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Helen B. Chin, *Emory University*
Melanie H. Jacobson, *Emory University*
Julia D. Interrante, *Emory University*
[Ann Mertens](#), *Emory University*
[Jessica Spencer](#), *Emory University*
[Penelope Howards](#), *Emory University*

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

Helen B. Chin, PhD^a, Melanie H. Jacobson, MPH^a, Julia D. Interrante, MPH^a, Ann C. Mertens, PhD^b, Jessica B. Spencer, MD^c, and Penelope P. Howards, PhD^a

^aDepartment of Epidemiology, Rollins School of Public Health, Emory University, 1518 Clifton Rd., NE, Atlanta, GA 30322

^bAflac Cancer Center, Department of Pediatrics, Emory University School of Medicine, 2015 Upper Gate Dr., NE, Atlanta, GA 30322

^cDepartment of Gynecology and Obstetrics, Emory University School of Medicine, Medical Office Tower, Suite 1800 550 Peachtree Street, NE, Atlanta, GA 30308

Abstract

Objective—To determine if 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.

Patients—A total of 1,282 cancer survivors participated in the study, of which 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.

Results—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% 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).

Corresponding author: Helen B. Chin, PhD, MPH, Department of Epidemiology, Rollins School of Public Health, Emory University, 1518 Clifton Rd., NE, CNR 3rd Floor, Atlanta, GA 30322, Tel: 404-727-4795; fax: 404-727-8737, hbchin@alumni.emory.edu.

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Conclusion—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.

Keywords

hypothyroidism; cancer survivors; infertility

Introduction

Women who are diagnosed with cancer are often treated with potentially gonadotoxic regimens which 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 aged women (11). In a study of pregnant women, researchers 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 if 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.

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 years old), had a working telephone, and spoke English. In addition, cancer survivors had to be diagnosed with a malignant cancer or ductal carcinoma in situ between the ages of 20–35 and be at least 2 years post diagnosis at recruitment. Eligible cancer survivors were identified and contacted by the Georgia Cancer Registry (GCR) who shared information about the study with women diagnosed with cancer 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 diagnosed with thyroid cancer were excluded because their cancer directly affected their thyroid. In addition, women were ineligible if they reported having a bilateral oophorectomy or hysterectomy before cancer diagnosis because they could not get pregnant after cancer. During the interview, women were asked whether or not they had ever been diagnosed with hypothyroidism by a medical professional and if so, their age at diagnosis. Women diagnosed with hypothyroidism before or in the same year as their cancer diagnosis were also excluded. Cancer type and treatment information were limited to first cancer diagnosis. We used self-reported race, age, ever treated with chemotherapy, and ever treated with radiation therapy from the interview. The type of cancer women were diagnosed with was obtained from the GCR.

SAS 9.4 was used for all statistical analyses (Cary, N.C.). 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 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 sub-analyses using fewer children than desired as the outcome. One analysis was restricted to breast cancer survivors, the most common cancer in our study, in order to minimize 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 who were diagnosed with a reproductive cancer because their cancer may affect reproductive function directly rather than through hypothyroidism. For these analyses, women diagnosed with cervical, ovarian, or uterine cancers 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 restricting to women who were childless at the time of cancer diagnosis or had given birth to fewer children than they reported wanting at the time of diagnosis to assess the association between hypothyroidism and fewer children than desired among women who would be most likely to attempt pregnancy after treatment.

Results

A total of 1,282 cancer survivors participated in the study (56.4% of those who agreed to study contact). Two hundred and thirty-three participants were excluded because they were diagnosed with thyroid cancer ($n = 87$), hypothyroidism before or in the same year as their cancer diagnosis ($n = 60$), both ($n = 36$), or had missing information on thyroid disease ($n = 50$). Further exclusion of women who were not able to get pregnant at the time they were diagnosed with cancer ($n = 145$) (i.e. due to hysterectomy or bilateral oophorectomy) resulted in 904 women being included in our analysis. Women were interviewed a median of 7.5 years after diagnosis (IQR: 5, 11). Eight percent of the women in our analysis reported that they were diagnosed with hypothyroidism after cancer treatment, of which 90% were taking medications to treat their condition. The characteristics of the sample stratified by hypothyroidism status are presented in Table 1 and Supplemental Table 1. More women diagnosed with lymphomas reported having hypothyroidism, with 21% who reported developing hypothyroidism after cancer treatment, compared with less than 7% in the other cancer groups. Women who reported receiving radiation compared with not receiving radiation and black women compared with white women were also more likely to report hypothyroidism after cancer treatment (12% vs. 5% and 10% vs. 2%, respectively). Over half of the women in our study reported having fewer children than they desired at the time of the interview (Table 2 and Supplemental Table 1). As expected, a higher proportion of younger women reported not achieving their desired family size. There was similar reporting of having fewer children than desired across cancer types, cancer treatment, and race groups.

