# Lifestyle, distress and pregnancy outcomes in the Childhood Cancer Survivor Study cohort

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## Abstract

**OBJECTIVE—**To evaluate associations between prepregnancy lifestyle factors, psychological distress and adverse pregnancy outcomes among female survivors of childhood cancer.

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Condensation: Childhood cancer survivors exposed to > 2.5 Gy uterine radiation who had a history of smoking had an increased risk of miscarriage.

**STUDY DESIGN**—We examined pregnancies of 1,192 female participants from the Childhood Cancer Survivor Study. Generalized linear models, adjusted for age at diagnosis, age at pregnancy, parity, and education were used to calculate the odds ratio (OR) and confidence interval (CI) for associations between prepregnancy inactivity, overweight or obese status, smoking status, risky drinking, psychological distress and pregnancy outcomes. Interactions between lifestyle factors, psychological distress, type of cancer and cancer treatment were assessed in multivariable models.

**RESULTS**—The median age of study participants at the beginning of pregnancy was 28 years (range: 14–45). Among 1,858 reported pregnancies, there were 1,300 singleton live births (310 were preterm), 21 stillbirths, 397 miscarriages, and 140 medical abortions. Prepregnancy physical inactivity, risky drinking, distress and depression were not associated with any pregnancy outcomes. Compared to those who had never smoked, survivors with > 5 pack-years smoking history had a higher risk for miscarriage among those treated with > 2.5 Gy uterine radiation (OR: 53.9; 95% CI: 2.2, 1,326.1) than among those treated with $\leq$ 2.5 Gy uterine radiation (OR: 1.9; 95% CI: 1.2, 3.0). There was a significant interaction between smoking and uterine radiation ($P_{interaction} = 0.01$).

**CONCLUSION**—While most lifestyle factors and psychological distress were not predictive of adverse pregnancy outcomes, the risk for miscarriage was significantly increased among survivors exposed to > 2.5 Gy uterine radiation who had a history of smoking.

### Keywords

## INTRODUCTION

In the United States, approximately 10,450 new cases of childhood cancer are expected to occur among children younger than 15 years of age in 2014; 80% of these children will survive for at least five years.[1] Because most of these survivors will reach reproductive age, adverse pregnancy outcomes including preterm birth, stillbirth, and miscarriage are of concern. Overall, when compared to their siblings, female survivors of childhood cancer are not at increased risk for stillbirth or miscarriage,[2] but do have an increased risk of preterm birth.[3] Previous studies have identified treatment-related risks, reporting an increased risk of preterm birth following $\geq$ 5 Gray (Gy) of uterine radiation,[3] stillbirth following $\geq$ 10 Gy of uterine and ovarian radiation,[4] and miscarriage following abdominal radiation.[5, 6] However, the influence of potentially modifiable prepregnancy lifestyle factors such as body mass index (BMI), smoking, heavy alcohol consumption, physical inactivity, and psychological distress on adverse pregnancy outcomes in childhood cancer survivors has not been evaluated.

In the general population, prepregnancy BMI and smoking are associated with adverse pregnancy outcomes;[7–14] however, limited evidence exists regarding the influence of prepregnancy heavy alcohol consumption, physical inactivity, and psychological distress. Adult female survivors of childhood cancer have high rates of both underweight and obesity,[15] physical inactivity,[16] and psychological distress.[17] However, survivors are less likely than siblings to report smoking[18, 19] and heavy alcohol consumption.[20] Lifestyle and

psychological factors may explain a portion of the risk for adverse pregnancy outcomes not explained by treatment exposures. If additional risk is observed due to the presence of these factors before pregnancy, health care providers could provide targeted counseling and interventions to help modify lifestyle and psychological status of vulnerable survivors.

The current study was designed to evaluate potential associations between prepregnancy lifestyle factors, psychological distress and adverse pregnancy outcomes among female survivors of childhood cancer.

