THYROID
Volume 27, Number 8, 2017

DOI: 10.1089/thy.2017.0063

Hyperthyroidism, Hypothyroidism, and Cause-Specific Mortality in a Large Cohort of Women

Neige M.Y. Journy,[1] Marie-Odile Bernier,[1,2] Michele M. Doody,[1] Bruce H. Alexander,[3] Martha S. Linet,[1] and Cari M. Kitahara[1]

Background: The prevalence of hyperthyroidism and hypothyroidism is 0.5–4% in iodine-replete communities, but it is 5–10 times higher in women than in men. Those conditions are associated with a broad range of metabolic disorders and cardiovascular diseases. Biological evidence of a role of thyroid hormones in carcinogenesis also exists. However, the association between thyroid dysfunction and cardiovascular disease or cancer mortality risk remains controversial. In a large cohort of women, the associations of hyperthyroidism and hypothyroidism with cause-specific mortality were evaluated after nearly 30 years of follow-up.
Methods: The prospective study included 75,076 women aged 20–89 years who were certified as radiologic technologists in the United States in 1926–1982, completed baseline questionnaires in 1983–1998 from which medical history was ascertained, and reported no malignant disease or benign thyroid disease except thyroid dysfunction. A passive follow-up of this cohort was performed through the Social Security Administration database and the National Death Index-Plus. Cause-specific mortality risks were compared according to self-reported thyroid status, with proportional hazards models adjusted for baseline year and age, race/ethnicity, body mass index, family history of breast cancer, and life-style and reproductive factors.
Results: During a median follow-up of 28 years, 2609 cancer, 1789 cardiovascular or cerebrovascular, and 2442 other non-cancer deaths were recorded. Women with hyperthyroidism had an elevated risk of breast cancer mortality after 60 years of age (hazard ratio [HR] = 2.04 [confidence interval (CI) 1.16–3.60], 13 cases in hyperthyroid women) compared to women without thyroid disease. Hypothyroid women had increased mortality risks for diabetes mellitus (HR = 1.58 [CI 1.03–2.41], 27 cases in hypothyroid women), cardiovascular disease (HR = 1.20 [CI 1.01–1.42], 179 cases), and cerebrovascular disease (HR = 1.45 [CI 1.01–2.08], 35 cases, when restricting the follow-up to ≥10 years after baseline). Other causes of death were not associated with hyperthyroidism or hypothyroidism, though there was a suggestion of an elevated risk of ovarian cancer mortality in hyperthyroid women based on very few cases.
Conclusion: The excess mortality risks observed in a large, prospective 30-year follow-up of patients with thyroid dysfunction require confirmation, and, if replicated, further investigation will be needed because of the clinical implications.

Keywords: hyperthyroidism, hypothyroidism, breast cancer, ovarian cancer, cardiovascular mortality, women's health

Introduction

Thyroid dysfunction can present with elevated (hyperthyroidism) or decreased (hypothyroidism) production of hormones by the thyroid gland. The prevalence of these conditions is 0.5–4% in iodine-replete communities, and it is 5–10 times higher in women than in men (1,2). Both hyperthyroidism and hypothyroidism have been associated with an increased risk of digestive and behavioral/mental disorders (3,4), infertility and other reproductive disorders

[1]Radiation Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Bethesda, Maryland.
[2]Laboratoire d'épidémiologie des rayonnements ionisants, Service de Radiobiologie et d'Epidémiologie, Institut de Radioprotection et de Sûreté Nucléaire, Fontenay-aux-Roses, France.
[3]Division of Environmental Health Sciences, School of Public Health, University of Minnesota, Minneapolis, Minnesota.

(5), metabolic disorders (e.g., dyslipidemia, homocysteine alterations), and a broad range of cardiovascular and cerebrovascular diseases (6).

Thyroid hormones may also be involved in carcinogenesis. *In vitro* and *in vivo* studies have showed that they play a role in regulating cancer-cell proliferation through mechanisms including angiogenesis, immunoreactivity, and estrogen-like pathways (7–12). Epidemiological studies have also reported increased risks of breast (13–19), lung (13,20–23), upper aerodigestive tract (15), pancreas (20), stomach (14,22), kidney (13,14), prostate (18,21), ovarian (24), and uterine (25) cancer in individuals with hyperthyroidism, and decreased risks in those with hypothyroidism (17,26). However, results have not been consistent (26–28).

The overall impact of thyroid dysfunction on mortality remains uncertain. Recent meta-analyses of epidemiological studies have estimated that clinically diagnosed hyperthyroidism (29,30) and hypothyroidism (31) are each associated with approximately a 20% increase in all-cause and cardiovascular mortality. Results were inconsistent across the studies, however, which likely reflects differences in study designs and methods (29–31). Some studies also had insufficient statistical power to investigate cancer-specific mortality (16,20,22,23,32,33). Large registry-based studies, with diagnoses of hyperthyroidism and hypothyroidism ascertained from hospital discharge claims (22,34,35) or blood measurements recorded in laboratory databases (36,37), provided very good statistical power but generally lacked information on comorbidities (22,37), disease-risk factors, and treatments (22,34–37). Those limitations make it difficult to evaluate whether the reported excess risks of cancer and cardiovascular mortality were attributable to thyroid dysfunction, treatments for this disorder, or confounding factors (29–31,36).

The current study evaluated the association between self-reported hyperthyroidism or hypothyroidism and cause-specific mortality while accounting for potential confounding factors and treatment by radioactive iodine among 75,000 women enrolled in the U.S. Radiologic Technologists (USRT) cohort study (38,39).

Material and Methods

Source population

The USRT study was primarily designed to investigate occupational radiation exposure and cancer risks. Details on the methods and population characteristics can be found in previous publications (38–40) and at the study Web site (https://radtechstudy.nci.nih.gov/). Briefly, the cohort enrolled all radiologic technologists identified from records of the American Registry of Radiologic Technologists during 1926–1982, who were certified for at least two years and resided in the United States. With a participation rate of 76%, the cohort included 110,418 individuals (83,748 women) who responded to at least one of two baseline questionnaire surveys administered in 1983–1989 and 1994–1998. These questionnaires elicited information regarding employment as a radiologic technologist, socio-demographic information, life-style factors and other disease risk factors, and reproductive and past medical history, including specific thyroid conditions and treatments. Vital status was ascertained through December 31, 2012, by linkage of the cohort with the Social Security Administration database. Individuals who died or were presumed to have died or for whom vital status was unknown were linked with the National Death Index-Plus (40). The study was approved by the Institutional Review Boards of the National Cancer Institute and the University of Minnesota.

