Obesity, obesity-related metabolic conditions, and risk of thyroid cancer in women: results from a prospective cohort study (Sister Study)

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Summary

Background Thyroid cancer incidence has increased worldwide. Obesity trends may play a role, but the underlying biological pathways are not well-characterized. Therefore, we examined associations of excess adiposity and obesity-related metabolic conditions with thyroid cancer incidence.

Methods From the Sister Study, a cohort of sisters of women with breast cancer, we included 47,739 women who were cancer-free at baseline (2003–2009). Height, weight, waist and hip circumference, and blood pressure were measured at baseline and medical history was self-reported. Cox proportional hazards regression models were adjusted for age (time scale), race/ethnicity, smoking, baseline history of benign thyroid disease, and frequency of routine healthcare visits.

Findings During follow-up (median = 12.5; max = 15.9 years), 259 women reported incident thyroid cancer. Body mass index (BMI) (hazard ratio $[HR]_{per\text{-}5\ kg/m^2}$ = 1.25, 95% CI = 1.14–1.37), waist circumference ($HR_{per\text{-}5\ cm\ increase}$ = 1.11, 95% CI = 1.06–1.15), and waist-to-hip ratio ($HR_{\geq 0.85\text{-}versus\text{-}<0.85}$ = 1.49, 95% CI = 1.14–1.94) were positively associated with thyroid cancer incidence, as were metabolic syndrome (HR = 1.67, 95% CI = 1.24–2.25), dyslipidemia (HR = 1.46, 95% CI = 1.13–1.90), borderline diabetes (HR = 2.06, 95% CI = 1.15–3.69), hypertension (HR = 1.49, 95% CI = 1.12–1.96), and polycystic ovary syndrome (PCOS, HR = 2.10, 95% CI = 1.20–3.67). These associations were attenuated with additional BMI adjustment, although dyslipidemia (HR = 1.35, 95% CI = 1.04–1.75) and PCOS (HR = 1.86, 95% CI = 1.06–3.28) remained associated with thyroid cancer incidence. Hypothyroidism was not associated with thyroid cancer.

Interpretation In this cohort of sisters of women diagnosed with breast cancer, excess adiposity and several obesity-related metabolic conditions were associated with thyroid cancer incidence. These findings provide insights into potential biological mechanisms linking obesity and thyroid cancer.

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Keywords: Thyroid cancer; Obesity; Obesity associated diseases; Diabetes; Risk factors; Epidemiology

Introduction

Thyroid cancer incidence almost tripled over the past 30–40 years worldwide, including in the United States.[1] Greater medical surveillance and more widespread use of diagnostic imaging techniques most likely explain the rapid increases in small, early-stage thyroid cancers.[2] However, incidence of larger and more aggressive thyroid cancer subtypes also rose over time, suggesting a potential role of environmental or lifestyle risk factors.[3] The growing

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Research in context

Evidence before this study

The biological mechanisms linking obesity and thyroid cancer are not well-understood. We searched PubMed on 9/9/2022, using the terms ((“body mass index” OR “waist circumference” OR “obesity” OR “metabolic syndrome” OR “dyslipidemia” OR “hypertension” OR “diabetes” OR “polycystic ovary syndrome” OR “metformin” OR “hypothyroidism”) AND “thyroid cancer”), retrieving 2938 results. Bibliographies of relevant systematic reviews were also screened. Selection was limited to cohort or case–control studies written in English. Based on three large, pooled analyses of cohort studies (international [n = 2,094,047], in Asia [n = 538,857], and in Australia [n = 367,058]), body mass index, per 5-kg/m^2 increment, was associated with a 10%–25% increased risk of thyroid cancer. Inconsistent associations were found between metabolic syndrome (3 cohorts), dyslipidemia (6 cohorts), hypertension (2 cohorts), diabetes (7 cohorts, 1 case–control), hypothyroidism (4 cohorts, 2 case–control), metformin use (2 cohorts, 1 case–control) and thyroid cancer risk. No study examined the association of polycystic ovary syndrome (PCOS) with thyroid cancer risk. Only one cohort examined the joint association of metabolic syndrome and obesity with thyroid cancer risk; compared to subjects without obesity or metabolic syndrome, thyroid cancer risk was 30% higher for subjects with obesity and metabolic syndrome (sub-multiplicative interaction).