## MATERIALS AND METHODS

### Study population

Participants were members of the Childhood Cancer Survivor Study (CCSS) cohort, described in detail previously.[21, 22] Briefly, participants were at least 5 year survivors of childhood cancer, diagnosed when younger than age 21 years at one of 26 institutions in North America between 1970 and 1986. The protocol was approved by institutional review boards at all institutions. Consent was obtained from survivors older than 18 years and from parents of survivors younger than 18 years of age. Of 20,691 eligible survivors, 14,358 survivors were enrolled. Study participants completed a baseline questionnaire in 1995 and follow-up questionnaires thereafter (http://www.stjude.org/ccss). The baseline questionnaire gathered information on demographics, cancer type, medications, psychological status, pregnancy history, and lifestyle factors. The medical records of those who consented were abstracted. The follow-up 2000 pregnancy questionnaire gathered information on parent's age at pregnancy, time to pregnancy, fertility problems, infertility treatment such as medications or in-vitro fertilization, chemotherapy or radiotherapy received by either parents during or a year before pregnancy, antenatal care, substance abuse, medical complications during pregnancy, and dates and outcomes of pregnancies. The follow-up 2003 questionnaire was similar to the baseline questionnaire and in addition collected information on neurocognitive functions, short form-36 health survey, dental and bone health, and post-traumatic stress. The follow-up 2007 questionnaire gathered information similar to the baseline questionnaire. Survivors who reported relapse or second neoplasms before pregnancy were excluded.

For the current study, we restricted our sample to survivors who consented to medical record abstraction for treatment information, and included pregnancies reported by female survivors 14 to 45 years of age who had previously completed a questionnaire reporting lifestyle factors and psychological distress (Figure 1). Non-singleton pregnancies, pregnancies resulting from in-vitro fertilization (IVF), or reported pregnancies without a known outcome, were not included (Figure 1).

### Adverse pregnancy outcomes

Pregnancy outcomes including preterm birth, stillbirth and miscarriage were obtained from the 2000 and 2007 CCSS questionnaires. Pregnancy outcomes were self-reported by survivors as live birth, stillbirth, miscarriage or medical abortion. We defined preterm birth as a reported gestational age of less than 37 weeks for a live birth. Stillbirth was defined as

fetal death occurring after 20 weeks of gestation or later and a miscarriage was defined as fetal death occurring before 20 weeks of gestation. Self-reported pregnancy outcomes of live birth, stillbirth, miscarriage or medical (elective) abortion were further validated by expert review with additional clarification through a telephone interview.[22]

### Independent variables

Variables of interest, including BMI, smoking, alcohol consumption, physical inactivity, and psychological distress were obtained from the baseline and 2003 questionnaires completed prior to pregnancy. Alcohol consumption was only captured on the baseline questionnaire and thus evaluated in separate multivariable models only including pregnancies reported on the 2000 questionnaire. We defined BMI as self-reported weight in kilograms (kg) divided by self-reported height in meters squared ($m^2$) and categorized survivors as underweight (< 18.5 $kg/m^2$), normal (18.5–24.9 $kg/m^2$), overweight (25–29.9 $kg/m^2$), and obese ( 30 $kg/m^2$).[23] Pack-years of smoking were calculated by dividing the product of the average number of cigarettes smoked per day and the number of years smoked by twenty. Smoking status was categorized based on pack-years of smoking as 0, 0.1 to 5 or > 5 pack-years (0 was assigned for those who never smoked). Survivors who reported either > 3 drinks/day or > 7 drinks/week were classified as risky drinkers, per the National Institute on Alcohol Abuse and Alcoholism guidelines.[24] Survivors were classified as physically inactive if they reported < 150 minutes of moderate or < 60 minutes of vigorous physical activity per week.[25,26] Information from the Brief Symptom Inventory (BSI)-18 was used to identify survivors with global psychological distress or depression.[27] Survivors with T-score 63 for the total BSI-18 were classified as having global distress and those with T-score score 63 for the depression subscale as having depression.[28]

Cancer and treatment variables were obtained from medical records. Analyses included organ-specific radiotherapy and chemotherapeutic exposures previously reported to influence adverse pregnancy outcomes.[2–4, 29] Organ-specific radiation dose was estimated by medical physicists and the sum of all radiation treatments was used as the total radiation dose[30] to the uterus, ovaries, and pituitary, which was categorized as 2.5 Gy and > 2.5 Gy for analysis.[3] The alkylating agent score was calculated by dividing the cumulative sum of the tertile scores of all alkylating agents into tertiles and given a score of 1 to 3.[3] Anthracycline treatment was also categorized in cumulative dose tertiles. Other variables including race, annual household income, level of educational attainment, marital status, and insurance status, were self-reported by survivors on questionnaires completed prior to pregnancy.

### Statistics

Demographic factors and treatment exposures of survivors with eligible pregnancies were examined as frequencies and percentages. To evaluate participation bias, we compared the demographics, treatment characteristics, and exposure distribution of the participants of baseline to 2000 and 2003 to 2007 intervals to the survivors (non-participants) who did not complete 2000 and 2007 questionnaires. Data analysis was performed using SAS software, version 9.2 (SAS Institute., Cary, NC).

