Infertility, infertility treatment, and achievement of pregnancy in female survivors of childhood cancer: a report from the Childhood Cancer Survivor Study cohort

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Abstract

Background—Prior studies have documented decreased pregnancy rates and early menopause in female cancer survivors; however, infertility rates and reproductive interventions have not been studied. This study investigates infertility and time to pregnancy among female childhood cancer

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survivors, and analyzes treatment characteristics associated with infertility and subsequent pregnancy.

Methods—The Childhood Cancer Survivor Study (CCSS) is a cohort study including five-year cancer survivors from 26 institutions who were <21 years old at the time of diagnosis between January 1, 1970, and December 31, 1986, and a sibling control group. CCSS females ages 18–39 years reporting they had ever been sexually active (3,531 survivors and 1,366 female controls) were studied. Self-reported infertility, medical treatment for infertility, the time to first pregnancy in survivors and siblings, and the risk of infertility in survivors by demographic, disease, and treatment variables were analyzed.

Findings—Survivors had an increased risk of clinical infertility (>1 year of attempts at conception without success) compared to siblings which was most pronounced at early reproductive ages (24 years Relative Risk (RR)=2·92, 95% Confidence Interval (CI) 1·18–7·20; 25–29 years RR=1·61, 95% CI 1·05–2·48; 30–39 years RR=1·37, 95% CI 1·11–1·69). Despite being equally likely to seek treatment for infertility, survivors were less likely to be prescribed medication for treatment of infertility (RR=0·57, 95% CI 0·46–0·70). Increasing doses of uterine radiation and alkylating agent chemotherapy were most strongly associated with infertility. Although survivors had an increased time to pregnancy interval (p=0·032), 64·2% (292/455) with infertility achieved a pregnancy.

Interpretation—A more comprehensive understanding of infertility after cancer is critical for counseling and decision-making regarding future attempts at conception as well as fertility preservation.

Significant improvements in cancer therapy have dramatically increased the five-year survival rate for childhood cancers, which now exceeds 80%.[1] When considering the long term effects of cancer therapy, infertility is reported as a primary concern, particularly among female survivors.[2, 3] Menstrual cyclicity is not sensitive in identifying gonadotoxic effects of therapy and many childhood cancer survivors are at risk for unrecognized infertility.[4]

The risk of non-surgical premature menopause is increased for cancer survivors with a cumulative incidence of 8% by age 40.[5] In addition, cancer survivors are less likely to become pregnant when compared to their siblings.[6, 7] Likelihood of pregnancy as a measure of fertility does not take into account individual desires for childbearing or attempts at pregnancy and thus does not assess the prevalence of infertility. Furthermore, self-reported parenthood does not reflect time to pregnancy or the use of infertility treatments in those who conceive. Therefore, prior studies may underestimate the risk of infertility in childhood cancer survivors.

In this study, we aim to quantify the risk of infertility in childhood cancer survivors using clinical definitions of infertility, and to identify disease and treatment characteristics in childhood cancer that increase the risk of infertility. Additionally, we evaluate if the length of time to pregnancy is longer in survivors than siblings who conceive.

Materials and Methods

Details of the Childhood Cancer Survivor Study (CCSS) study design, cohort characteristics, and baseline data collection have been published previously.[8, 9] In brief, CCSS is a collaborative study of 26 clinical centers in the United States and Canada that assembled a cohort of five-year cancer survivors who were diagnosed with an eligible malignancy before age 21 between January 1, 1970 and December 31, 1986. Eligible malignancies included leukemia, CNS cancer, Hodgkin lymphoma, non-Hodgkin lymphoma (NHL), Wilms (kidney) tumor, neuroblastoma, soft tissue sarcoma, or bone tumor. In subjects who had

survived at least five years but subsequently died, the next-of-kin, typically parents or a spouse, was contacted. In addition, survivors were asked to identify all their living siblings, from which a random sample of the closest aged sibling was asked to participate. 4,775 eligible siblings were contacted and 4,023 participated (84·3%).[9] For this study, female subjects between 18 and 40 years of age at completion of the baseline questionnaire between 1994 and 2005 who reported they had ever been sexually active were included. 14.8% of eligible survivors were unable to be located after intensive tracing efforts (3,058/20,690). Among survivors contacted, 81.4% (14,358/17,632) provided a baseline questionnaire (Figure 1).

Previously published CCSS data indicates no differences in clinical or demographic characteristics amongst participants and non-participants other than a higher rate of nonparticipation among the next-of-kin of those subjects who had died and a somewhat lower portion of males among participants.[8] The baseline questionnaire collected information on demographics, medical care, and medical conditions, including reproductive history. The questions asked of siblings were identical to those acquired from survivors, with the exception of cancer-specific questions. Individuals who reported a pregnancy were sent a supplemental pregnancy/offspring questionnaire.

The institutional review board at each participating institution approved this study. Informed consent was obtained from all participants.

Exposure variables

Data regarding disease and treatment characteristics (type and dose of chemotherapeutic agents; radiation field size, site, and dose) were collected by medical record abstraction at each collaborating institution.[5]

The total exposure to alkylating agents (AA) was quantified by reporting an alkylating agent score (AA score), which accounted for the number of AA and the doses of each individual agent (in total dose per square meter of body surface area). A distribution of doses of each AA was determined and each subject was assigned a score of 0 to 3, with 0 being no exposure and 1, 2, and 3 representing the lower, middle, and upper tertile of doses of that drug, respectively. Doses of individual AA used to derive the AA score have been previously published.[6] Individual drug scores for each subject were summed, and an overall AA score of 0 to 3 was assigned to each subject.[10] Individual chemotherapeutic agents, bone marrow transplant, history of relapse, and history of second malignancy prior to completion of the baseline questionnaire were considered as additional exposures.