Women diagnosed with hypothyroidism after cancer treatment were more likely to report each of the outcomes indicating reduced fertility that we examined in this study (Table 3). Women reporting hypothyroidism after cancer treatment were twice as likely to fail to achieve their desired family size (i.e., have fewer children than they desired) at the time of the interview (adjusted odds ratio (aOR) = 1.91, 95% CI: 1.09, 3.33) and be childless at the time of the interview (aOR = 2.13, 95% CI: 1.25, 3.65). The association between

hypothyroidism and having fewer children than desired was stronger and reached statistical significance in the fully adjusted model compared with the unadjusted estimate. Age at cancer diagnosis and age at interview were the strongest confounders. The association between hypothyroidism after cancer treatment and experiencing a period of infertility was weaker and not statistically significant (aOR = 1.37, 95% CI: 0.66, 2.83).

We had similar results in our subgroup analysis (Table 4). Among women with breast cancer those who developed hypothyroidism had a smaller but not significant increased odds of failing to achieve their desired family size compared with those who did not report hypothyroidism by the study interview (aOR = 1.37, 95% CI 0.48, 3.96), but the sample was small with only 8 women with hypothyroidism reporting that they had fewer children than desired. When women with reproductive cancers were removed from the overall analysis sample, there was still an increased likelihood of women with hypothyroidism failing to achieve their desired family size (aOR = 1.86, 95% CI: 1.05, 3.31). When we restricted to women who were childless or had not yet met their reproductive goals at the time of their cancer diagnosis the association between hypothyroidism and indicators of reduced fertility remained (data not shown).

Because radiation is suspected to induce hypothyroidism in some cancer patients, we also conducted analyses stratified by receipt of radiation as part of cancer treatment (Supplemental Table 2) (17). The effects of hypothyroidism on having fewer children than desired differed by strata of radiation exposure. Among cancer survivors who were treated with radiation, those who were diagnosed with hypothyroidism after treatment were more likely to fail to achieve their desired family size compared with those who were not diagnosed with hypothyroidism although this estimate was imprecise (aOR = 2.84, 95% CI 1.30, 6.18). Among women who were not treated with radiation, there was a non-significant association between being diagnosed with hypothyroidism and failing to achieve desired family size (aOR = 1.30, 95% CI 0.55, 3.07).

Discussion

As a population-based study, the FUCHSIA Women's Study provides the opportunity to consider whether there is an association between post-cancer hypothyroidism and the ability of women diagnosed with cancer to meet their reproductive goals. Our results suggest that women who are diagnosed with hypothyroidism after cancer treatment during their reproductive years have an increased likelihood of experiencing all of the indicators of reduced fertility that we assessed in our analysis. They were more likely to fail to achieve their desired family size, be childless, and experience a period of infertility compared with cancer survivors who were not subsequently diagnosed with hypothyroidism after adjusting for treatment, age, and other potential confounders.

There is limited literature on cancer treatment-induced hypothyroidism, but the existing research suggests that treatment with radiation contributes to hypothyroidism after cancer (14, 17). We found that a higher proportion of cancer survivors treated with radiation reported developing hypothyroidism after cancer diagnosis compared with those not treated with radiation. This treatment-induced hypothyroidism may later have detrimental effects on

fertility. In our study, women with hypothyroidism after radiation treatment were substantially less likely to have the family size they desired compared with women without hypothyroidism after radiation treatment. However, our results suggest that even among women who were not treated with radiation, a diagnosis of hypothyroidism after cancer diagnosis may be associated with impaired fertility. These results highlight the importance of considering other medical conditions that occur after cancer treatment when estimating the effects of cancer and cancer treatment on future fertility.

A strength of our study is that it is population-based. We recruited female cancer survivors for our study from the Georgia Cancer Registry, which collects information on all incident cancer cases in the state. The ability to recruit women with all types of cancer gave us the flexibility to conduct subgroup analyses in breast cancer survivors only and women without reproductive cancers. The ability to test our hypothesis in cancer survivors overall and in both a single cancer group likely receiving similar treatments and a group whose cancer did not directly affect their reproductive function strengthened our findings. Our conclusions are also made stronger by our use of multiple measures of impaired fertility. Childlessness is often used in observational studies as a proxy for infertility, but this assumes that all women want children (5, 10). Our study was able to assess failure to achieve desired family size, as well as infertility as marked by periods of unprotected intercourse without a pregnancy, in addition to childlessness. Failure to achieve desired family size is a unique measure in that it captures both women who were never able to have children as well as women who wanted to have more children, but were unable, which may indicate subfertility. However, having fewer children than desired could also be a result of survivorship issues that are unrelated to subfertility, such as delays in childbearing as a result of cancer treatment.