To evaluate associations between factors of interest and adverse pregnancy outcomes, multivariable regression models with a generalized estimating equation[31] adjustment to account for correlated data from women who had more than one pregnancy were used. The COPY method (10,000 copies of original data) was applied to estimate the maximum likelihood when models did not converge.[32] A minimally sufficient set of covariates including age at diagnosis, age at pregnancy, educational attainment, and parity was identified *a priori*.[33] Potential interactions between lifestyle factors or psychological distress and age at start of pregnancy, parity, type of cancer and treatment were evaluated in multivariable models. Results are reported as odds ratios (OR) with 95% confidence intervals (CI). P values < 0.05 were considered significant, except for interaction analyses where we used $P < 0.15$.[34] When interaction terms were significant, ORs for each strata of the significant effect modifier are presented. Our results may be subject to selection bias because not all eligible survivors participated. To assess this potential bias, we performed a sensitivity analyses (see supplement).[35]

## RESULTS

The demographic, treatment, lifestyle, and psychological characteristics of the eligible pregnancies (N=1,858) reported by 1,192 participants are presented in Table 1. Of the 1,192 participants, 722 contributed one eligible pregnancy each and 470 reported at least two eligible pregnancies contributing to the remaining 1,136 eligible pregnancies. The difference between age at pregnancy and age at exposure assessment questionnaires for female survivors was an average of 2.20 years (standard deviation=1.54 years; range: 0 to 7.58 years). We also compared the study participants with non-participants. Participants were more likely to be non-Hispanic white women, have a college education, health insurance, and an annual household income of more than $ 20,000. Among the 1,858 eligible pregnancies reported by the survivors, there were 1,300 live births, 140 medical abortions, 21 stillbirths, and 397 miscarriages. Of the 1,300 live births with available gestational age, 310 were preterm and 959 were delivered full term.

The association between lifestyle factors, psychological distress, and adverse pregnancy outcomes after controlling for age at pregnancy, age at diagnosis, educational attainment and parity are shown in Table 2. Physical inactivity, BMI, smoking, and global psychological distress were not associated with preterm birth and stillbirth. The null associations of these factors were also observed in a model that 1) replaced global distress with depression; and, 2) additionally controlled for risky drinking. We did not observe any interaction between lifestyle factors or psychological distress and age, parity, type of cancer, and cancer treatment while evaluating the risk for preterm birth and stillbirth.

The multivariable association between smoking and miscarriage was modified by uterine radiation (Table 2). Compared to those who had never smoked, survivors with > 5 pack-years smoking history had higher risk for miscarriage among those with > 2.5 Gy uterine radiation (OR: 53.9; 95% CI: 2.2, 1,326.1) than among those with 2.5 Gy of uterine radiation (OR: 1.9; 95% CI: 1.2, 3.0; $P_{interaction} = 0.01$). The interaction between smoking and uterine radiation for risk of miscarriage was also observed after replacing global distress with depression in the multivariable model ($P_{interaction} = 0.02$). Other interaction terms

between lifestyle factors or psychological distress and age, parity, type of cancer and cancer treatment were not significant when evaluating the risk for miscarriage. In separate multivariable models, no association was observed between risky drinking and preterm birth, stillbirth, or miscarriage.

In the sensitivity analysis, we calculated the lower and upper confidence bounds of our unadjusted estimates for risk of miscarriage among those who smoked > 5 pack-years and had received > 2.5 Gy uterine radiation (see supplement). We estimated confidence bounds assuming both no association (OR: 1.0) and a 2-fold protective association (OR: 0.5) between smoking > 5 pack-years and miscarriage among non-participants. With miscarriage rate estimates of 30, 25, 20, and 15%, summary OR ranged from 3.7 to 6.3 for the null assumption and 3.0 to 4.4 for the 2-fold protective assumption.

## COMMENT

To our knowledge this is the first study to evaluate the associations between prepregnancy lifestyle factors, psychological distress, and adverse pregnancy outcomes in a large cohort of female survivors of childhood cancer. We found no associations between prepregnancy BMI, risky drinking, physical inactivity, or psychological distress, and adverse pregnancy outcomes. However, we observed a positive interaction between prepregnancy smoking and uterine radiation for risk of miscarriage. Female survivors of childhood cancer who smoked > 5 pack-years of cigarettes before pregnancy had higher risk for miscarriage compared to those who never smoked, regardless of radiation exposure. However, risk for miscarriage was particularly high among those who received > 2.5 Gy uterine radiation when compared to those who received 2.5 Gy of uterine radiation during cancer treatment.