Radiation therapy (RT) doses to the ovaries, uterus, and hypothalamus/pituitary were estimated as previously described by Stovall et al.[11, 12] RT doses are reported in gray (Gy). Maximum ovarian RT dose was highly correlated with uterine RT dose, i.e. the majority of subject's maximum ovarian dose and uterine dose were within the same RT category. Given the high correlation between these variables, it was not possible to fit a multivariable model that included both uterine RT dose and maximum ovarian RT dose; therefore, uterine dose is reported in this study to represent both uterine and gonadal exposure. Any shielding used during RT was accounted for in dose estimations.

Infertility questions

Two definitions of infertility were used. The first, 'clinical infertility' used the commonly accepted definition for infertility, and included anyone who responded yes to the question, "Was there ever a period in your life when you and a partner tried for one year or more to become pregnant, without success?".[13] The second definition of infertility, 'total infertility', included women with 'clinical infertility' as well as those who reported ovarian failure.

Ovarian failure was defined as never having had a menstrual period or menstrual periods stopping five years or more from time of baseline questionnaire. Total infertility is inclusive of **both** those women who attempted to become pregnant for one year or more, without success (the 'clinical infertility' group) as well as those with ovarian failure who may not have attempted pregnancy. Only subjects with 'clinical infertility' answered nested questions regarding the use of infertility services.

Pregnancy questions

Participants who reported at least one pregnancy at any point after their cancer diagnosis on the baseline questionnaire were asked to complete a pregnancy questionnaire. The pregnancy questionnaire asked if the pregnancy was planned, and if so, how many months the participant tried to get pregnant. This study used data only from the first reported pregnancy. Time to first pregnancy among survivors and siblings as well as between cancer treatment groups was compared.

Statistical analysis

Subjects were asked to recall any instance of infertility that occurred up to the time of the baseline questionnaire. Subjects were not asked when they began trying to become pregnant or when they experienced infertility, therefore we were not able to account for individual differences in follow-up time. Infertility was treated as a binary outcome. The covariates examined in statistical analyses were chosen on the basis of their clinical relevance and previously established associations with infertility. Inclusion of covariates in the multivariable models was based on clinical judgment and examination of the univariate estimates.

Risk of total infertility and clinical infertility were first evaluated in a model comparing survivors and siblings. All subsequent analyses including sociodemographic, behavioral, and treatment variables were performed on the group reporting clinical infertility. Univariate analyses were performed using a Chi-squared or Fisher's exact test. Potential factors for inclusion in multivariable models included age at baseline questionnaire, race, education level, smoking status, and body mass index (BMI). It was hypothesized that the risk of infertility would increase with age and that the relative risk comparing survivors to siblings would decline with age at baseline questionnaire. Thus, interaction terms between age at baseline questionnaire and survivor-sibling group were also considered. In a second model of infertility risk in the survivor group, the effects of disease and treatment factors were evaluated. In addition to factors considered for inclusion in the first model, potential risk factors included history of bone marrow transplant, history of relapse, history of a second malignancy prior to the baseline questionnaire, AA score, RT exposures (any RT, RT to the abdomen, RT to the brain, RT to the head, RT to the pelvis, total body irradiation (TBI)), uterine RT dose, and use of chemotherapy agents. Variables strongly correlated with chemotherapy and RT treatment variables were excluded from the multivariable model. All relative risk (RR) estimates and 95% confidence intervals (CI) were determined using a modified Poisson regression with robust variance estimates.[14]

Using data from the supplemental pregnancy questionnaire, time to first conception was compared between survivors and siblings. Survivors and siblings were included if they reported at least one planned pregnancy. In these analyses, histograms showed a highly skewed distribution even after transforming the data. To describe differences between groups defined by survivor status (survivor versus sibling), or among survivors, between treatment exposures, empirical cumulative distribution plots were examined and Wilcoxon rank-sum or Kruskal-Wallis tests were used. All tests were two-sided with a 0·05

significance level without adjustment for multiple tests. All analyses were performed using Statistical Analysis Software, version 9·2 (SAS Institute).

Role of the funding source

The study sponsor had no role in study design; in collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the paper for publication. JN and WL had full access to raw data. The corresponding author (SB) had full access to all of the data and the final responsibility to submit for publication.

Results

Median age at the time of the baseline questionnaire was 27·6 years (interquartile range (IQR) 23·5–32·3 years) in the survivor group, and 33·6 years (IQR 24·4–33·6 years) in the control group. Demographics of the two groups are listed in Table 1. The majority of participants were still menstruating at the time of the baseline questionnaire (82·0% [2894/3531] of survivors and 86·8% [1186/1366] of siblings).

Survivors had an increased risk compared to siblings of both clinical and total infertility. The relative risk was more pronounced when the 107 survivors with ovarian failure were included in the definition of infertility ('total infertility', Table 2). After adjusting for known sociodemographic and behavioral risk factors, the relative risk of clinical infertility in survivors was 1·48 compared to siblings (95% CI 1·23–1·78). This adjusted risk of clinical infertility was more pronounced at younger ages at study participation (24 years RR=2·92, [95% CI 1·18–7·20], p=0·020; 25–29 years RR=1·61, [95% CI 1·05–2·48], p=0·029; 30–40 years RR=1·37, [95% CI 1·11–1·69], p=0·0035).

Comparison of survivors and siblings that reported clinical infertility revealed no differences in the likelihood of visiting a doctor for infertility. Survivors were slightly less likely to have the doctor find a reason for their infertility, although this difference did not reach statistical significance. However, survivors were significantly less likely to receive medication to help them become pregnant (RR=0·57, 95% CI 0·46–0·70) (Table 2).