A limitation of this work is that the number of women in our cohort with hypothyroidism was small in some of our analyses, which led to imprecise estimates. Nevertheless, our study provides preliminary results to a question that has not been thoroughly examined in the field. Because we only had information on ever use of chemotherapy and radiation therapy, we were limited in our ability to control for cancer treatment in our models. In our analysis restricted to breast cancer survivors, we limited to the effects different cancer diagnoses have on the development of hypothyroidism, which may have also reduced the variability in the type of treatment women received. In these analyses, we saw results in the same direction and magnitude as the main analysis. Another potential limitation is that the data are restricted to self-reported information on hypothyroidism diagnosis without verification of these visits with medical records. However, another study found that there is high sensitivity for self-reported hypothyroidism diagnosis when compared to medical records (21).

In 2006, the National Cancer Institute called for more research on individuals with young adult cancers (22). Our study provides information on hypothyroidism that may be induced by cancer treatment and its potential effects on meeting reproductive goals. Previously, the literature has focused on hypothyroidism and infertility after cancer treatment as two separate survivorship issues. Although it is well established that some cancer treatments compromise fertility by affecting the reproductive system and reducing ovarian function (1, 2, 7), it is not known whether reproductive function differs between women who do and do

not develop hypothyroidism after cancer. There is some evidence that hypothyroidism can affect fertility (11).

Our study considers fertility outcomes among female cancer survivors who develop hypothyroidism after cancer treatment as a first step in assessing two potential pathways. Hypothyroidism may directly affect fertility by disrupting the balance of reproductive hormones, which can lead to anovulation (13). It may also serve as a marker of more intense gonadotoxic cancer treatment without directly affecting fertility itself. However, after adjusting for chemotherapy and radiation therapy, treatments that are known to have gonadotoxic effects, hypothyroidism was still associated with infertility (1, 2). When results were stratified by radiation exposure, the magnitude of the association between hypothyroidism and failure to meet desired family size was stronger among women who received radiation therapy, which suggests that radiation exposure modifies the effect of hypothyroidism.

Our study provides preliminary results for future research on the association between hypothyroidism after cancer treatment and poor fertility outcomes. Regardless of the mechanism, clinicians who care for cancer survivors who develop hypothyroidism need to counsel their patients that they may be at risk for impaired fertility or a shorter reproductive window. This could allow some women to plan their pregnancies before the potential decline in their reproductive capacity as a result of cancer treatment and subsequent hypothyroidism. This is especially important because hypothyroidism may be more prevalent among cancer survivors and timely and appropriate control of this condition may improve fertility outcomes (23, 24).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Characteristics of a Cohort of Young Adult Female Cancer Survivors by Hypothyroidism Status^a

Table 1

	Total (n=904)		Hypothyroidism after cancer (n=71)		No Hypothyroidism (n=833)	
	No.	%	No.	%	No.	%
Age at cancer diagnosis						
20–24	140	15.5	21	15.0	119	85.0
25–29	280	31.0	17	6.1	263	93.9
30–35	484	53.5	33	6.8	451	93.2
Age at interview						
22–29	67	7.4	1	1.5	66	98.5
30–39	489	54.1	34	7.0	455	93.1
40–45	348	38.5	36	10.3	312	89.7
Cancer Type						
Breast	358	39.6	17	4.8	341	95.3
Lymphomas	162	17.9	34	21.0	128	79.0
Reproductive ^b	60	6.6	4	6.7	56	93.3
Other	324	35.8	15	4.6	284	95.4
Chemotherapy (ever)						
Yes	587	64.9	53	9.0	534	91.0
No	317	35.1	18	5.7	299	94.3
Radiation (ever)						
Yes	388	42.9	46	11.9	342	88.1
No	516	57.1	25	4.8	491	95.2
Race/Ethnicity						
Black	250	27.8	6	2.4	244	97.6
White	608	67.7	61	10.0	547	90.0
Other race	40	4.5	3	7.5	37	92.5
Missing	6		1		5	