Previous CCSS reports have observed adverse pregnancy outcomes and treatment-related risk factors among female survivors of childhood cancer.[2–4] Green et al[2] identified a non-significant increased risk for miscarriage among those treated with ovarian radiation (relative risk [RR] = 1.86; 95% CI: 0.82, 4.18) or with ovaries near a radiation field (RR = 1.64; 95% CI: 0.97, 2.78). Signorello et al[3] observed that survivors had almost twice the risk for a preterm birth compared to the siblings, and also identified a dose-response association between uterine radiation and risk for preterm birth. Another CCSS study reported that survivors treated with uterine and ovarian radiation > 10 Gy have 9 times the risk for stillbirth and neonatal deaths compared to those treated with no radiation.[4] In this study we observed 70% live births, 7.5% medical abortions, 1.1% stillbirths, 21.4% miscarriages, and 24.4% preterm births among female childhood cancer survivors. Previous CCSS reports have observed 70.9% live births, 11.6% medical abortions, 0.7% stillbirths, 25.5% miscarriages,[2] and 12.6% preterm births[3] among female siblings of childhood cancer survivors.

Although no study has reported an interaction between uterine radiation and prepregnancy smoking on risk for miscarriage, previous studies indicate that a history of abdominal or uterine radiation in female survivors of childhood cancer[5, 6] and prepregnancy smoking in the general population[12] are independent risk factors for miscarriage. The British Childhood Cancer Survivor Study observed an increased risk for miscarriage among female survivors

(4,113 singleton pregnancies) who were treated with abdominal radiation (OR: 1.4; 95% CI: 1.0, 1.9).[5] Similarly, a report from the Danish Cancer Registry found a higher risk for miscarriage among the 1479 pregnancies of female survivors who were treated with uterine and ovarian radiation (range: 1 to 40 Gy) when compared to the 5,092 pregnancies among their sisters (Proportion Ratio: 2.8; 95% CI: 1.7, 4.7).[6] Elevated risk for miscarriage is reported in the general population among women with history of heavy prepregnancy smoking. In a nested case-control study of prospectively collected data from 1,921 women, Nielsen et al[12] observed that the risk for miscarriage increased by 20% for every five cigarettes smoked per day (OR: 1.20; 95% CI: 1.04, 1.39).

The increase in risk for miscarriage among female survivors treated with > 2.5 Gy uterine radiation and a smoking history is likely explained by the combined effects of radiation and smoking on uterine myometrium, endometrium, and vasculature. Uterine radiation during childhood is associated with smaller adult uterine size,[36, 37] absence of endometrial growth in response to exogenous estrogen[36] and progesterone,[37] and impairment of uterine blood flow as measured by Doppler ultrasound.[37] Some investigators propose that radiation-induced uterine and abdominopelvic fibrosis restricts uterine expansion thus impairing the maintenance of pregnancy.[38, 39] Cigarette smoking influences the uterus by increasing the production of myometrial oxytocin receptors and myometrial contractility, and reducing progesterone synthesis and endometrial vascularity.[40, 41] Additionally, smoking also reduces the endothelium-dependent nitric oxide-mediated relaxation in the small arteries of the uterus, which may persist despite smoking cessation during early pregnancy.[42] Uterine radiation exposure > 2.5 Gy is likely a result of direct abdominal or pelvic radiotherapy whereas uterine radiation < 2.5 Gy is likely because of exposure to total body, or scatter from spinal, chest, or proximal lower extremity irradiation.

Several limitations need to be considered when interpreting our study findings. First, our results may be subject to selection bias because not all eligible survivors participated. In the sensitivity analyses,[42] even if the direction of the association between smoking and miscarriage among non-participants differed from participants, the positive association between smoking > 5 pack-years and miscarriage among survivors exposed to > 2.5 Gy uterine radiation remained. Second, miscarriage is often underestimated because not all pregnancy losses are recognized.[43] If this underestimation is unrelated to a survivor's smoking status then the resulting bias would only produce conservative estimates.[44] Third, smoking status of survivors in our study may be underestimated because of the self-reported nature of the assessment.[45] However, we believe the magnitude of this bias would be minimal because self-reported cigarette smoking underestimates prevalence of serum cotinine 15 ng/mL by only 0.6% in general US population.[45] Fourth, we may have failed to detect an association between other lifestyle factors and adverse pregnancy outcomes due to small sample size. For instance, we had 53% power to detect an odds ratio of 2.0 for an association between smoking and preterm birth among 1,269 live births with available gestational age.[9] Fifth, our results may also be biased due to unmeasured confounders such as other drug abuse, which is associated with both smoking and miscarriage.[46] Finally, we did not have information about the lifestyle factors and psychological status during pregnancy or about changes in these risk factors between self-report and conception.