Added value of this study

This nationwide U.S. cohort of women is a unique resource for understanding the associations between obesity, obesity-related medical conditions, and thyroid cancer incidence, owing to the large study population, prospective design with long duration of follow-up, large proportion of participants with obesity (30%), availability of examiner-measured baseline weight, height, and waist and hip circumference, and comprehensive medical and pharmacological history. We found that excess adiposity, assessed using body mass index, waist circumference, and waist-to-hip ratio, was positively associated with thyroid cancer incidence. We also showed that obesity-related metabolic disorders were positively associated with thyroid cancer incidence after adjusting for frequency of healthcare visits, cancer screening, and other potential confounding factors; these associations were attenuated with additional adjustment for body mass index, although dyslipidemia and PCOS remained associated with increased thyroid cancer risk. Compared to women without obesity or baseline history of any obesity-related condition, those with both obesity and one or more obesity-related metabolic conditions had a 2.13-fold higher incidence of thyroid cancer (p-interaction = 0.11, indicating a sub-multiplicative interaction).

Implications of all the available evidence

The growing prevalence of obesity and obesity-related metabolic conditions may have contributed, in part, to the rising incidence of thyroid cancer worldwide. Our findings provide further evidence that public health interventions targeting obesity and related comorbidities may help to avoid a substantial number of future thyroid cancers.

prevalence of obesity occurred in parallel with the rising incidence of thyroid cancer,[3] and body mass index (BMI), adulthood BMI gain, and waist circumference have been consistently associated with thyroid cancer risk in epidemiologic studies.[4–6] However, little is known about the underling causal mechanisms linking obesity and thyroid cancer.

It is possible that metabolic abnormalities commonly associated with obesity may play a direct role in thyroid cancer development.[7,8] Some obesity-associated metabolic conditions, such as type-2 diabetes, metabolic syndrome, hypothyroidism, have been found to be associated with thyroid cancer risk, although the evidence has been limited.[9–14] These conditions are characterized by metabolic alterations, including hyperinsulinemia, inflammation, estrogen-progesterone imbalance, and elevated thyroid stimulating hormone (TSH), and these mechanisms have been hypothesized to play a role in the pathophysiology of obesity-induced thyroid cancer.[7] Treatment with metformin, an insulin sensitizer drug, has shown antineoplastic activity mainly in pre-clinical studies and has been associated with lower incidence of thyroid cancer in some epidemiological studies.[14] On the other hand, the observed associations between obesity and thyroid cancer incidence may be partly explained by detection bias, whereby obesity contributes to more opportunities for incidental detection and diagnosis of thyroid cancer because of more frequent interaction with the healthcare system and greater monitoring of potential thyroid disease.[2,15]

To gain insight into the causal nature of the obesity and thyroid cancer association, the current study explored the independent and joint associations of excess adiposity, obesity-associated medical conditions, and thyroid cancer risk in the Sister Study, a large U.S. nationwide cohort of women with a family history of breast cancer,[16] taking into account multiple indicators of medical surveillance. Specifically, we evaluated indicators of excess adiposity (BMI, waist circumference, waist-to-hip ratio, a body shape index [ABSI][17]), obesity-related medical conditions (metabolic syndrome, type-2 diabetes [overall and for metformin-treated disease], hypertension, dyslipidemia, polycystic ovary syndrome [PCOS], and hypothyroidism).[18,19]

Methods

Study design

Between 2003 and 2009, the Sister Study cohort enrolled 50,884 women aged 35 to 74 residing in the U.S. (including Puerto Rico) who had a sister with a prior breast cancer diagnosis but no personal history of breast cancer.[16] All participants completed a baseline questionnaire via computer-assisted telephone interview, which inquired about medical and pharmacological history, lifestyle, and reproductive factors and received an in-home visit, during which weight, height, waist and hip circumference, and blood pressure were measured by trained examiners. Participants received a short follow-up questionnaire annually and a more detailed questionnaire every 2–3 years, with response rates around 90%.[16,20]

Cohort definition

We excluded participants who, at enrollment, reported a history of thyroid cancer (n = 273), any other invasive cancer (n = 2441) or total thyroidectomy (n = 65). We further excluded 4 participants who withdrew from the cohort, those with follow-up of less than or equal to 1 year (n = 416), those with unclear timing of thyroid cancer diagnosis (n = 16), and those with missing information on baseline height or weight (n = 17). After exclusions, the analytic population included 47,739 women. Person-time accrued from the date of enrollment to the date of diagnosis of a first thyroid cancer, death, loss to follow-up, or 10/12/2020, whichever came first.