Subsequent analyses analyzed demographic and behavioral factors in survivors and their associations with clinical infertility. As seen in Table 3, unadjusted increases in risk of infertility were observed in women who were older at childhood cancer diagnosis, older at study entry, that were currently or previously married, in those with high BMI, lower educational attainment, and in smokers. In adjusted models (data not shown), only associations with older age (>29 vs. 24–29) at the time of the baseline questionnaire (RR=1·68, 95% CI 1·26–2·24), marital status (RR=7·91, 95% CI 4·58–13·68 if currently married), and BMI >30 kg/m^2 (RR=1·71, 95% CI 1·30–2·26) remained significant. Notably, a significant association between age at primary diagnosis and infertility was not observed after adjustment.

Specific diagnosis and treatment variables that were associated with clinical infertility were analyzed. In unadjusted models, as shown in Table 3, those with a history of lymphoma, those who received any RT, TBI, and RT to the abdomen or pelvis, had an increased risk of infertility. Additionally, increasing dose of RT to the uterus, exposure to higher cumulative doses of AA (AA score of 3; see Methods), and pituitary radiation doses between 1 to 30 Gy significantly increased the risk of infertility. In adjusted models, uterine RT doses greater than 5 Gy (RR=2·48, [95% CI 1·54–4·01] for 5·1–10 Gy; RR=2·02, [95% CI 1·27–3·23] for 10·1–20 Gy; RR=1·95, [95% CI 1·19–3·19] for >20 Gy) and the AA score of 3 (RR=1·48, 95% CI 1·10–1·99) remained significant.

There were 704 participants who reported a planned first pregnancy. Data regarding time to first conception were available for 676 pregnancies (423 survivors and 253 siblings). As shown in Figure 2, survivors took significantly longer to become pregnant than siblings (p=0·032). For example, 13.0% (55/423) of survivors required more than twelve months of attempts to achieve pregnancy, compared to 8·3% (21/253) of siblings. When survivors were grouped according to cancer treatment, survivors who had received abdominal RT took significantly longer to become pregnant than those who did not, and there was a trend toward increasing time to pregnancy in those who had received high doses of AA. Interestingly, survivors that received RT to the brain or head had a significantly decreased time to pregnancy compared to other survivors.

Finally, survivors with clinical infertility were analyzed to characterize the likelihood of achieving a pregnancy. Nearly two-thirds of survivors with self-reported clinical infertility achieved a pregnancy (292/455, 64·2%). In adjusted analyses, infertile survivors who received more than 10 Gy of uterine RT were less likely to become pregnant (RR=0·33, 95% CI 0·14–0·75 for 10·1–20 Gy and RR=0·21, 95% CI 0·08–0·60 for >20 Gy) than those who were not exposed to uterine RT. Additionally, those with AA scores of 2 or 3 were less likely to become pregnant (RR=0·59, 95% CI 0·43–0·82 and RR=0·77, 95% CI 0·62–0·97 respectively).

Comment

These data demonstrate an increased risk for infertility in childhood cancer survivors starting at a very young reproductive age. RT to pelvic organs and treatment regimens containing AA increased the risk for infertility in a dose dependent fashion. Overall, survivors had a slightly increased time to pregnancy interval, and were less likely to be given medical treatment for infertility; however nearly two-thirds of survivors with clinical infertility reported a pregnancy. Treatment for childhood malignancy has variable effects on reproductive function, and counseling regarding likelihood of fertility in survivors remains challenging. Prior studies have characterized risk factors for childlessness or pregnancy, but were not evaluating a group of women who desired pregnancy and reported an inability to conceive within a year. Clinicians caring for survivors who request information on likelihood of pregnancy or success of treatment for infertility have a paucity of data on which to base their recommendations. To our knowledge, this is the first large study of female childhood cancer survivors which quantifies the risk of infertility using a clinical definition and characterizes the use and success of infertility treatments in this setting.

Interestingly, survivors who had received RT to the brain had a shorter time to pregnancy than other survivors. Survivors who receive high doses of brain RT may experience significant neurocognitive impairments and may be less likely to partner or attempt pregnancy.[15] The shortened time to pregnancy in this survivor group in our study likely reflects selection bias for a good prognosis group that received low dose RT that did not impact ovarian reserve.

It is concerning that survivors were half as likely to be medically treated for infertility as their siblings. Data are lacking as to why providers did not prescribe infertility medications, but do raise concern regarding a provider bias against treating cancer survivors for infertility. It is possible that providers assessed the chance of success as poor and therefore the decision was made not to attempt therapy, or that survivors were less motivated to take medications after having been treated extensively in the past for another condition. Alternatively, reproductive medicine providers may have been uncomfortable with perceived medical co-morbidities.

One major challenge for providers is quantifying the risk of reproductive dysfunction after cancer treatment. Menstruation is not sensitive in identifying women with diminished ovarian reserve. Indeed, in the present study, despite an increased risk of infertility, the majority of cancer survivors were still menstruating. Uterine RT has been demonstrated to negatively impact reproductive function independently of the ovarian effect of RT. Small uterine volumes, impaired blood flow, and endometrial damage may play a role in infertility or adverse pregnancy outcomes (increased low birth weight and miscarriage rates, and lower live birth rates) in survivors that received uterine RT.[16–19]

This is the most comprehensive study of infertility in childhood cancer survivors that we are aware of to-date. The strengths of this study include the large sample size, a well-characterized cohort, availability of detailed cancer treatment information, and the inclusion of an appropriate control group. We elected to report achievement of pregnancy, as opposed to live birth, in estimations of fertility. Importantly, previous CCSS work did not demonstrate an overall increased risk in miscarriage or still birth in survivors compared to siblings, despite a lower live birth rate in survivors. Additionally, previous reports have shown an increased rate of elective termination of pregnancy in young survivors, lowering the live birth rate but not reflecting fertility potential. Therefore, we believe that in this cohort pregnancy gives a more comprehensive view of fertility.[19]