Analytic cohort

The current analyses were conducted among women enrolled in the USRT cohort who were cancer free (apart from non-melanoma skin cancer) at the time of the baseline questionnaire ($N = 80{,}074$) to avoid the inclusion of participants with cancer-related thyroid dysfunction. Due to small numbers of male participants and the low prevalence of thyroid dysfunction among them, men were excluded from the analytic population. Women who reported thyroid disease of unknown or unspecified type ($n = 3535$); thyroiditis, goiter of unknown etiology, or thyroid nodules without thyroid dysfunction ($n = 1410$); and those aged ≥90 years at study entry ($n = 19$) or with less than a year of follow-up ($n = 34$) were also excluded. Women who reported bilateral oophorectomy prior to baseline were removed in analyses of ovarian cancer mortality ($n = 4152$).

After these exclusions, the analytic cohort comprised 75,076 women (70,924 in ovarian cancer analyses), of whom 62,996 responded to the first questionnaire (1983–1989) and 12,080 to the second questionnaire as baseline (1994–1998). Participants were classified as having no thyroid disease if they did not report any prior diagnosis of hypothyroidism, hyperthyroidism, thyroiditis, goiter, malignant tumor, or benign nodule. Hypothyroidism and hyperthyroidism were considered mutually exclusive for the purposes of the analysis. Women who reported both hyperthyroidism and hypothyroidism at baseline were recoded as only having hyperthyroidism, since hypothyroidism in these women was likely induced by a previous treatment for hyperthyroidism (4). Classification of the causes of death is detailed in Supplementary Table S1 (Supplementary Data are available online at www.liebertpub.com/thy).

Statistical analyses

Cumulative absolute (crude) risks of death were estimated depending on baseline thyroid disease status (hyperthyroidism, hypothyroidism, or no thyroid disease) as the probability of dying from a specific cause between baseline and a given attained age, accounting for competing causes of death and the fact that cohort members had various ages at study entry. Multivariable adjusted hazard ratios (HRs) compared the risk of deaths from specific causes between women who reported a history of hyperthyroidism or hypothyroidism and those who did not. HRs were estimated in Cox proportional hazards models fitted with age as timescale (as an adjustment for age) and stratified on baseline year (1983–1985, 1986–1990, 1991–1995, and 1996–1998) to account for secular trends in mortality rates and variable times since ascertainment of thyroid status and possible confounders. Entry age was defined as age at completion of the first questionnaire and exit age as age at death, age 90, or December 31, 2012, whichever occurred first.

Possible confounding factors were outcome specific and defined prior to analyses. These factors included race/ethnicity,

body mass index (BMI), smoking status, alcohol consumption, first-degree family history of breast cancer and reproductive factors, which included use of hormone replacement therapy (HRT) for menopause, duration of use of oral contraceptives, age at menarche, and age at first live birth, depending on the outcome considered (Supplementary Table S2) (41,42). Additional adjustment for marital status, education, and organ doses from occupational radiation exposures (as estimated by Simon *et al.*) (43), for which there was no *a priori* hypothesis on a potential relation to thyroid dysfunction, did not change the risk estimates for any of the outcomes examined and were thus not included in the final models. Results for breast and gynecological cancers also did not change with alternative adjustment for number of pregnancies, number of live births, age at first use of HRT for menopause, age at first use of oral contraception, or duration of the reproductive life (defined as age at menopause or age 52 when age at menopause was unknown, minus age at menarche). These factors were also not included in the final models. BMI, race/ethnicity, smoking, alcohol consumption, and reproductive factors were evaluated as potential effect modifiers. Effect modification of the hyperthyroidism results by radioactive iodine treatment was evaluated among the first questionnaire respondents (treatment information was not collected in the second questionnaire).

To validate the proportional hazards assumption, plots of scaled Schoenfeld residuals for thyroid status against age were investigated, and the correlation between these residuals and the natural logarithm of age was formally tested (44). For breast cancer, the proportionality assumption was validated only after stratifying the analyses by attained age ≤60 or >60 years. The results are thus reported separately by attained age category for this outcome. HRs are not reported for unknown causes of death. The analyses were performed using SAS v9.3 and ''survival'' package in R v3.1.3 software (45).

Results

In 75,076 women, baseline prevalence of hyperthyroidism and hypothyroidism was 2.0% and 5.9%, respectively, overall, with increasing rates with age (Fig. 1). At baseline questionnaire completion, women with thyroid dysfunction were older and more likely to be current or former smokers, to be overweight or obese, to have had more pregnancies (data not shown), to be postmenopausal (data not shown), to have received HRT, and to have never used oral contraceptives than women without thyroid disease were (Table 1). Hyperthyroidism and hypothyroidism were diagnosed ≥10 years before study entry in 62.1% and 67.4% of women, respectively. Treatment by radioactive iodine was reported at baseline in 22.8% of first questionnaire-respondents reporting hyperthyroidism.

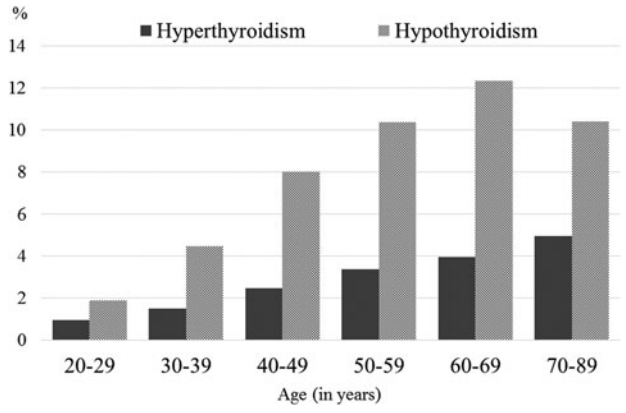

FIG. 1. Baseline prevalence of self-reported thyroid dysfunction by age group.

During a median follow-up of 28 years (maximum 30 years), 2609 (3.5%) women died from cancer, 1789 (2.4%) from cardiovascular or cerebrovascular disease, 2442 (3.3%) from other non-cancer causes, and 177 (0.2%) from unknown causes. Overall, cumulative absolute risks of cancer (14–16%) and non-cancer (43–50%) mortality by the age of 90 years varied little with thyroid status (Supplementary Table S3). However, cumulative absolute risks of death from breast (4.2%) and ovarian (1.6%) cancer by 90 years of age was almost twice as high among women with hyperthyroidism than it was among women with hypothyroidism or no thyroid disease (Fig. 2 and Supplementary Table S3). Conversely, cumulative absolute risks of death from diabetes mellitus (2.2%) or cardiovascular disease (19.1%) by 90 years of age were the highest among women with hypothyroidism.