Female survivors of childhood cancer, especially those treated with ovarian or uterine radiation, are more likely to be infertile.[29] Therefore, it is vital to identify factors detrimental for normal progress of pregnancy among female survivors. Our findings indicate that smoking more than 5 pack-years of cigarettes before pregnancy increases the risk of miscarriage, particularly among survivors treated with > 2.5 Gy uterine radiation. Given the current evidence about smoking-related adverse health outcomes, female survivors of childhood cancer who smoke and are planning to become pregnant should be provided with tools to promote smoking cessation. In addition, young female survivors of childhood cancer exposed to uterine radiation should be counseled early about this risk to discourage smoking initiation. Future large prospective studies are required to evaluate the null associations we observed between prepregnancy BMI, risky drinking, physical inactivity, or psychological distress, and adverse pregnancy outcomes.

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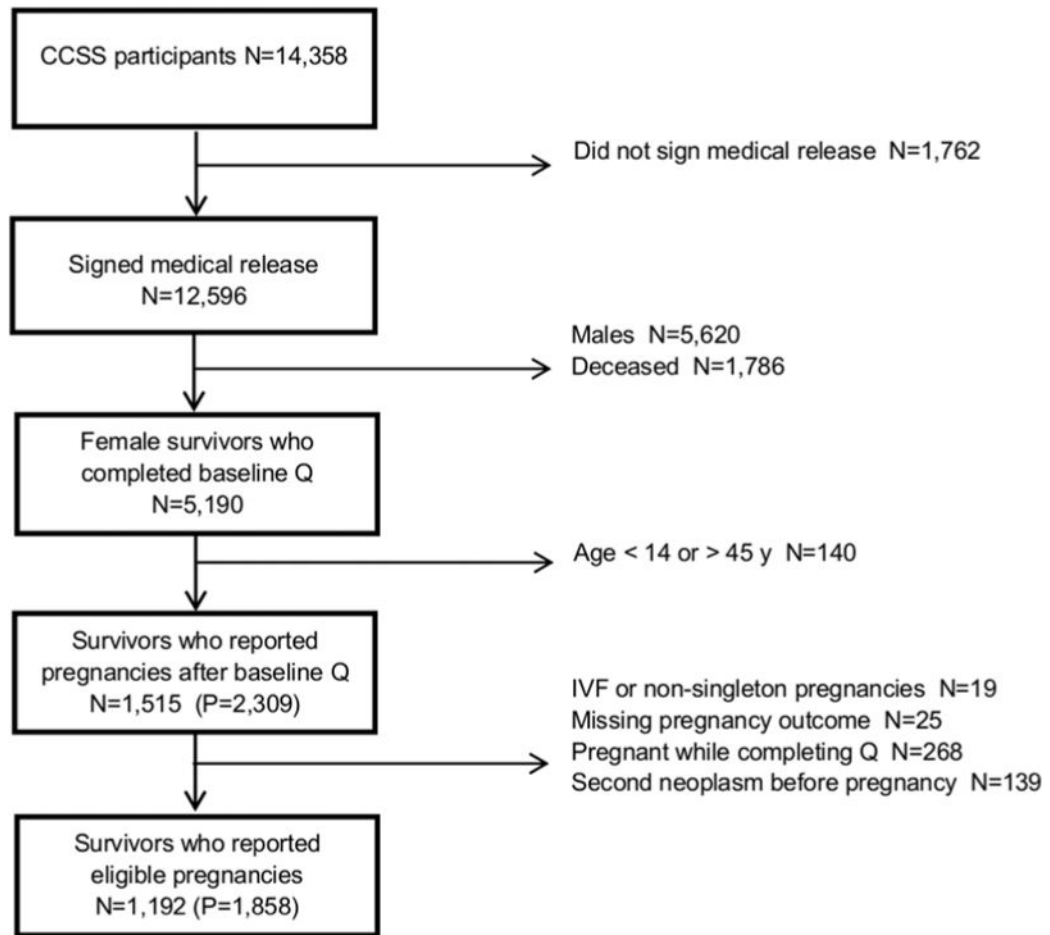
**Figure 1.**
Flowchart illustrating the selection of eligible pregnancies from the Childhood Cancer
Survivor Study (Q = questionnaire; IVF = in-vitro fertilization; P = pregnancies)

