GYNECOLOGY

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

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

STUDY DESIGN: We examined pregnancies of 1192 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, psychologic distress and pregnancy outcomes. Interactions between lifestyle factors, psychologic 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 1858 reported pregnancies, there were 1300 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 with those who had never smoked, survivors with >5 pack-years smoking history had a higher risk for miscarriage among those treated with >2.5 Gray (Gy) uterine radiation (OR, 53.9; 95% CI, 2.2–1326.1) than among those treated with ≤2.5 Gy uterine radiation (OR, 1.9; 95% CI, 1.2–3.0). There was a significant interaction between smoking and uterine radiation ($P_{interaction} = .01$).

CONCLUSION: Although most lifestyle factors and psychologic 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.

Key words: childhood cancer survivors, lifestyle, pregnancy, smoking, uterine radiation

Cite this article as: Gawade PL, Oeffinger KC, Sklar CA, et al. Lifestyle, distress, and pregnancy outcomes in the Childhood Cancer Survivor Study cohort. Am J Obstet Gynecol 2015;212:45.e1-10.

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 5 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 with 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 ≥5 Gray (Gy) of uterine radiation,[3] stillbirth following ≥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 psychologic 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 psychologic distress. Adult female survivors of childhood cancer have high rates of both underweight and obesity,[15] physical inactivity,[16] and psychologic distress.[17] However, survivors are less likely than siblings to report smoking[18,19] and heavy alcohol consumption.[20] Lifestyle and psychologic factors may explain a portion of the risk

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Received April 24, 2014; revised July 2, 2014; accepted July 22, 2014.

The authors report no conflict of interest.

This work was supported by a grant from the National Cancer Institute (U24 CA55727, L.L.R., Principal Investigator) and by the American Lebanese Syrian Associated Charities (ALSAC).

Preliminary results were presented at the 13th International Conference on Long-Term Complications of Treatment of Children and Adolescents of Cancer organized by St. Jude Children's Research Hospital, Memphis, TN, June 13-15, 2013.

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0002-9378/$36.00 • http://dx.doi.org/10.1016/j.ajog.2014.07.036

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

The current study was designed to evaluate potential associations between prepregnancy lifestyle factors, psychologic 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 1 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, psychologic 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 posttraumatic 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 psychologic distress (Figure). Nonsingleton pregnancies, pregnancies resulting from in vitro fertilization, or reported pregnancies without a known outcome, were not included (Figure).

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 psychologic distress were obtained from the baseline and 2003 questionnaires completed before 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 20. 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 psychologic 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 before pregnancy.

Statistics

Demographic factors and treatment exposures of survivors with eligible pregnancies were examined as frequencies and percentages. To evaluate