In multivariable-adjusted models, hyperthyroidism was associated with a significantly higher risk of breast cancer mortality after 60 years of age (HR = 2.04 [confidence interval (CI) 1.16–3.60]), but not at younger ages, and a non-significant increased risk of ovarian cancer mortality (HR = 1.65 [CI 0.81–3.37]; Table 2). Hypothyroidism was associated with a significantly higher risk of death from diabetes mellitus (HR = 1.57 [CI 1.03–2.40]) and cardiovascular disease (HR = 1.21 [CI 1.04–1.42]). No other increased risks were observed for either hyperthyroidism or hypothyroidism.

No evidence was observed of effect modification of these associations by BMI, race/ethnicity, smoking, alcohol consumption, or reproductive factors. The association between hyperthyroidism and breast cancer mortality was not modified by radioactive iodine treatment (Table 3). However, the positive association with ovarian cancer mortality appeared to be restricted to women treated with radioactive iodine (HR = 5.33 [CI 2.17–13.08]), based on 5 and 143 cases in the exposed and unexposed groups, respectively.

In sensitivity analyses, the results were mostly confirmed after excluding the first 10 years of follow-up (to reduce the probability of reverse association due to prior disease or treatment; $n = 74{,}014$), with the exception that the risk of death from cerebrovascular disease was significantly increased in women with hypothyroidism (HR = 1.45 [CI 1.01–2.08]; 35 cases). The risk estimates were unchanged when excluding women with hypothyroidism who reported treatment with radioactive iodine ($n = 18$), which likely reflects prior unreported hyperthyroidism, or who had missing treatment information ($n = 173$; results not shown).

Discussion

In this large cohort, an increase in breast cancer mortality after 60 years of age was found among women with hyperthyroidism and increases in diabetes mellitus, cardiovascular disease, and cerebrovascular disease mortality among women with hypothyroidism. No significant association was

Table 1. Main Baseline Characteristics of the Study Population (%)

		No thyroid disease (N = 69,119)	*Hyperthyroidism (N = 1501)*		*Hypothyroidism (N = 4456)*	
		%	%	p	%	p
Socio-demographic characteristics						
Year of study entry	1983–1985	59	53	<0.001	55	<0.001
	1986–1990	25	23		23	
	1991–1995	8	12		10	
	1995–1998	8	12		12	
Age at baseline (years)	<30	19	9	<0.001	6	<0.001
	30–39	43	32		32	
	40–49	24	31		34	
	50–59	9	17		18	
	≥60	5	12		11	
Age at study exit (years)	<60	38	22	<0.001	19	<0.001
	60–69	41	40		41	
	≥70	21	38		40	
Race/ethnicity	White	96	93	<0.001	97	<0.001
	Black	3	5		1	
	Others/unknown	2	2		2	
Life-style factors and medical history						
Smoking status	Never smoked	51	43	<0.001	46	<0.001
	Former smoker <10 pack-years	16	15		17	
	Former smoker ≥10 pack-years	8	13		14	
	Current smoker <10 pack-years	7	7		5	
	Current smoker ≥10 pack-years	14	19		16	
	Unknown status, quantity or duration	2	3		3	
Alcohol consumption	Never or <1 drink a week	60	62	<0.001	64	<0.001
	1–6 drinks a week	30	26		25	
	>6 drinks a week	9	9		9	
	Unknown	2	4		3	
Body-mass index (kg/m^2)	<18.5	4	4	NS	3	<0.001
	18.5–24.9	69	66		52	
	25.0–29.9	17	18		25	
	≥30.0	7	9		18	
	Unknown	3	3		3	
1st-degree family history of breast cancer	No	94	93	NS	93	<0.01
	Yes	6	7		7	
Reproductive factors						
Age at menarche (years)	<12	20	20	<0.01	24	<0.001
	12–14.9	70	67		65	
	≥15	9	11		9	
	Unknown	2	3		2	
Age at first live birth (years)	No live birth	23	21	NS	19	<0.001
	<21	18	17		17	
	21–25.9	30	29		31	
	26–30.9	13	14		16	
	≥31	6	8		9	
	Unknown	11	12		9	
Use of oral contraceptives	Never took oral contraceptives	23	32		30	
	>0–2 years	21	20	<0.001	23	<0.001
	3–4 years	16	14		13	
	5–9 years	25	20		19	
	≥10 years	11	11		10	
	Unknown	4	4		5	
Use of hormone replacement therapy for menopause	No	77	60	<0.001	56	<0.001
	Yes	22	39		43	
	Unknown	1	2		1	

N, number of women; %, column percentages; p, *p*-value for heterogeneity; NS, not significant ($p \geq 0.05$).