Our study has a number of limitations that should be considered when evaluating the observed risk of infertility in survivors. It is important to acknowledge that women with ovarian failure were not included in the analysis of likelihood of pregnancy; the percentage of infertile survivors achieving pregnancy would be lower if that group was included. Because of the young age of our cohort (median 27·6 years), as well as the lower marriage rate in survivors, we may also be underestimating the overall burden of infertility in their lifespan of survivors as they marry, age, and attempt pregnancy. Previous reports in childhood cancer survivors have shown diminished ovarian reserve even with regular menstruation and timely puberty [20–22] and studies of adult cancer survivors have concluded that amenorrhea underestimates infertility.[23, 24] Similarly, survivors may also be at risk for secondary infertility if they desire more than one child.

Another significant limitation of these data is that participants answered infertility questions starting in 1994, when use of assisted reproduction such as in vitro fertilization was less common and less successful. Additionally, details regarding fertility diagnoses and specifics of infertility treatment were limited by subject recall, and records for infertility treatment were not available. Survivors may have been more aware of the risks of infertility due to treatment, and therefore over reported infertility. Finally, antineoplatic therapies have evolved toward gonadal sparing regimens in some cases, and the late reproductive effects of these more contemporary regimens may be less pronounced. It is important to note that alkylating agents and pelvic radiation remain anticancer therapies today. This underlines the importance of the current analysis, particularly in light of the advances in reproductive technology.

Modern reproductive medicine offers increased options for fertility preservation prior to therapy. The American Society of Clinical Oncology recommends that oncologists should refer "interested and appropriate" patients to reproductive specialists as soon as possible.[25] As assisted reproductive outcomes after cancer therapy appear to be poor, fertility preservation interventions are preferred at diagnosis when possible.[26] Fertility preservation techniques prior to or early in cancer therapy may include oophoropexy or cryopreservation of oocytes, ovarian tissue, or embryos depending upon demographic and clinical factors as well as resource availability. Importantly, multiple live births have now been reported from ovarian tissue freezing.[27–29]

In conclusion, some female childhood cancer survivors are at risk for infertility at a young reproductive age, regardless of age at diagnosis. Pelvic RT and high dose AA chemotherapy are the most significant treatment related risk factors. Although time to pregnancy is slightly increased in cancer survivors, it is encouraging that nearly two-thirds of survivors that reported trying to conceive for at least a year without success can eventually achieve a pregnancy. Collaboration between oncologists and reproductive medicine providers may increase timely access to fertility preservation for those in need, and prevent provider bias when treating cancer survivors for infertility.

Research in Context

Systematic Review: Published works regarding fertility in cancer survivors typically report amenorrhea, pregnancy, and/or live birth as an outcome to estimate fertility. We were familiar with earlier CCSS work by Dr. Green et al (JCO, 2009) which reported on relative risk of pregnancy in childhood cancer survivors compared to siblings. Questioning survivors directly regarding attempts at conception may reveal differences in attempts and desires for children, as well as differences in the need to use medical treatment for infertility to achieve a pregnancy. A search was performed using the PubMed database with combinations of the following terms: fertility, infertility, parenthood, live birth, cancer, and survivorship. Our search was limited to publications including human subjects, and publications in English. Inclusion criteria for studies that reported fertility/infertility in childhood or young adult cancer survivors were examined. In addition, review articles addressing ovarian function and/or fertility after cancer treatment were reviewed. All previously published work used surrogate measures of fertility (most often pregnancy or parenthood). Additionally, the majority of publications have included relatively small numbers of childhood cancer survivors. Finally, no publications were encountered describing the use of infertility treatment or time to pregnancy in female childhood cancer survivors. Since beginning work on this study, Letourneau et al (Cancer, 2012) published of a survey using direct questions about infertility in adult female cancer survivors (aged 18–40). To our knowledge, no previous studies to-date including childhood cancer survivors have used direct measures of infertility.

Interpretation: These data support earlier work demonstrating that cancer therapies have negative gonadal effects on young female cancer survivors leading to an increased risk of infertility and childlessness. Consistent with previous reports, pelvic radiation and alkylating agent chemotherapy are significant treatment related risk factors for infertility. Our data differ from other studies which suggest that earlier age at cancer diagnosis is protective against the development of infertility. This is likely due to the fact that our multivariable models adjusted for treatment related factors (radiation and chemotherapy doses) and sociodemographic variables known to be associated with infertility. We hypothesize that the age distribution of disease and associated treatments accounts for the lower risk of infertility by young age at diagnoses, rather than a different biologic effect of cancer therapies on reproductive organs at a younger age.

Additionally, for those survivors who have infertility but are still menstruating, these data provide useful information for survivors regarding the likelihood of pregnancy, taking into account treatments they may have received. Furthermore, we provide data regarding the length of time to conception in survivors able to conceive. Importantly, the increased risk of infertility is seen in cancer survivors at very young ages, even though the majority of young female cancer survivors resume menstruation (over 50% of our cohort was <30 years of age when they answered questions about infertility). This highlights that ongoing menstrual function does not equate to normal fecundity. Clinicians should alert cancer survivors with ongoing ovarian function in survivorship that they are at risk for infertility, and refer to

reproductive specialists for consideration of fertility preservation if they are not ready to attempt conception at young reproductive ages.