**Table 1**

Demographics, treatment characteristics, and exposure distribution of eligible pregnancies sample and comparison between female participants and non-participants

|  | Eligible pregnancies N=1,858 | Participants N=4,492 | Non-participants N=558 | P |
|---|---|---|---|---|
| Age at diagnosis (years) |  |  |  |  |
| 0–4 | 836 (45.0) | 1,990 (44.3) | 255 (45.7) | 0.47 |
| 5–9 | 455 (24.5) | 965 (21.5) | 126 (22.6) |  |
| 10–14 | 363 (19.5) | 891 (19.8) | 110 (19.7) |  |
| 15–20 | 204 (11.0) | 646 (14.4) | 67 (12.0) |  |
| Age at start of pregnancy (years) |  |  |  |  |
| 14–20 | 214 (11.5) | – | – | – |
| 21–25 | 435 (23.4) | – | – | – |
| 26–30 | 648 (34.9) | – | – | – |
| 31–35 | 389 (20.9) | – | – | – |
| 35–45 | 172 (9.3) | – | – | – |
| Race/ethnicity |  |  |  |  |
| White, non-Hispanic | 1,576 (84.8) | 3,847 (85.6) | 407 (72.9) | <0.001 |
| Black and Other, non-Hispanic | 196 (10.6) | 428 (9.5) | 105 (18.8) |  |
| Hispanic/Latino | 86 (4.6) | 217 (4.9) | 46 (8.2) |  |
| Parity |  |  |  |  |
| Nulliparous | 1,063 (57.2) | – | – | – |
| Multiparous | 795 (42.8) | – | – | – |
| Education level |  |  |  |  |
| Did not graduate high school | 313 (17.0) | 1,482 (34.8) | 202 (39.4) | <0.001 |
| Graduated from high school | 767 (41.7) | 1,720 (40.3) | 225 (43.9) |  |
| Graduated from college | 758 (41.3) | 1,063 (24.9) | 86 (16.7) |  |
| Health Insurance |  |  |  |  |
| Yes | 1,615 (86.9) | 3,963 (89.3) | 441 (81.2) | <0.001 |
| No | 243 (13.1) | 474 (10.7) | 102 (18.8) |  |
| Annual household income (US$) |  |  |  |  |
| < 20,000 | 641 (36.6) | 776 (18.9) | 163 (33.7) | <0.001 |
| 20,000 | 1,112 (63.4) | 3,336 (81.1) | 321 (66.3) |  |
| Cancer diagnosis |  |  |  |  |
| Leukemia | 741 (39.9) | 1,627 (36.2) | 210 (37.6) | 0.79 |
| Central nervous system | 121 (6.5) | 529 (11.8) | 70 (12.5) |  |
| Hodgkin lymphoma | 162 (8.7) | 492 (11.0) | 51 (9.2) |  |
| Non-Hodgkin lymphoma | 97 (5.2) | 218 (4.9) | 24 (4.3) |  |
| Renal tumor | 249 (13.4) | 487 (10.8) | 61 (10.9) |  |
| Neuroblastoma | 166 (8.9) | 368 (8.2) | 50 (9.0) |  |
| Soft tissue sarcoma | 161 (8.7) | 384 (8.5) | 51 (9.1) |  |
| Bone cancer | 161 (8.7) | 387 (8.6) | 41 (7.4) |  |
| Pituitary radiation |  |  |  |  |