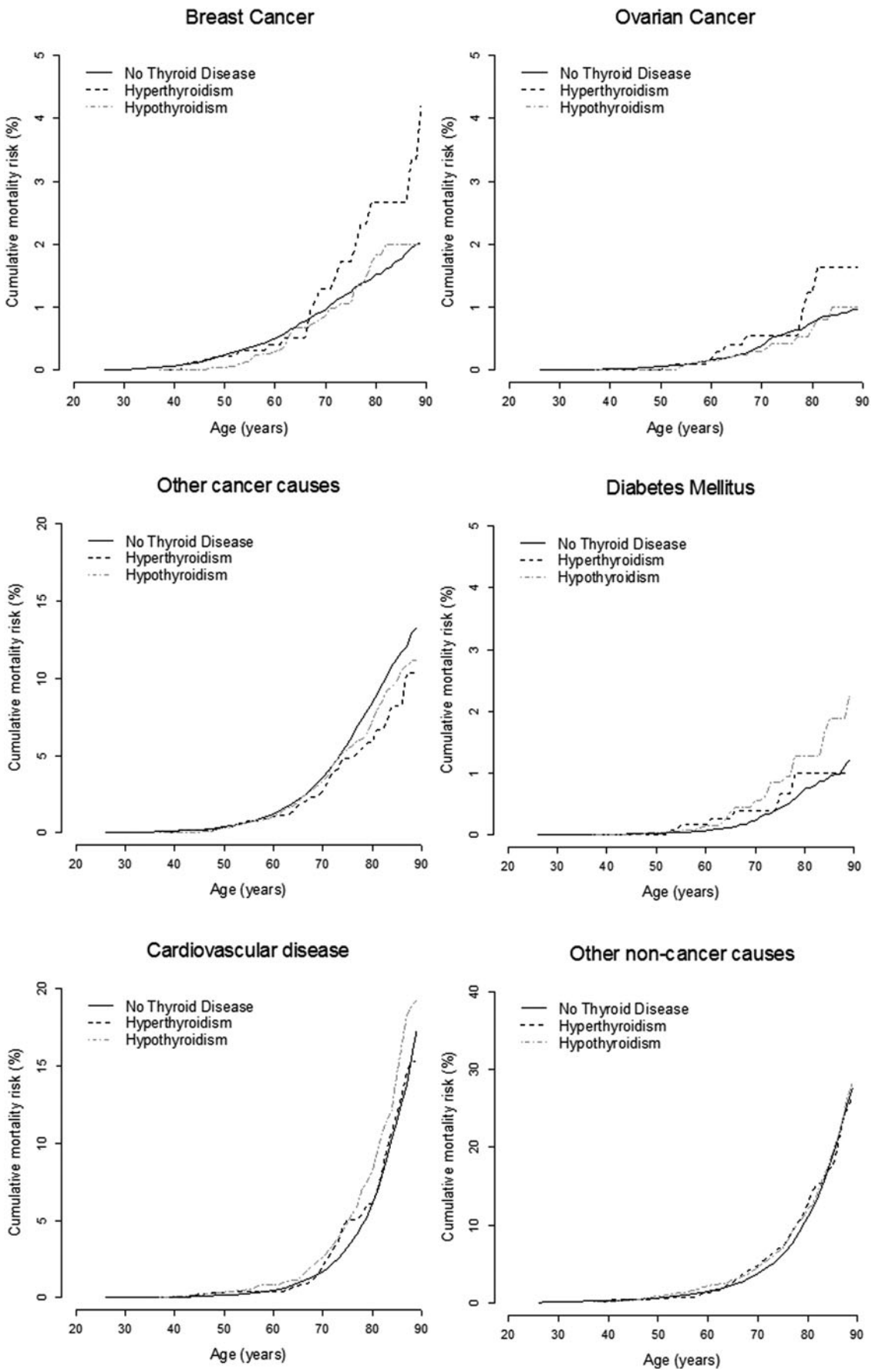

FIG. 2. Cumulative absolute risks of death from specific cause depending on baseline thyroid dysfunction.

Table 2. Cause-Specific Hazard Ratios of Mortality Associated with Thyroid Dysfunction Versus no Thyroid Disease

	No thyroid disease (N = 69,119)	*Hyperthyroidism (N = 1501)*			*Hypothyroidism (N = 4456)*		
	Cases	*Cases*	*HR*	*CI*	*Cases*	*HR*	*CI*
Cancer mortality							
Colon and rectum	201	1	0.15	[0.02–1.07]	12	0.61	[0.34–1.09]
Pancreas	144	3	0.60	[0.19–1.89]	9	0.65	[0.33–1.27]
Digestive system (except colon, rectum, pancreas)	118	4	1.00	[0.37–2.72]	15	1.30	[0.76–2.25]
Lung and bronchus	568	19	0.87	[0.55–1.37]	59	1.07	[0.82–1.40]
Breast (age ≤60 years)[a]	251	4	0.85	[0.32–2.28]	10	0.74	[0.39–1.39]
Breast (age >60 years)[a]	183	13	**2.04**	**[1.16–3.60]**	26	1.30	[0.86–1.97]
Ovary[b]	172	8	1.65	[0.81–3.37]	15	0.96	[0.55–1.67]
Female genital system (except ovary)	85	2	0.82	[0.20–3.36]	6	0.72	[0.31–1.67]
Brain and other nervous system	94	2	0.83	[0.20–3.37]	7	0.92	[0.42–1.99]
Hematopoietic tumor	213	4	0.59	[0.22–1.60]	20	0.91	[0.57–1.44]
Other malignant cancer	304	9	0.89	[0.46–1.74]	28	0.92	[0.62–1.36]
Non-cancer mortality							
Infectious and parasitic diseases	124	3	0.70	[0.22–2.21]	16	1.20	[0.71–2.03]
Diabetes mellitus	130	6	1.34	[0.59–3.06]	27	**1.57**	**[1.03–2.40]**
Alzheimer's disease	98	2	0.43	[0.11–1.75]	11	0.85	[0.46–1.59]
Cerebrovascular disease	308	14	1.08	[0.63–1.86]	43	1.28	[0.92–1.76]
Cardiovascular disease	1197	48	0.97	[0.73–1.30]	179	**1.21**	**[1.04–1.42]**
Pneumonia and influenza	108	3	0.67	[0.21–2.10]	15	1.23	[0.71–2.13]
Chronic obstructive pulmonary disease	288	15	1.13	[0.67–1.90]	38	1.13	[0.80–1.59]
Chronic liver disease and cirrhosis	88	3	1.27	[0.40–4.02]	4	0.49	[0.18–1.34]
Nephritis, nephrotic syndrome and nephrosis	73	1	0.31	[0.04–2.23]	6	0.59	[0.25–1.36]
Suicide and external cause	303	11	1.31	[0.72–2.41]	28	1.14	[0.77–1.68]
Other non-cancer causes	892	37	1.13	[0.81–1.57]	112	1.16	[0.95–1.41]

[a]Right (age ≤60 years) or left (age >60 years) truncature to fulfill the assumption of hazards proportionality.
[b]Excluding women who had undergone a bilateral oophorectomy before study entry. Bold indicates that CI does not include 1.
HR, hazard ratio; CI, confidence interval.

found between hyperthyroidism or hypothyroidism and other causes of death, although there was a suggestion of an elevated risk of ovarian cancer mortality among women with hyperthyroidism based on very few cases. These results provide evidence linking thyroid dysfunction with cause-specific mortality outcomes. The multivariable-adjusted risk of breast cancer mortality (cumulative absolute risk: 4%) was estimated to be about twofold higher among women with hyperthyroidism compared to women without thyroid disease. In hypothyroid women, the risk of dying from diabetes mellitus, cerebrovascular disease, or cardiovascular disease (cumulative absolute risks: 2%, 5%, and 19%, respectively) was respectively about 60%, 30%, and 20% higher than among women without thyroid disease.