Acknowledgments

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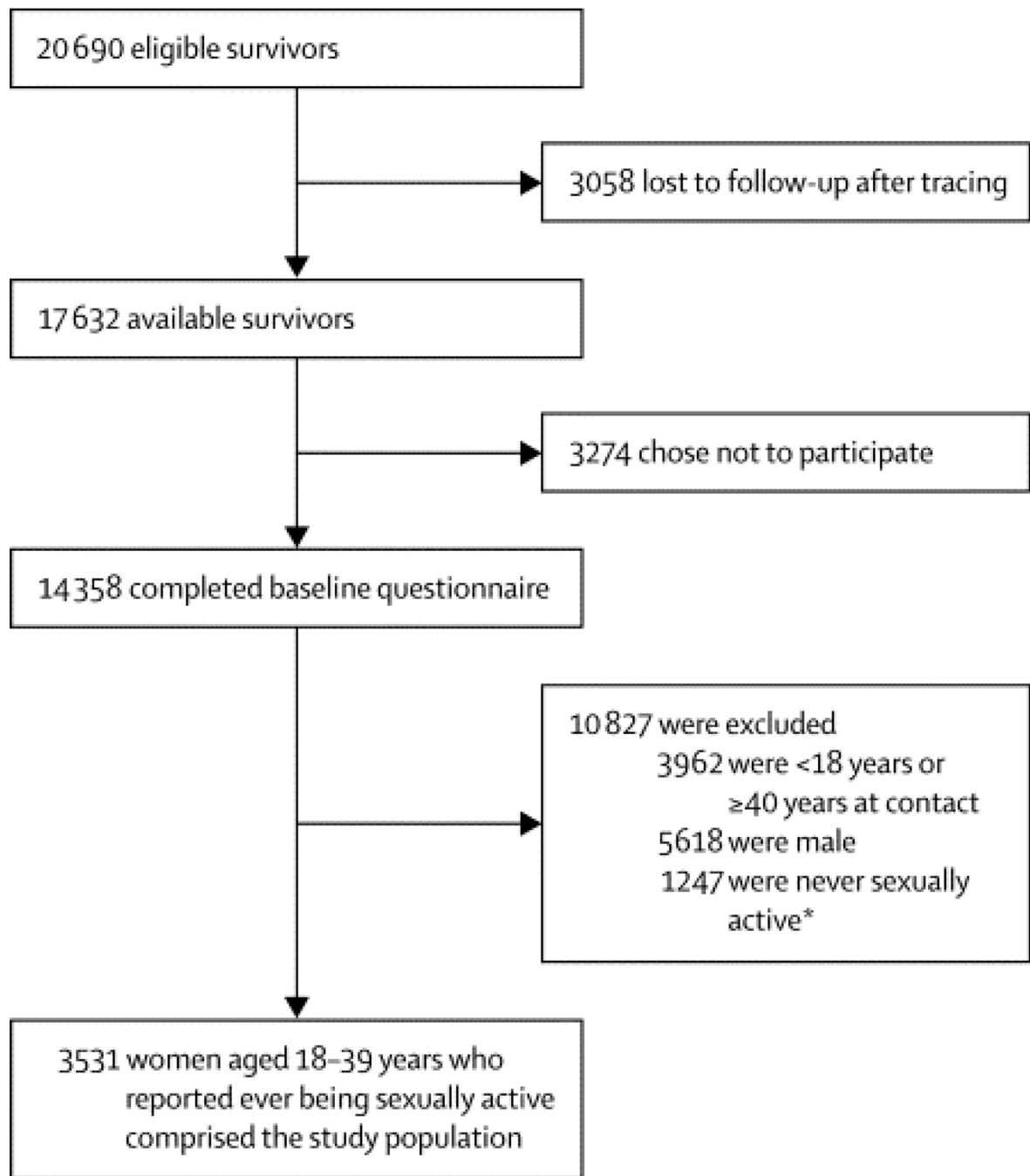
Figure 1. Flowchart of the cancer survivor cohort included in the infertility analyses
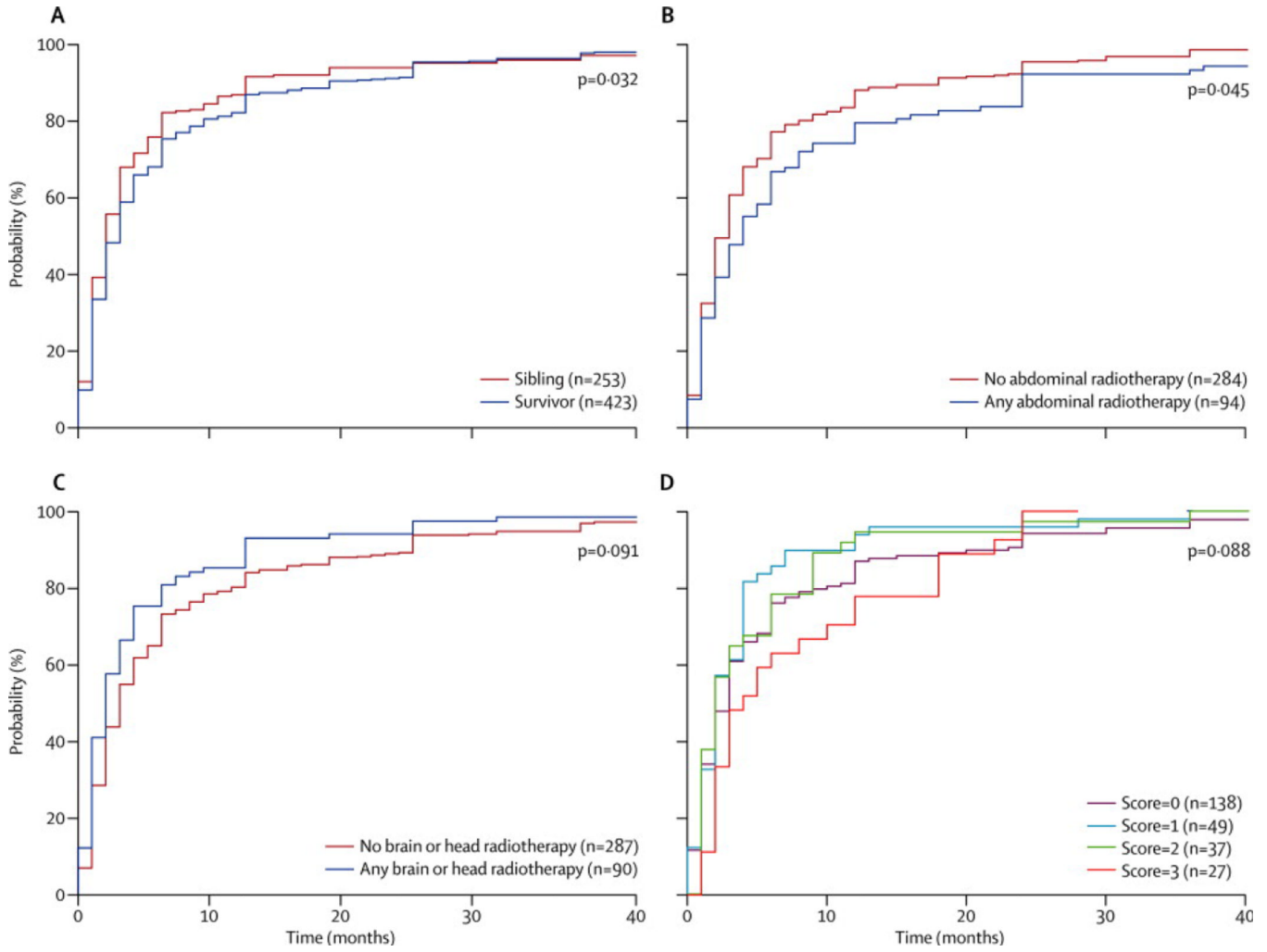
Figure 2. Distribution of time to first pregnancy among survivors and siblings
The distribution of time to first pregnancy in months was summarized using the empirically estimated cumulative distribution function in CCSS participants who reported having a first planned pregnancy and who completed the pregnancy questionnaire. In each panel, the horizontal axis indicates number of months to first pregnancy and the vertical axis indicates estimated probabilities. The height of the distribution curve at *x* months indicates the estimated probability of pregnancy in subjects achieving pregnancy in *x* months or less. For presentation purposes, plots were truncated at 40 months, however all available data were used in estimating distributions and group comparisons. Upper left panel, p=0.032; upper right panel p=0.045; lower left panel p=0.0091; lower right panel p=0.088.