| | Eligible pregnancies N=1,858 | Participants N=4,492 | Non-participants N=558 | P |
|---|---|---|---|---|
| 0–2.5 Gy | 1,364 (75.3) | 2,852 (65.4) | 329 (63.4) | 0.21 |
| > 2.5 Gy | 446 (24.7) | 1,512 (34.6) | 190 (36.6) | |
| Uterine radiation | | | | |
| 0–2.5 Gy | 1,703 (91.9) | 3,867 (88.6) | 470 (91.3) | 0.07 |
| > 2.5 Gy | 149 (8.1) | 497 (11.4) | 45 (8.7) | |
| Ovarian radiation | | | | |
| 0–2.5 Gy | 1,666 (91.8) | 3,749 (86.0) | 447 (86.6) | 0.69 |
| > 2.5 Gy | 149 (8.2) | 610 (14.0) | 69 (13.4) | |
| Alkylating agent score[a] | | | | |
| 0 (no alkylators) | 1,007 (56.7) | 2,329 (56.0) | 278 (54.9) | 0.86 |
| 1 | 415 (23.4) | 919 (22.1) | 109 (21.5) | |
| 2 | 254 (14.3) | 582 (14.0) | 77 (15.2) | |
| 3 | 100 (5.6) | 327 (7.9) | 42 (8.3) | |
| Anthracycline score | | | | |
| 0 (no anthracycline) | 1,127 (61.9) | 2,779 (64.0) | 345 (64.5) | 0.35 |
| 1 | 200 (11.0) | 541 (12.4) | 70 (13.1) | |
| 2 | 302 (16.6) | 537 (12.4) | 53 (9.9) | |
| 3 | 191 (10.5) | 487 (11.2) | 67 (12.5) | |
| Physically inactive | | | | |
| Yes | 916 (52.3) | 2,646 (60.5) | 353 (65.5) | 0.03 |
| No | 835(47.7) | 1,725 (39.5) | 186 (34.5) | |
| Body mass index (kg/m$^2$) | | | | |
| Underweight: <18.5 | 114 (6.7) | 581 (13.5) | 71 (13.5) | 0.13 |
| Normal: 18.5–25 | 1,056 (62.3) | 2,510 (58.4) | 282 (53.6) | |
| Overweight: 25–30 | 321 (18.9) | 750 (17.4) | 105 (20.0) | |
| Obese: 30 | 205 (12.1) | 460 (10.7) | 68 (12.9) | |
| Smoking (pack-years) | | | | |
| 0 (Never) | 1,286 (75.1) | 3,456 (82.2) | 398 (77.4) | 0.03 |
| 0.1–5 | 293 (17.1) | 471 (11.2) | 74 (14.4) | |
| > 5 | 133 (7.8) | 277 (6.6) | 42 (8.2) | |
| Risky drinking[b] | | | | |
| Yes | 217 (31.2) | 732 (28.8) | 95 (32.6) | 0.16 |
| No | 479 (68.8) | 1,813 (71.2) | 196 (67.4) | |
| Psychological status[c] | | | | |
| Global distress | | | | |
| Yes | 116 (7.9) | 264 (8.6) | 36 (9.7) | 0.49 |
| No | 1,347 (92.1) | 2,794 (91.4) | 335 (90.3) | |
| Depression | | | | |
| Yes | 128 (8.7) | 291 (9.5) | 38 (10.2) | 0.65 |
| No | 1,338 (91.3) | 2,773 (90.5) | 334 (89.8) | |
| Pregnancy outcomes | | | | |

| | Eligible pregnancies N=1,858 | Participants N=4,492 | Non-participants N=558 | P |
|---|---|---|---|---|
| Live birth | 1,300 (70.0) | – | – | – |
| Stillbirth | 21 (1.1) | – | – | – |
| Miscarriage | 397 (21.4) | – | – | – |
| Medical abortion | 140 (7.5) | – | – | – |
| Preterm birth | | | | |
| Yes | 310 (24.4) | – | – | – |
| No | 959 (75.6) | – | – | – |

Participants were those who completed 1) both baseline and 2000 questionnaire or
2) both 2003 and 2007 questionnaire
Non-participants were those who completed 1) baseline but not the 2000 questionnaire or
2) 2003 but not the 2007 questionnaire

P value was calculated for chi-squared test

[a] non-platinum alkylators

[b] defined as >3 drinks/day or >7 drinks/week based on the National Institute on Alcohol Abuse and Alcoholism guidelines based on only 1995–2000 interval

[c] from Brief Symptom Inventory-18 (T score 63)
Numbers may not equal total because of unanswered questions

**Table 2**

Adjusted risk of adverse pregnancy outcomes in female survivors of childhood cancer