Table 3. Cause-Specific Hazard Ratios of Mortality Associated with Hyperthyroidism Versus no Thyroid Disease in Women who Had Ever or Never Been Treated by Radioactive Iodine at the Baseline Questionnaire in 1983–1989

	No thyroid disease (N = 58,362)	*Hyperthyroidism*					
		Not treated by radioactive iodine (N = 818)			*Treated by radioactive iodine (N = 261)*		
	Cases	*Cases*	*HR*	*CI*	*Cases*	*HR*	*CI*
Breast cancer (age ≤60 years)[a]	233	2	0.66	[0.16–2.66]	0	0.00	N/A
Breast cancer (age >60 years)[a]	165	8	**2.29**	**[1.12–4.67]**	2	1.48	[0.37–6.02]
Ovary cancer[b]	143	2	0.79	[0.19–3.18]	5	**5.32**	**[2.16–13.08]**
Other cancer site	1492	25	0.75	[0.50–1.11]	10	0.92	[0.50–1.72]
All non-cancer causes	3062	79	1.05	[0.84–1.32]	27	1.10	[0.75–1.61]

[a]Right (age ≤60 years) or left (age >60 years) truncature to fulfill the assumption of hazards proportionality.
[b]Excluding women who had undergone a bilateral oophorectomy before study entry. Bold indicates that CI does not include 1.

Breast cancer

Because thyroid hormone regulates normal breast tissue development (46) and also plays a role in regulating sex steroid hormone levels (47), the possible association between thyroid dysfunction and risk of breast cancer has been extensively studied. A recent meta-analysis found an overall null association between breast cancer risk and hypothyroidism (28). Another meta-analysis analysis investigating hyperthyroidism concluded that there is inconsistent evidence demonstrating an increased risk of breast cancer associated with hyperthyroidism (27). This conclusion was, however, based on only four case-control studies that met the authors' selection criteria among many other published findings. The present results are in line with recent prospective studies (14,16,48,49). In particular, a nationwide registry-based study in Denmark showed a significantly increased risk with hyperthyroidism ($N = 80,343$; 2122 cases) but not with hypothyroidism ($N = 61,873$; 970 cases), which persisted after exclusion of women with obesity or alcohol-related disease diagnoses (17). In this study, the overall relative risk (RR = 1.1) was lower than in the present study (HR = 2.0), even in subgroups of age, which was likely influenced by a shorter median duration of follow-up (7 vs. 28 years in the present study). Two other prospective studies have shown a positive and strong association between free thyroxine (fT4) (49) or triiodothyronine (T3) levels (16,48) and breast cancer incidence and mortality in postmenopausal women, but no significant association in premenopausal women (16,48). No association was found, however, with thyrotropin (TSH) levels (21,48,49). The authors suggested that the apparently conflicting results for fT4 and TSH may have been due to naturally altered regulation in the hypothalamic–pituitary–thyroid axis with age (49).

Ovarian cancer

Few previous studies have investigated the relation between thyroid dysfunction and ovarian cancer (24,25,50). Ness *et al*. found an almost twofold increased risk in women aged 20–69 years with prior hyperthyroidism, but no association with hypothyroidism, while accounting for a wide range of life-style and reproductive factors in a case-control study of 767 ovarian tumors (24). Conversely, two prospective studies reported no association between thyroid disease and ovarian cancer. Those studies nevertheless focused on premenopausal women (25), had limited information on potential confounders (25), and included very few cases of ovarian cancers in hyperthyroid women (25,50). Previous studies also lacked treatment information (24,25,50). The present study also has limited information on treatment and included few cases of ovarian cancer in women with hyperthyroidism. Thus, the finding of an increased risk of ovarian cancer mortality after radioactive iodine treatment should be interpreted cautiously. Increased risk of ovarian cancer has been documented after external radiation exposure (51), but the existence and magnitude of risk after treatment with radioactive iodine is unknown. Previous studies investigating long-term outcomes related to this treatment have studied all gynecological or genitourinary cancers combined together as a single outcome (13,14,22,23,52,53), and to the authors' knowledge, none has reported associations with risk of ovarian cancer alone.

Cardiovascular and cerebrovascular diseases

Evidence on the association between hypothyroidism and cardiovascular mortality is conflicting (54). Though lacking information on life-style factors, consistent with the present findings, a large registry-based study found an increased cardiovascular mortality in hypothyroid individuals ($N = 15,889$; 251 cases) but not in hyperthyroid individuals ($N = 3888$; 11 cases) compared to the general population (55). The study reported, however, no excess cerebrovascular mortality in relation to thyroid dysfunction, with a maximal follow-up of eight years. Another prospective study with baseline measurements of serum TSH levels and information on major risk factors showed no association between hypothyroidism and mortality from cardiovascular or cerebrovascular disease in older individuals, but the study had a very small sample size (51 individuals with overt hypothyroidism) (56). Numerous studies investigating subclinical hypothyroidism suggested an increased cardiovascular mortality overall, especially in populations with a mean baseline age of <65 years (57,58).

Two meta-analyses estimated a 20% increase in cardiovascular mortality associated with treated (30) or subclinical (29) hyperthyroidism but noted that the results were very heterogeneous across studies due to differences in sample sizes, follow-up times, definitions of thyroid dysfunction and outcomes, data collected on comorbidities, and potential confounders. Very few have considered major risk factors such as obesity and smoking (56,59). In contrast to the lack of association of hyperthyroidism with cardiovascular or cerebrovascular disease in the present investigation, Bauer *et al*. estimated a 46% increase in mortality from cardiovascular and cerebrovascular diseases (all taken together) in 900 white women aged >65 years at diagnosis of hyperthyroidism and followed for 12 years on average compared to 8600 without this condition (59). It is hypothesized that those conflicting results might reflect differences in the age of participants (mean baseline age = 72 years in the study by Bauer *et al*. vs. 39 years in the present population) or in treatment modalities of hyperthyroidism (33).

Diabetes mellitus

Higher mortality from diabetes mellitus in women with thyroid dysfunction compared to those with normal thyroid function is not surprising considering that endocrine pathologies often coexist, with a high prevalence of thyroid dysfunction in women with diabetes (10–40% depending on type of diabetes) (60). This can result from autoimmune pathways (diabetes type 1) or impaired glucose metabolism and insulin resistance worsened by, or coexisting with, thyroid dysfunction (diabetes type 2) (60,61). Obesity, dyslipidemia, and cardiovascular disease can be mediating factors. Overall, hyperthyroid individuals have been reported to have a 45% increase of risk of prevalent or subsequent diabetes mellitus (62), and a 50–75% increased risk of diabetes mellitus has also been reported in hypothyroid individuals (63). Literature on mortality from complications of diabetes in hypo- or hyperthyroid individuals is, however, very sparse, diabetes being often analyzed as a comorbid condition for cardiovascular mortality (31,35,56,59). The reliability of mortality analyses based on death certificates can indeed been questioned, since diabetes has been found to be coded as the underlying cause of death in <10% of diabetic individuals, while the remaining often have cardiovascular disease

recorded as the main death cause (64). The estimates for the mortality risk from or associated with diabetes mellitus in women with hypothyroidism are thus likely underestimates.