Table 1

Demographic characteristics of female survivors of childhood cancer and of siblings at completion of the baseline questionnaire.

Characteristic	Survivors (N=3531)	Siblings (n=1366)
Age	N (%)	N (%)
<20	227 (6.4%)	80 (5.9%)
20–24	749 (21.2%)	238 (17.4%)
>24–29	1040 (29.5%)	371 (27.2%)
>29–34	916 (25.9%)	364 (26.7%)
>34–39	542 (15.4%)	275 (20.1%)
>39	57 (1.6%)	38 (2.8%)
Race		
White non-Hispanic	2952 (83.6%)	1197 (87.6%)
Hispanic	80 (2.3%)	14 (1.0%)
Black	172 (4.9%)	44 (3.2%)
Other	315 (8.9%)	66 (4.8%)
Unknown	12 (<1%)	45 (3.3%)
Education		
Not HS graduate	278 (7.9%)	70 (5.1%)
Completed HS	645 (18.3%)	229 (16.8%)
Post HS, some college	1287 (36.5%)	470 (34.4%)
College graduate	1107 (31.4%)	551 (40.3%)
Unknown	214 (6.1%)	46 (3.4%)
Marital status		
Married/Living as married	1908 (54.0%)	879 (64.4%)
Widowed/Divorced/Separated	354 (10.0%)	108 (7.9%)
Never married	1103 (31.2%)	356 (26.1%)
Unknown	166 (4.7%)	23 (1.7%)
Smoking status		
Current smoker	688 (19.5%)	343 (25.1%)
Former smoker	465 (13.2%)	239 (17.5%)
Never smoked	2321 (65.7%)	779 (57.0%)
Unknown	57 (1.6%)	5 (0.4%)
BMI		
<18.5	332 (9.4%)	68 (5.0%)
18.5 – <25	2054 (58.2%)	820 (60.0%)
25.0 – <30	660 (18.7%)	252 (18.5%)
>=30	410 (11.6%)	193 (14.1%)
Unknown	75 (2.1%)	33 (2.4%)

Table 2

Comparison of infertility and the use of medical services for infertility between survivors and siblings.