^a Cancer survivors with thyroid cancer and diagnosed with hypothyroidism at or before cancer were excluded^b Reproductive cancers: uterine, ovarian, and cervical

Characteristics of a Cohort of Young Adult Female Cancer Survivors by Fewer Children Than Desired at Time of Interview^a

Table 2

	Total (n=894)		Fewer Children (n=487)		Not Fewer Children (n=407)	
	No.	%	No.	%	No.	%
Age at cancer diagnosis						
20–24	137	15.3	95	69.3	42	30.7
25–29	279	31.2	162	58.1	117	41.9
30–35	478	53.5	230	48.1	248	51.9
Age at interview						
22–29	65	7.3	54	83.1	11	16.9
30–39	484	54.1	297	61.4	187	38.6
40–45	345	38.6	136	39.4	209	60.6
Cancer Type						
Breast	355	39.7	181	51.0	174	49.0
Lymphomas	159	17.8	90	56.6	69	43.4
Reproductive ^b	60	6.7	40	66.7	20	33.3
Other	320	35.8	162	54.9	133	45.1
Chemotherapy (ever)						
Yes	581	65.0	322	55.4	259	44.6
No	313	35.0	165	52.7	148	47.3
Radiation (ever)						
Yes	383	42.8	204	53.3	179	46.7
No	511	57.2	283	55.4	228	44.6
Race/Ethnicity						
Black	248	27.9	140	56.5	108	43.5
White	601	67.7	323	53.7	278	46.3
Other race	39	4.4	20	51.3	19	48.7
Missing	6		4		2	

^a Cancer survivors with thyroid cancer and diagnosed with hypothyroidism at or before cancer were excluded^b Reproductive cancers: uterine, ovarian, and cervical

Missing data: Fewer children than desired (n=10)

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Crude and adjusted odds ratios of the association between hypothyroidism after cancer and fertility-related outcomes at the time of the interview^a

Table 3

	Total no.	Fertility-related outcome no.	Unadjusted		Adjusted ^b	
			OR	95% CI	OR	95% CI
Had fewer children than desired^c						
No hypothyroidism	825	445	1.00	reference	1.00	reference
Hypothyroidism after cancer	69	42	1.33	0.80 2.20	1.91	1.09 3.33
Childless^d						
			OR	95% CI	OR	95% CI
No hypothyroidism	833	245	1.00	reference	1.00	reference
Hypothyroidism after cancer	71	32	1.97	1.21 3.22	2.13	1.25 3.65
Infertility period of 6 months after cancer^e						
			OR	95% CI	OR	95% CI
No hypothyroidism	797	101	1.00	reference	1.00	reference
Hypothyroidism after cancer	67	14	1.82	0.98 3.41	1.37	0.66 2.83

OR: odds ratio; 95% CI: 95% confidence interval

^aCancer survivors with thyroid cancer and diagnosed with hypothyroidism at or before cancer were excluded

^bAdjusted: race, cancer type (breast, lymphoma, reproductive, other), cancer treatment (chemotherapy ever, radiation ever), age at interview, age at diagnosis

^cFewer children than desired: calculated by subtracting the number of children women gave birth to from the total number they reported they desired

^dChildless: not having given birth to a child by the time of the interview

^eInfertility: at least a 6 month period where the participant had regular unprotected intercourse, but did not become pregnant at a time after cancer diagnosis

Crude and adjusted odds ratios for subgroup analysis of the association between hypothyroidism after cancer and having fewer children than desired at the time of the interview^d

Table 4

	Total	Had fewer children than desired ^b	Unadjusted		Adjusted ^c	
			OR	95% CI	OR	95% CI
Breast cancer survivors						
No hypothyroidism	339	173	1.00	reference	1.00	reference
Hypothyroidism after cancer	16	8	0.96	0.35 2.62	1.37	0.48 3.96
Survivors of non-reproductive cancers^d						
No hypothyroidism	769	408	1.00	reference	1.00	reference
Hypothyroidism after cancer	65	39	1.33	0.79 2.22	1.86	1.05 3.31

OR: odds ratio; 95% CI: 95% confidence interval

^a Cancer survivors diagnosed with hypothyroidism at or before cancer were excluded

^b Fewer children than desired: calculated by subtracting the number of children women gave birth to from the total number they reported they desired

^c Adjusted: race, cancer treatment (chemotherapy ever, radiation ever), age at interview, age at diagnosis

^d Cancer survivors diagnosed reproductive cancers (uterine, ovarian, and cervical) were excluded and adjusted models also included cancer type (breast, lymphoma, other)