Strengths and limitations

The major strengths of the present study are the prospective nature and large population size, the inclusion of a broad range of ages at baseline, a long follow-up (>60% of the cohort members were >60 years old at study exit), the completeness of follow-up through the National Death Index (the death cause was known for 97.4% of cases), and the availability of information on major disease risk factors, including life-style characteristics and reproductive history, which were unavailable in many previous studies. Unlike registry-based studies, which provide medically confirmed diagnoses (often from hospital discharge information) (15,17,18,22, 34,36,37) but have very limited information about potential confounding exposures, the questionnaire-based study included collection of detailed information on a broad range of risk factors. This population-based study, albeit in an occupational worker cohort, also provides more generalizable results than a hospital-based study, as thyroid dysfunctions were found to act differently in people with severe comorbidities or past history of cardiovascular events (29). Selection bias was minimized due to a recruitment of participants independent of thyroid disease status and a high participation rate.

The main limitation of this study is the small numbers of cases for studying specific cancer sites, such as ovarian cancer, and other infrequent outcomes, especially for subgroups, for example ovarian cancer patients who received radioactive iodine treatment. Considering the limited statistical power and the multiple comparisons that were performed, the preliminary results reported in the present study must be interpreted cautiously and replicated in other study populations. Another limitation is the reliance on self-reported medical history information. However, compared to the general population, radiologic technologists would generally be expected to have a greater understanding and recall of previously diagnosed medical conditions, which is supported by similarities in the self-reported prevalence of hyperthyroidism (2.0%) and hypothyroidism (5.9%) in the USRT cohort and prevalence estimates based on blood measurements of thyroid hormones in community-based surveys conducted in the United States and Europe (hyperthyroidism: 0.3–1.4%; hypothyroidism: 5.1–5.5%) (1,2). The high level of agreement in the cohort between self-reported thyroid dysfunction and radioactive iodine treatment (22.8% of women with hyperthyroidism, 0.5% of women with hypothyroidism, and 0.0% of women with no thyroid disease reported radioactive iodine treatment) also suggests a low proportion of misclassification. The present study, however, lacks information on thyroid HRT, antithyroid drugs or surgery, reverse over- or under-production of thyroid hormones, and radioactive iodine treatment for second questionnaire respondents. The unavailability of repeatedly administered questionnaires also prevented considering the possible modification of thyroid status and life-style factors over time, which is likely to have occurred considering the very long study period.

Further directions

After nearly 30 years of follow-up, this large prospective study suggests an elevated risk of breast cancer mortality in hyperthyroid women, and increased risks of diabetes mellitus and cardiovascular or cerebrovascular disease mortality in hypothyroid women. A possible increase of ovarian cancer mortality was also found in hyperthyroid women based on very few cases. However, while current epidemiological and clinical evidence on the relation between hyperthyroidism, or its treatment, and the development and progression of ovarian tumor remains weak, further investigations are needed to confirm this finding because of the important clinical implications. More generally, further studies should investigate the role of thyroid dysfunction across the natural history of these conditions to gain a better understanding of the underlying mechanisms. Specific analyses on cancer incidence and survival with adequate sample sizes are necessary to clarify the role of thyroid dysfunction on tumor initiation, aggressiveness, progression and prognosis, and modification by age and menopausal status.

Acknowledgments

This work was supported by the intramural research program of the National Cancer Institute at the U.S. National Institutes of Health. The funding source had no role in design and conduct of the study, collection, management, analysis, or interpretation of the data; preparation, review, or approval of the manuscript; or decision to submit the manuscript for publication.

Author Disclosure Statement

The authors have no conflict of interest to disclose.

References

1. Hollowell JG, Staehling NW, Flanders WD, Hannon WH, Gunter EW, Spencer CA, Braverman LE 2002 Serum TSH, T(4), and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III). J Clin Endocrinol Metab **87:**489–499.
2. Garmendia Madariaga A, Santos Palacios S, Guillen-Grima F, Galofre JC 2014 The incidence and prevalence of thyroid dysfunction in Europe: a meta-analysis. J Clin Endocrinol Metab **99:**923–931.
3. Chakera AJ, Pearce SH, Vaidya B 2012 Treatment for primary hypothyroidism: current approaches and future possibilities. Drug Des Devel Ther **6:**1–11.
4. De Leo S, Lee SY, Braverman LE 2016 Hyperthyroidism. Lancet **388:**906–918.
5. Poppe K, Velkeniers B, Glinoer D 2007 Thyroid disease and female reproduction. Clin Endocrinol (Oxf) **66:**309–321.
6. Klein I, Danzi S 2016 Thyroid disease and the heart. Curr Probl Cardiol **41:**65–92.
7. Pinto M, Soares P, Ribatti D 2011 Thyroid hormone as a regulator of tumor induced angiogenesis. Cancer Lett **301:**119–126.
8. Moeller LC, Fuhrer D 2013 Thyroid hormone, thyroid hormone receptors, and cancer: a clinical perspective. Endocr Relat Cancer **20:**R19–29.
9. Gunter MJ, Hoover DR, Yu H, Wassertheil-Smoller S, Rohan TE, Manson JE, Li J, Ho GY, Xue X, Anderson GL,