Outcome variable	Survivors (N=3531)	Siblings[a] (N=1366)	RR[b] (95% CI)	P[b]
	N (%)	N (%)		
Total infertility[c]				
Unknown	206 (5.8%)	29 (2.1%)		
No	2763 (78.3%)	1190 (87.1%)		
Yes	562 (15.9%)	147(10.8%)	1.54 (1.30–1.82)	**<0.0001**
Clinical infertility[d]				
Unknown	178 (5.0%)	14 (1.0%)		
No	2898 (82.1%)	1215 (89.0%)		
Yes	455 (12.9%)	137 (10.0%)	1.34 (1.12–1.60)	**0.0015**
Visit to a doctor for infertility	N=455	N=137		
Unknown	3 (0.7%)	3 (2.2%)		
No	137 (30.1%)	34 (24.8%)		
Yes	315 (69.2%)	100 (73.0%)	0.93 (0.83–1.05)	0.25
Doctor found a reason for infertility	N=315	N=100		
Unknown	11 (3.5%)	0 (0.0%)		
No	96 (30.5%)	25 (25.0%)		
Yes	208 (66.0%)	75 (75.0%)	0.91 (0.80–1.05)	0.19
Medication to help you get pregnant	N=208	N=75		
Unknown	3 (1.4%)	0 (0.0%)		
No	118 (56.7%)	19 (25.3%)		
Yes	87 (41.8%)	56 (74.7%)	0.57 (0.46–0.70)	**<0.0001**

[a]Sibling group is the reference group when calculating relative risks.

[b]Unadjusted relative risks (RR) are displayed and are based on available data. P-values are two sided and p<0.05 was considered statistically significant.

[c]Total infertility refers to the overall prevalence of infertility including those reporting trying for > 1 year without success and those with ovarian failure (defined as never getting a menstrual period or last period > 5 years before the baseline questionnaire).

[d]Clinical infertility is defined as trying for > 1 year without success. Only those subjects reporting yes to this definition of infertility went on to answer the subsequent nested questions about the use of infertility services.

Table 3

The unadjusted relative risk of clinical infertility by demographic, disease and treatment characteristics in survivors of childhood cancer.

Variable	N[a]	Unknown n (%)[b]	No n (%)[b]	Yes n (%)[b]	RR (95% CI)[c]	P
Age at diagnosis						
0–4	633	32 (5.1%)	542 (85.6%)	59 (9.3%)	0.55 (0.42–0.73)	<0.0001
5–9	771	34 (4.4%)	658 (85.3%)	79 (10.3%)	0.60 (0.47–0.78)	0.0001
10–14	1123	46 (4.1%)	918 (81.8%)	159 (14.2%)	0.83 (0.68–1.02)	0.078
15–<21	890	62 (7.0%)	681 (76.5%)	147 (16.5%)	Referent	
Unknown	114	4 (3.5%)	99 (86.8%)	11 (9.7%)		
Age at baseline questionnaire						
<20	227	39 (17.2%)	176 (77.5%)	12 (5.3%)	0.54 (0.30–0.95)	0.033
20–24	749	16 (2.1%)	695 (92.8%)	38 (5.1%)	0.44 (0.31–0.62)	<0.0001
>24–29	1040	30 (2.9%)	890 (85.6%)	120 (11.5%)	Referent	
>29–34	916	41 (4.5%)	716 (78.2%)	159 (17.4%)	1.53 (1.23–1.90)	0.0001
>34–39	542	47 (8.7%)	383 (70.7%)	112 (20.7%)	1.90 (1.51–2.41)	<0.0001
>39–<40	57	5 (8.8%)	38 (66.7%)	14 (24.6%)	2.27 (1.40–3.66)	0.0008
Unknown	0					
Education						
Not HS graduate	278	33 (11.9%)	205 (73.7%)	40 (14.4%)	Referent	
Completed HS	645	44 (6.8%)	509 (78.9%)	92 (14.3%)	0.94 (0.67–1.32)	0.71
Post HS, some college	1287	89 (6.9%)	1036 (80.5%)	162 (12.6%)	0.83 (0.60–1.14)	0.24
College graduate	1107	5 (0.5%)	980 (88.5%)	122 (11.0%)	0.68 (0.49–0.94)	0.021
Unknown	214	7 (3.3%)	168 (78.5%)	39 (18.2%)		
Race						
White non-Hispanic	2952	155 (5.3%)	2419 (81.9%)	378 (12.8%)	Referent	
Hispanic	80	2 (2.5%)	69 (86.3%)	9 (11.3%)	0.85 (0.46–1.59)	0.62
Black	172	11 (6.4%)	137 (79.7%)	24 (14.0%)	1.10 (0.75–1.61)	0.61
Other	315	10 (3.2%)	264 (83.8%)	41 (13.0%)	0.99 (0.74–1.34)	0.97
Unknown	12	0 (0.0%)	9 (75.0%)	3 (25.0%)		

Variable	N[a]	Unknown n (%)[b]	No n (%)[b]	Yes n (%)[b]	RR (95% CI)[c]	P
Marital status						
Married/Living as married	1908	28 (1.5%)	1514 (79.4%)	366 (19.2%)	8.70 (5.75–13.17)	<0.0001
Widowed, Divorced, Separated	354	9 (2.5%)	295 (83.3%)	50 (14.1%)	6.48 (4.01–10.45)	<0.0001
Never married	1103	75 (6.8%)	1005 (91.1%)	23 (2.1%)	Referent	
Unknown	166	66 (39.8%)	84 (50.6%)	16 (9.6%)		
Smoking status						
Current smoker	688	13 (1.9%)	566 (82.3%)	109 (15.8%)	1.27 (1.04–1.56)	0.020
Former smoker	465	6 (1.3%)	393 (84.5%)	66 (14.2%)	1.13 (0.88–1.45)	0.32
Never smoked	2321	122 (5.3%)	1920 (82.7%)	279 (12.0%)	Referent	
Unknown	57	37 (64.9%)	19 (33.3%)	1 (1.8%)		
BMI						
<18.5	332	46 (13.9%)	262 (78.9%)	24 (7.2%)	0.72 (0.48–1.08)	0.11
18.5 – <25	2054	97 (4.7%)	1730 (84.2%)	227 (11.1%)	Referent	
25.0 – <30	660	17 (2.6%)	546 (82.7%)	97 (14.7%)	1.30 (1.04–1.62)	0.020
30	410	11 (2.7%)	301 (73.4%)	98 (23.9%)	2.12 (1.71–2.62)	<0.0001
Unknown	75	7 (9.3%)	59 (78.7%)	9 (12.0%)		
Primary diagnosis						
Leukemia	1006	46 (4.6%)	850 (84.5%)	110 (10.9%)	Referent	
Hodgkin lymphoma or NHL	927	44 (4.8%)	709 (76.5%)	174 (18.8%)	1.72 (1.38–2.14)	<0.0001
CNS	323	17 (5.3%)	270 (83.6%)	36 (11.2%)	1.03 (0.72–1.46)	0.88
Solid tumor	1275	71 (5.6%)	1069 (83.8%)	135 (10.6%)	0.98 (0.77–1.24)	0.86
Radiation						
Any RT						
No	962	43 (4.5%)	828 (86.1%)	91 (9.5%)	Referent	
Yes	2194	110 (5.0%)	1774 (80.9%)	310 (14.1%)	1.50 (1.21–1.87)	0.0003
Unknown	375	25 (6.7%)	296 (78.9%)	54 (14.4%)		
Abdomen RT						
No	2225	97 (4.4%)	1871 (84.1%)	257 (11.6%)	Referent	
Yes	853	50 (5.9%)	670 (78.6%)	133 (15.6%)	1.37 (1.13–1.66)	0.0013

