up periods.[12,25,26] Although we may have studied too few survivors to detect a statistically significant effect of early age at diagnosis, our data support the idea that the testis in prepubertal boys is relatively resistant to alkylating agents.

The fertility deficits we observed were more pronounced when data on subjects presumed not to be at risk for pregnancy were retained in the analysis. More survivors than controls were known to be sterile before marriage (2.4 vs. 0.06 percent; Table 1), more survivors who were childless stated that they would have children by adoption (1.4 vs. 0.4 percent), and more said that they did not want to have children (4.1 vs. 3.2 percent). In addition to the substantial number of survivors who became sterile as a result of treatment, there appear to have been a number of survivors who decided not to have children naturally. Previous analyses of data from this study have shown that cancer survivors are less likely to marry, that they have more trouble obtaining life insurance and health insurance, and that some do less well in school.[27-30] These considerations, among others, may influence survivors of cancer against parenthood.

Several factors may limit interpretation of our results. To receive permission to contact long-term survivors, we had to keep the subjects unaware of our hypothesis linking childhood cancer with reproductive problems; hence, we could not pursue questions related to possible treatment effects in survivors. Also, we assumed that every married subject stayed married throughout the follow-up period. However, some subjects divorced and remarried, thereby changing their pregnancy risk. This may have resulted in a slight underestimate of risk.

This study and others highlight the considerable differences that exist in the rates of serious side effects, such as infertility, that can accompany cancer therapy. Citing one general estimate conceals the fact that many survivors of cancer have no need to anticipate fertility problems. Counseling of patients with cancer and their families about the risk of side effects should take into account the sex of the patient, the type of cancer, and the type of treatment available. Tailoring the risk estimates to individual circumstances will help patients and physicians deal more effectively with the consequences of disease.

We are indebted to the many interviewers who collected the data, to Westat, Inc., and ORI, Inc., for technical help, to Mary McAdams and David Pee of IMS, Inc., for their assistance, and particularly, to the survivors of cancer and their families, whose courage and cooperation made this study possible.

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SPECIAL ARTICLE

PAIN AND ITS EFFECTS IN THE HUMAN NEONATE AND FETUS

K.J.S. ANAND, M.B.B.S., D.PHIL., AND P.R. HICKEY, M.D.

THE evaluation of pain in the human fetus and neonate is difficult because pain is generally defined as a subjective phenomenon.[1] Early studies of neurologic development concluded that neonatal responses to painful stimuli were decorticate in nature and that perception or localization of pain was not present.[2] Furthermore, because neonates may not have memories of painful experiences, they were not thought capable of interpreting pain in a manner similar to that of adults.[3-5] On a theoretical basis, it was also argued that a high threshold of painful stimuli may be adaptive in protecting infants from pain during birth.[6] These traditional views have led to a widespread belief in the medical community that the human neonate or fetus may not be capable of perceiving pain.[7,8]

Strictly speaking, nociceptive activity, rather than pain, should be discussed with regard to the neonate, because pain is a sensation with strong emotional associations. The focus on pain perception in neonates and confusion over its differentiation from nociceptive activity and the accompanying physiologic responses have obscured the mounting evidence that nociception is important in the biology of the neonate. This is true regardless of any philosophical view on consciousness and "pain perception" in newborns. In the literature, terms relating to pain and nociception are used interchangeably; in this review, no further distinction between the two will generally be made.

One result of the pervasive view of neonatal pain is that newborns are frequently not given analgesic or anesthetic agents during invasive procedures, including surgery.[9-19] Despite recommendations to the contrary in textbooks on pediatric anesthesiology, the clinical practice of inducing minimal or no anesthesia in newborns, particularly if they are premature, is widespread.[9-19] Unfortunately, recommendations on neonatal anesthesia are made without reference to recent data about the development of perceptual mechanisms of pain and the physiologic responses to nociceptive activity in preterm and full-term neonates. Even Robinson and Gregory's landmark paper demonstrating the safety of narcotic anesthesia in preterm neonates cites "philosophic objections" rather than any physiologic rationale as a basis for using this technique.[20] Although methodologic and other issues related to the study of pain in neonates have been discussed,[21-23] the body of scientific evidence regarding the mechanisms and effects of nociceptive

From the Department of Anaesthesia, Harvard Medical School, and Children's Hospital, Boston. Address reprint requests to Dr. Anand at the Department of Anesthesia, Children's Hospital, 300 Longwood Ave., Boston, MA 02115.