Kaplan RC, Harris TG, Howard BV, Wylie-Rosett J, Burk RD, Strickler HD 2009 Insulin, insulin-like growth factor-I, and risk of breast cancer in postmenopausal women. J Natl Cancer Inst **101:**48–60.
10. Micali S, Bulotta S, Puppin C, Territo A, Navarra M, Bianchi G, Damante G, Filetti S, Russo D 2014 Sodium iodide symporter (NIS) in extrathyroidal malignancies: focus on breast and urological cancer. BMC Cancer **14:**303.
11. Muller I, Giani C, Zhang L, Grennan-Jones FA, Fiore E, Belardi V, Rosellini V, Funel N, Campani D, Giustarini E, Lewis MD, Bakhsh AD, Roncella M, Ghilli M, Vitti P, Dayan CM, Ludgate ME 2014 Does thyroid peroxidase provide an antigenic link between thyroid autoimmunity and breast cancer? Int J Cancer **134:**1706–1714.
12. Dinda S, Sanchez A, Moudgil V 2002 Estrogen-like effects of thyroid hormone on the regulation of tumor suppressor proteins, p53 and retinoblastoma, in breast cancer cells. Oncogene **21:**761–768.
13. Ron E, Doody MM, Becker DV, Brill AB, Curtis RE, Goldman MB, Harris BS 3rd, Hoffman DA, McConahey WM, Maxon HR, Preston-Martin S, Warshauer ME, Wong FL, Boice JD Jr 1998 Cancer mortality following treatment for adult hyperthyroidism. Cooperative Thyrotoxicosis Therapy Follow-up Study Group. JAMA **280:**347–355.
14. Metso S, Auvinen A, Huhtala H, Salmi J, Oksala H, Jaatinen P 2007 Increased cancer incidence after radioiodine treatment for hyperthyroidism. Cancer **109:**1972–1979.
15. Shu X, Ji J, Li X, Sundquist J, Sundquist K, Hemminki K 2010 Cancer risk in patients hospitalised for Graves' disease: a population-based cohort study in Sweden. Br J Cancer **102:**1397–1399.
16. Tosovic A, Bondeson AG, Bondeson L, Ericsson UB, Manjer J 2013 Triiodothyronine levels in relation to mortality from breast cancer and all causes: a population-based prospective cohort study. Eur J Endocrinol **168:** 483–490.
17. Sogaard M, Farkas DK, Ehrenstein V, Jorgensen JO, Dekkers OM, Sorensen HT 2016 Hypothyroidism and hyperthyroidism and breast cancer risk: a nationwide cohort study. Eur J Endocrinol **174:**409–414.
18. Chen YK, Lin CL, Chang YJ, Cheng FT, Peng CL, Sung FC, Cheng YH, Kao CH 2013 Cancer risk in patients with Graves' disease: a nationwide cohort study. Thyroid **23:**879–884.
19. Turken O, Narin Y, Demirbas S, Onde ME, Sayan O, Kandemir EG, Yaylaci M, Ozturk A 2003 Breast cancer in association with thyroid disorders. Breast cancer Res **5:**R110–113.
20. Goldman MB, Monson RR, Maloof F 1990 Cancer mortality in women with thyroid disease. Cancer Res **50:**2283–2289.
21. Hellevik AI, Asvold BO, Bjoro T, Romundstad PR, Nilsen TI, Vatten LJ 2009 Thyroid function and cancer risk: a prospective population study. Cancer Epidemiol Biomarkers Prev **18:**570–574.
22. Ryodi E, Metso S, Jaatinen P, Huhtala H, Saaristo R, Valimaki M, Auvinen A 2015 Cancer incidence and mortality in patients treated either with RAI or thyroidectomy for hyperthyroidism. J Clin Endocrinol Metab **100:**3710–3717.
23. Hall P, Berg G, Bjelkengren G, Boice JD Jr, Ericsson UB, Hallquist A, Lidberg M, Lundell G, Tennvall J, Wiklund K, et al. 1992 Cancer mortality after iodine-131 therapy for hyperthyroidism. Int J Cancer **50:**886–890.
24. Ness RB, Grisso JA, Cottreau C, Klapper J, Vergona R, Wheeler JE, Morgan M, Schlesselman JJ 2000 Factors related to inflammation of the ovarian epithelium and risk of ovarian cancer. Epidemiology **11:**111–117.
25. Brinton LA, Sakoda LC, Frederiksen K, Sherman ME, Kjaer SK, Graubard BI, Olsen JH, Mellemkjaer L 2007 Relationships of uterine and ovarian tumors to pre-existing chronic conditions. Gynecol Oncol **107:**487–494.
26. Selmer C, Olesen JB, Hansen ML, von Kappelgaard LM, Madsen JC, Hansen PR, Pedersen OD, Faber J, Torp-Pedersen C, Gislason GH 2014 Subclinical and overt thyroid dysfunction and risk of all-cause mortality and cardiovascular events: a large population study. J Clin Endocrinol Metab **99:**2372–2382.
27. Hardefeldt PJ, Eslick GD, Edirimanne S 2012 Benign thyroid disease is associated with breast cancer: a meta-analysis. Breast Cancer Res Treat **133:**1169–1177.
28. Angelousi AG, Anagnostou VK, Stamatakos MK, Georgiopoulos GA, Kontzoglou KC 2012 Mechanisms in endocrinology: primary HT and risk for breast cancer: a systematic review and meta-analysis. Eur J Endocrinol **166:**373–381.
29. Yang LB, Jiang DQ, Qi WB, Zhang T, Feng YL, Gao L, Zhao J 2012 Subclinical hyperthyroidism and the risk of cardiovascular events and all-cause mortality: an updated meta-analysis of cohort studies. Eur J Endocrinol **167:**75–84.
30. Brandt F, Green A, Hegedus L, Brix TH 2011 A critical review and meta-analysis of the association between overt hyperthyroidism and mortality. Eur J Endocrinol **165:**491–497.
31. Thvilum M, Brandt F, Brix TH, Hegedus L 2012 A review of the evidence for and against increased mortality in hypothyroidism. Nat Rev Endocrinol **8:**417–424.
32. Franklyn JA, Maisonneuve P, Sheppard MC, Betteridge J, Boyle P 1998 Mortality after the treatment of hyperthyroidism with radioactive iodine. N Engl J Med **338:**712–718.
33. Franklyn JA, Sheppard MC, Maisonneuve P 2005 Thyroid function and mortality in patients treated for hyperthyroidism. JAMA **294:**71–80.
34. Thvilum M, Brandt F, Almind D, Christensen K, Hegedus L, Brix TH 2013 Excess mortality in patients diagnosed with hypothyroidism: a nationwide cohort study of singletons and twins. J Clin Endocrinol Metab **98:**1069–1075.
35. Brandt F, Almind D, Christensen K, Green A, Brix TH, Hegedus L 2012 Excess mortality in hyperthyroidism: the influence of preexisting comorbidity and genetic confounding: a danish nationwide register-based cohort study of twins and singletons. J Clin Endocrinol Metab **97:**4123–4129.
36. Laulund AS, Nybo M, Brix TH, Abrahamsen B, Jorgensen HL, Hegedus L 2014 Duration of thyroid dysfunction correlates with all-cause mortality. the OPENTHYRO Register Cohort. PLoS One **9:**e110437.
37. Kovar FM, Fang IF, Perkmann T, Haslacher H, Slavka G, Fodinger M, Endler G, Wagner OF 2015 Subclinical hypothyroidism and mortality in a large Austrian cohort: a possible impact on treatment? Wien Klin Wochenschr **127:**924–930.
38. Boice JD, Mandel JS, Doody MM, Yoder RC, Mcgowan R 1992 A health survey of radiologic technologists. Cancer **69:**586–598.
39. Doody MM, Mandel JS, Lubin JH, Boice JD 1998 Mortality among United States radiologic technologists, 1926–90. Cancer Cause Control **9:**67–75.
40. Doody MM, Hayes HM, Bilgrad R 2001 Comparability of National Death Index Plus and standard procedures for determining causes of death in epidemiologic studies. Ann Epidemiol **11:**46–50.