Variable	N^a	Unknown n (%)^b	No n (%)^b	Yes n (%)^b	RR (95% CI)^c	P
Unknown	453	31 (6.8%)	357 (78.8%)	65 (14.4%)		
Brain or head RT						
No	2156	104 (4.8%)	1771 (82.1%)	281 (13.0%)	Referent	
Yes	924	43 (4.7%)	772 (83.6%)	109 (11.8%)	0.90 (0.73–1.11)	0.34
Unknown	451	31 (6.9%)	355 (78.7%)	65 (14.1%)		
Pelvis RT						
No	2494	108 (4.3%)	2104 (84.4%)	282 (11.3%)	Referent	
Yes	583	39 (6.7%)	437 (75.0%)	107 (18.4%)	**1.66 (1.36–2.04)**	**<0.0001**
Unknown	454	31 (6.8%)	357 (78.6%)	66 (14.5%)		
TBI						
No	3041	145 (4.8%)	2517 (82.8%)	379 (12.5%)	Referent	
Yes	36	2 (5.6%)	24 (66.7%)	10 (27.8%)	**2.25 (1.32–3.81)**	**0.0027**
Unknown	454	31 (6.8%)	357 (78.6%)	66 (14.5%)		
Radiation dose (Gy)						
Uterine						
No RT	962	43 (4.5%)	828 (86.1%)	91 (9.5%)	Referent	
1–5	1799	79 (4.4%)	1494 (83.1%)	226 (12.6%)	**1.33 (1.05–1.67)**	**0.016**
5.1–10	81	5 (6.2%)	55 (67.9%)	21 (25.9%)	**2.79 (1.85–4.22)**	**<0.0001**
10.1–20	86	5 (5.8%)	63 (73.3%)	18 (20.9%)	**2.24 (1.43–3.53)**	**0.0005**
>20	120	11 (9.2%)	82 (68.3%)	27 (22.5%)	**2.50 (1.71–3.66)**	**<0.0001**
Unknown	483	35 (7.3%)	376 (77.9%)	72 (14.9%)		
Pituitary						
No RT	964	43 (4.5%)	830 (86.1%)	91 (9.4%)	Referent	
1–20	1482	75 (5.1%)	1194 (80.6%)	213 (14.4%)	**1.53 (1.22–1.93)**	**0.0003**
20.1–30	430	8 (1.9%)	357 (83.0%)	65 (15.1%)	**1.56 (1.16–2.10)**	**0.0034**
>30	171	15 (8.8%)	140 (81.9%)	16 (9.4%)	1.04 (0.63–1.72)	0.88
Unknown	484	37 (7.6%)	377 (77.9%)	70 (14.5%)		
Alkylating agent score						
0	1510	55 (3.6%)	1276 (84.5%)	179 (11.9%)	Referent	

Variable	N[a]	Unknown n (%)[b]	No n (%)[b]	Yes n (%)[b]	RR (95% CI)[c]	P
1	543	25 (4.6%)	460 (84.7%)	58 (10.7%)	0.91 (0.69–1.20)	0.51
2	429	17 (4.0%)	363 (84.6%)	49 (11.4%)	0.97 (0.72–1.30)	0.82
3	318	13 (4.1%)	242 (76.1%)	63 (19.8%)	**1.68 (1.30–2.18)**	**<0.0001**
Unknown	731	68 (9.3%)	557 (76.2%)	106 (14.5%)		
History of BMT						
No	3302	163 (4.9%)	2714 (82.2%)	425 (12.9%)	Referent	
Yes	83	15 (18.1%)	56 (67.5%)	12 (14.5%)	1.30 (0.77–2.19)	0.32
Unknown	146	0 (0.0%)	128 (87.7%)	18 (12.3%)		
History of relapse						
No	3183	124 (3.9%)	2646 (83.1%)	413 (13.0%)	Referent	
Yes	348	54 (15.5%)	252 (72.4%)	42 (12.1%)	1.06 (0.79–1.42)	0.71
Unknown	0					
History of second malignancy before baseline						
No	3388	156 (4.6%)	2798 (82.6%)	434 (12.8%)	Referent	
Yes	143	22 (15.4%)	100 (69.9%)	21 (14.7%)	1.29 (0.87–1.93)	0.21
Unknown	0					

[a]N includes survivors that reported have ever been sexually active.

[b]n (%) are out of total N.

[c]RR is based on available data.