Hypothyroidism after cancer and the ability to meet reproductive goals among a cohort of young adult female cancer survivors

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Objective: To determine whether developing hypothyroidism after cancer treatment is associated with a decreased probability of women being able to meet their reproductive goals.
Design: A population-based cohort study.
Setting: Not applicable.
Patient(s): A total of 1,282 cancer survivors, of whom 904 met the inclusion criteria for the analysis.
Intervention(s): None.
Main Outcome Measure(s): Three outcomes that may indicate reduced fertility, which include failure to achieve desired family size, childlessness, and not achieving pregnancy after at least 6 months of regular unprotected intercourse.
Result(s): We used data from the Furthering Understanding of Cancer Health and Survivorship in Adult (FUCHSIA) Women's Study to examine the association between being diagnosed with hypothyroidism after cancer and meeting reproductive goals. After adjusting for age and other potential confounders, women reporting hypothyroidism after cancer treatment were twice as likely to fail to achieve their desired family size (adjusted odds ratio [aOR] 1.91; 95% confidence interval [CI], 1.09, 3.33) and be childless (aOR 2.13; 95% CI, 1.25, 3.65). They were also more likely to report having unprotected intercourse for at least 6 months without conceiving (aOR 1.37; 95% CI, 0.66, 2.83).
Conclusion(s): Although cancer treatments themselves are gonadotoxic, it is important to consider other medical conditions such as hypothyroidism that occur after cancer treatment when counseling patients on the risks for impaired fertility or a shortened reproductive window. (Fertil Steril® 2015;■:■–■. ©2015 by American Society for Reproductive Medicine.)
Key Words: Cancer survivors, hypothyroidism, infertility

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Women with a cancer diagnosis are often treated with potentially gonadotoxic regimens that may put them at risk for infertility (1, 2). Studies in childhood cancer survivors have found that cancer treatment leads to reduced ovarian function (2–6). Studies in adolescents and adult women show this association as well (1, 7). There have also been several registry-based studies examining the effects of cancer treatment on fertility. These studies show decreased rates of childbearing and increased probabilities of childlessness among female cancer survivors (8–10).

Additionally, some research suggests that hypothyroidism can affect female fertility and pregnancy outcomes. For example, hypothyroidism has been reported to be associated with reduced fertility, menstrual irregularities, and anovulation in reproductive-age women (11). In a study of pregnant women, researchers

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found that hypothyroidism and subclinical hypothyroidism were associated with spontaneous abortion (12). Further, evidence from a clinic-based study of women with infertility suggests that the prevalence of hypothyroidism among these women is higher than the general population (13).

Some cancer treatments can influence the development of hypothyroidism. The vast majority of the literature on the development of hypothyroidism after cancer treatment focuses on radiation in the childhood cancer survivor population (14, 15). Children with lymphomas treated with total body irradiation have been found to have high rates of thyroid abnormalities (16). Additionally, a study in children with Hodgkin's lymphoma reported that radiation to the head and neck region increased the risk of developing hypothyroidism (17). This association is less established in adults, but in a study of adult larynx and pharynx cancer patients, radiation was associated with developing hypothyroidism after treatment (18). These studies support the hypothesis that hypothyroidism after cancer treatment may be caused by radiation and highlight the need for further examination of this association in adults, where the literature is sparse. In addition to radiation therapy, some chemotherapy agents have been associated with thyroid function changes (19, 20). However, most of the changes associated with chemotherapy have been shown to be small and transient and may not result in later diagnoses of hypothyroidism.

Thus, both cancer treatment and hypothyroidism have been shown to affect fertility outcomes in women. However, the association between hypothyroidism and infertility has not been assessed in a population of cancer survivors. The primary objective of this study is to determine whether developing hypothyroidism after cancer treatment is associated with a decreased probability of women being able to meet their reproductive goals compared with not developing hypothyroidism after treatment.

MATERIALS AND METHODS

The Furthering Understanding of Cancer Health and Survivorship in Adult (FUCHSIA) Women's Study is a population-based cohort study designed to examine how cancer treatment during the reproductive years affects future fertility and other women's health outcomes. Women were eligible to participate if they were of reproductive age (22–45 year old), had a working telephone, and spoke English. In addition, cancer survivors had to have received a diagnosis of a malignant cancer or ductal carcinoma in situ between the ages of 20 and 35 years and to be at least 2 years from the diagnosis at recruitment. Eligible cancer survivors were identified and contacted by the Georgia Cancer Registry, who shared information about the study with women who had cancer diagnoses between 1990 and 2009. Women who agreed to study contact were invited to complete a detailed interview about their reproductive histories. The interview included questions about all cancer diagnoses and treatments, medical conditions, experience with infertility, pregnancy history, desire for children, reproductive goals, demographic characteristics, and lifestyle factors. Women consented to participate in the study at the time of the interview. The Emory University and the Georgia Department of Public Health institutional review boards approved this study.

Women who had received a thyroid cancer diagnosis were excluded because their cancer directly affected their thyroid. In addition, women were ineligible if they reported having a bilateral oophorectomy or hysterectomy before the cancer diagnosis because they would not be able to become pregnant after cancer treatment. During the interview, women were asked whether they had ever been diagnosed with hypothyroidism by a medical professional, and if yes, what had been their age at diagnosis. Women with a hypothyroidism diagnosis before or in the same year as their cancer diagnosis were also excluded. Cancer type and treatment information were limited to the first cancer diagnosis. We used self-reported race, age, ever treated with chemotherapy, and ever treated with radiation therapy from the interview. The information about the type of cancer for each woman was obtained from the Georgia Cancer Registry.

We used SAS 9.4 (SAS Institute) for all statistical analyses. For our main analysis, we explored several outcomes that might indicate reduced fertility. The first outcome was having fewer children than desired at the time of the interview, which was calculated by subtracting the number of children women gave birth to from the total number they reported they desired. The second outcome, childlessness, was defined as not having given birth to a child by the time of the interview. The last outcome, impaired fertility after cancer diagnosis, was defined as at least a 6-month period where the participant had regular unprotected intercourse with a man but did not become pregnant after the cancer diagnosis. Covariates that were considered to influence the relationship between hypothyroidism and not meeting reproductive goals were race, cancer type, cancer treatment, age at interview, and age at cancer diagnosis.

We fit logistic regression models to assess the association between being diagnosed with hypothyroidism after cancer and each of these fertility-related outcomes. We obtained both a crude and adjusted estimate controlled for race (black, white, another race), cancer type (breast, reproductive, lymphoma, other cancer type), cancer treatment (radiation therapy ever, chemotherapy ever), age at interview (22–29, 30–39, 40–45 years), and age at cancer diagnosis (20–24, 25–29, 30–35 years).

We conducted several subanalyses using fewer children than desired as the outcome. One analysis was restricted to breast cancer survivors, the most common cancer in our study, to minimize the differences due to a specific cancer diagnosis between women who developed and did not develop hypothyroidism after cancer. We also fit models that excluded women in whom a reproductive cancer was diagnosed with because their cancer might affect reproductive function directly rather than through hypothyroidism. For theses analyses, the women with cervical, ovarian, or uterine cancers diagnosed were excluded. We conducted analyses stratified by radiation exposure to examine the effect of hypothyroidism within the group of women ever exposed and women never exposed to this type of treatment. Last, we ran a sensitivity analysis restricted to women who were