41. Stampfer MJ, Ridker PM, Dzau VJ 2004 Risk factor criteria. Circulation **109:**IV3–5.
42. Schottenfeld D, Fraumeni JF, editors. Cancer Epidemiology and Prevention. Third edition. New York, NY: Oxford University Press, 2006.
43. Simon SL, Preston DL, Linet MS, Miller JS, Sigurdson AJ, Alexander BH, Kwon D, Yoder RC, Bhatti P, Little MP, Rajaraman P, Melo D, Drozdovitch V, Weinstock RM, Doody MM 2014 Radiation organ doses received in a nationwide cohort of U.S. radiologic technologists: methods and findings. Radiat Res **182:**507–528.
44. Grambsch PM, Therneau TM 1994 Proportional hazards tests and diagnostics based on weighted residuals. Biometrika **81:**515–526.
45. Therneau T 2015 A Package for Survival Analysis in S. v2.38. Available at: http://CRAN.R-project.org/package=survival (accessed July 10, 2016).
46. Hall LC, Salazar EP, Kane SR, Liu N 2008 Effects of thyroid hormones on human breast cancer cell proliferation. J Steroid Biochem Mol Biol **109:**57–66.
47. Dittrich R, Beckmann MW, Oppelt PG, Hoffmann I, Lotz L, Kuwert T, Mueller A 2011 Thyroid hormone receptors and reproduction. J Reprod Immunol **90:**58–66.
48. Tosovic A, Bondeson AG, Bondeson L, Ericsson UB, Malm J, Manjer J 2010 Prospectively measured triiodothyronine levels are positively associated with breast cancer risk in postmenopausal women. Breast Cancer Res **12:**R33.
49. Khan SR, Chaker L, Ruiter R, Aerts JG, Hofman A, Dehghan A, Franco OH, Stricker BH, Peeters RP 2016 Thyroid function and cancer risk: The Rotterdam Study. J Clin Endocrinol Metab **101:**5030–5036.
50. Kang JH, Kueck AS, Stevens R, Curhan G, De Vivo I, Rosner B, Alexander E, Tworoger SS 2013 A large cohort study of hypothyroidism and hyperthyroidism in relation to gynecologic cancers. Obstet Gynecol Int **2013:**743721.
51. Ozasa K, Shimizu Y, Suyama A, Kasagi F, Soda M, Grant EJ, Sakata R, Sugiyama H, Kodama K 2012 Studies of the mortality of atomic bomb survivors, Report 14, 1950–2003: an overview of cancer and noncancer diseases. Radiat Res **177:**229–243.
52. Franklyn JA, Maisonneuve P, Sheppard M, Betteridge J, Boyle P 1999 Cancer incidence and mortality after radioiodine treatment for hyperthyroidism: a population-based cohort study. Lancet **353:**2111–2115.
53. Hieu TT, Russell AW, Cuneo R, Clark J, Kron T, Hall P, Doi SAR 2012 Cancer risk after medical exposure to radioactive iodine in benign thyroid diseases: a meta-analysis. Endocr Relat Cancer **19:**645–655.
54. Jabbar A, Pingitore A, Pearce SHS, Zaman A, Iervasi G, Razvi S 2016 Thyroid hormones and cardiovascular disease. Nat Rev Cardiol **14:**39–55.
55. Flynn RWV, Macdonald TM, Jung RT, Morris AD, Leese GP 2006 Mortality and vascular outcomes in patients treated for thyroid dysfunction. J Clin Endocrinol Metab **91:**2159–2164.
56. Cappola AR, Fried LP, Arnold AM, Danese MD, Kuller LH, Burke GL, Tracy RP, Ladenson PW 2006 Thyroid status, cardiovascular risk, and mortality in older adults. JAMA **295:**1033–1041.
57. Ochs N, Auer R, Bauer DC, Nanchen D, Gussekloo J, Cornuz J, Rodondi N 2008 Meta-analysis: subclinical thyroid dysfunction and the risk for coronary heart disease and mortality. Ann Intern Med **148:**832–845.
58. Rodondi N, den Elzen WP, Bauer DC, Cappola AR, Razvi S, Walsh JP, Asvold BO, Iervasi G, Imaizumi M, Collet TH, Bremner A, Maisonneuve P, Sgarbi JA, Khaw KT, Vanderpump MP, Newman AB, Cornuz J, Franklyn JA, Westendorp RG, Vittinghoff E, Gussekloo J; Thyroid Studies Collaboration 2010 Subclinical hypothyroidism and the risk of coronary heart disease and mortality. JAMA **304:**1365–1374.
59. Bauer DC, Rodondi N, Stone KL, Hillier TA; Study of Osteoporotic Fractures Research Group: Universities of California (San Francisco), Pittsburgh, Minnesota (Minneapolis); Kaiser Permanente Center for Health Research, Portland 2007 Thyroid hormone use, hyperthyroidism and mortality in older women. Am J Med **120:**343–349.
60. Kadiyala R, Peter R, Okosieme OE 2010 Thyroid dysfunction in patients with diabetes: clinical implications and screening strategies. Int J Clin Pract **64:**1130–1139.
61. Wang C 2013 The relationship between type 2 diabetes mellitus and related thyroid diseases. J Diabetes Res **2013:** 390534.
62. Brandt F, Thvilum M, Almind D, Christensen K, Green A, Hegedus L, Brix TH 2013 Morbidity before and after the diagnosis of hyperthyroidism: a nationwide register-based study. PloS One **8:**e66711.
63. Gronich N, Deftereos SN, Lavi I, Persidis AS, Abernethy DR, Rennert G 2015 Hypothyroidism is a risk factor for new-onset diabetes: a cohort study. Diabetes Care **38:** 1657–1664.
64. Bild DE, Stevenson JM 1992 Frequency of recording of diabetes on United-States death certificates—analysis of the 1986 National Mortality Followback Survey. J Clin Epidemiol **45:**275–281.

Address correspondence to:
Cari M. Kitahara, PhD
Radiation Epidemiology Branch
Division of Cancer Epidemiology and Genetics
National Cancer Institute, MSC 9778
9609 Medical Center Drive
Bethesda, MD 20892

E-mail: kitaharac@mail.nih.gov