| | N | Preterm birth (N=310) | | Stillbirth (N=21) | | Miscarriage[b] (N=397) | | Risk of Miscarriage by Uterine Radiation[c] | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| | | | | | | | | 0–2.5 Gy (N=1,703) | | > 2.5 Gy (N=149) | |
| | | Row % | RR (95% CI) | Row % | RR (95% CI) | Row % | RR (95% CI) | Row % | RR (95% CI) | Row % | RR (95% CI) |
| Physically inactive[a] | | | | | | | | | | | |
| Yes | 916 | 22.6 | 0.9 (0.6, 1.2) | 0.7 | 0.5 (0.1, 1.8) | 22.6 | 1.0 (0.8, 1.4) | 22.8 | 1.1 (0.8, 1.5) | 21.1 | 0.5 (0.2, 1.5) |
| No | 835 | 26.2 | 1.0 | 1.4 | 1.0 | 21.3 | 1.0 | 20.8 | 1.0 | 28.1 | 1.0 |
| Body Mass Index (kg/m2) | | | | | | | | | | | |
| Underweight: <18.5 | 114 | 18.3 | 1.0 (0.5, 2.1) | 1.8 | 1.3 (0.1, 17.9) | 18.4 | 0.8 (0.4, 1.4) | 18.8 | 0.9 (0.5, 1.6) | 15.4 | 0.2 (0.1, 0.7) |
| Normal weight: 18.5–25 | 1,056 | 22.7 | 1.0 | 0.7 | 1.0 | 21.2 | 1.0 | 21.1 | 1.0 | 23.5 | 1.0 |
| Overweight: 25–30 | 321 | 27.9 | 1.3 (0.9, 1.9) | 2.2 | 2.3 (0.5, 10.9) | 20.9 | 0.9 (0.6, 1.3) | 20.6 | 0.8 (0.5, 1.2) | 24.0 | 0.5 (0.1, 1.8) |
| Obese: ≥30 | 205 | 31.5 | 1.1 (0.7, 1.8) | 0.5 | 0.8 (0.1, 7.9) | 28.8 | 1.4 (0.8, 2.1) | 28.6 | 1.3 (0.8, 2.0) | 35.7 | 1.5 (0.4, 6.3) |
| Global distress | | | | | | | | | | | |
| Yes | 116 | 20.3 | 0.8 (0.4, 1.7) | 1.7 | 1.3 (0.1, 10.9) | 20.9 | 1.5 (0.9, 2.5) | 28.4 | 1.6 (0.9, 2.7) | 28.6 | 0.9 (0.3, 3.0) |
| No | 1,347 | 24.5 | 1.0 | 0.7 | 1.0 | 28.4 | 1.0 | 20.9 | 1.0 | 21.6 | 1.0 |
| Smoking (pack-years) | | | | | | | | | | | |
| 0 (Never) | 1,286 | 24.8 | 1.0 | 1.2 | 1.0 | 20.3 | 1.0 | 20.3 | 1.0 | 21.2 | 1.0 |
| 0–5 | 293 | 21.4 | 0.7 (0.5, 1.2) | 1.4 | 1.2 (0.3, 5.2) | 21.2 | 1.1 (0.7, 1.6) | 21.3 | 1.1 (0.8, 1.7) | 20.0 | 0.7 (0.3, 1.9) |
| > 5 | 133 | 35.1 | 1.6 (0.8, 3.0) | 0.8 | 1.4 (0.1, 16.1) | 34.6 | 2.2 (1.4, 3.5) | 31.2 | 1.9 (1.2, 3.0) | 87.5 | 53.9 (2.2, 1326.1) |

Risk presented as odds ratio (95% confidence interval); Models adjusted for age at pregnancy, age at diagnosis, educational attainment, and parity

[a] < 60 minutes vigorous or < 150 minutes moderate physical activity per week

[b] In a multivariable model evaluating risk for miscarriage, Pinteraction for smoking*uterine radiation = 0.01

[c] In a multivariable model adjusted for age at pregnancy, age at diagnosis, educational attainment, parity, inactivity, BMI, global distress, and smoking, the risk for miscarriage among those who were exposed to > 2.5 Gy of radiation was 1.2 (95% CI 0.8, 1.9).

**Table 3**

Sensitivity of association between smoking > 5 pack-years (versus 0 pack-years) and miscarriage among those who received > 2.5 Gy uterine radiation (N=121)[a] because of non-participation.

| Assumed prevalence of miscarriage among non-participants | Observed unadjusted odds ratio of 25.9[b] among participants (N=121) | Assumed odds ratio among non-participants (N=15)[c] | Summary odds ratio (N=136)[d] |
|---|---|---|---|
| 30% | 25.9 | 1.0 | 6.3 |
| 25% | 25.9 | 1.0 | 5.5 |
| 20% | 25.9 | 1.0 | 3.7 |
| 15% | 25.9 | 1.0 | 4.4 |
| 30% | 25.9 | 0.5 | 4.4 |
| 25% | 25.9 | 0.5 | 4.0 |
| 20% | 25.9 | 0.5 | 4.2 |
| 15% | 25.9 | 0.5 | 3.0 |

[a] Out of 149 pregnancies with > 2.5 Gy uterine radiation (see Table 2), 8 had history of > 5 pack-years and 113 had no history of smoking (N=121).

[b] Out of the 8 with history of > 5 pack-years 7 had miscarriages and out of the 113 with no history of smoking 24 had miscarriages. Thus, the observed unadjusted risk of miscarriage among those with history of smoking > 5 pack-years was 25.9.

[c] We assumed a non-participation rate of 11% (15 of 136) based on the observed 558 (11%) non-participants out of 5,050 eligible participants

[d] If exposure-outcome distribution of non-participants were combined with exposure-outcome distribution of participants