Outcome and exposure definitions

Outcomes

Thyroid cancer was self-reported and confirmed by medical records/pathology report when available. Of the 259 cases included here, 189 were confirmed by pathology reports or death certificate. Agreement between self-report and medical record thyroid cancer diagnosis was excellent (positive predictive value = 94.6%). Deaths were ascertained through linkage of the cohort to the National Death Index.

Exposure and covariates

Measured variables. Weight, height, waist, and hip circumference were measured by trained personnel at baseline. These measures were used to calculate BMI, waist-to-hip ratio, and ABSI. We calculated BMI as (weight in kg)/(height in m)^2, using self-reported height and/or weight at baseline only if measurements were missing (n = 229). ABSI was calculated as the ratio between the waist circumference (in m) and the product of BMI$^{2/3}$ and height$^{1/2}$ (in m), multiplied by 1000.[17] ABSI is an indicator of abdominal obesity and is less strongly corrected with BMI compared to waist circumference.[17] As there are no standard clinical cutpoints for ABSI, we categorized ABSI using quartiles based on the whole cohort. CDC cutpoints were used to classify BMI in categories of normal or underweight (<25 kg/m^2), overweight (25-<30 kg/m^2), and obese (≥30 kg/m^2). Waist circumference cutpoints of 80 and 88 cm were used to define moderate and high abdominal obesity, respectively, and for waist-to hip ratio we used a cutpoint of 0.85.[4,18,21] Three measurements of blood pressure were taken 1–2 min apart by a trained examinator at baseline; we averaged the last two measurements to derive a single blood pressure measurement. For 531 subjects lacking either the second or third measurement, we used the first measurement.

Self-reported variables.

Medical and pharmacological history. Dyslipidemia was defined as self-reported diagnosis of hypercholesterolemia or hypertriglyceridemia or use of prescription medication to lower triglycerides or raise high-density lipoprotein cholesterol (i.e., fibrates, niacin, long-chain omega-3 fatty acids, statins). Hypertension was defined as measured systolic blood pressure higher than 140 mmHg, or diastolic blood pressure higher than 90 mmHg, or self-reported use of antihypertensive medications. Because diabetes type (1, 2, or secondary) was not systematically captured in this study, for the purposes of the current analysis, diabetes type-2 was defined as self-reported diagnosis of diabetes, excluding participants with likely diabetes type-1 or secondary diabetes. Diabetes type-1 was defined as self-reported diagnosis of diabetes type-1 (as a free text option, n = 30) or diabetes diagnosed before age 20 or between ages 20–35 and use of insulin beginning ≤12 months from diagnosis (n = 130). Diabetes was considered secondary for those reporting a diagnosis of hemochromatosis, liver cirrhosis, hyperthyroidism, PCOS (n = 19), or gestational diabetes (n = 25) ≤12 months from diabetes diagnosis date. Survey questions ascertaining diagnoses of borderline diabetes were included beginning after the first year of recruitment. Subjects who reported both borderline diabetes and diabetes were considered to have diabetes type-2. The definition of metabolic syndrome was adapted from the consensus statement from the International Diabetes Federation.[21] Subjects were considered to have metabolic syndrome if they had a waist circumference ≥80 cm and at least two conditions among: a) diabetes type-2 or borderline diabetes, b) dyslipidemia, or c) use of antihypertensive medication or systolic/diastolic blood pressure ≥130/85 mmHg. PCOS was captured from a survey question inquiring about whether a doctor or health professional ever informed the patient that she had polycystic ovaries, PCOS, or Stein-Leventhal Syndrome. Primary hypothyroidism was identified among those who reported hypothyroidism by excluding those likely having secondary hypothyroidism, defined as subjects reporting a diagnosis of hypothyroidism before or at the

same age as hyperthyroidism (n = 544) or subjects reporting hypothyroidism following thyroidectomy or use of amiodarone, lithium, interferon, sodium-potassium iodine, or other iodine-based medications (n = 106). Participants were also asked to report any medically-confirmed diagnoses of benign thyroid nodules.

Covariates. Socioeconomic status (SES) was defined using baseline self-reported attained education level. We created a proxy indicator of healthcare utilization by identifying subjects who reported at baseline a recent (less than 1 year) medical or dental check-up and/or cervical or breast cancer screening. We classified participants as never, past, and current smokers as self-reported at baseline. Subjects were considered to have a baseline history of benign thyroid disease if they reported primary or secondary hyperthyroidism, hypothyroidism, or any other congenital or inflammatory thyroid conditions.

Statistical analysis

We calculated hazard ratios (HRs) and 95% CIs for thyroid cancer using Cox proportional hazards regression models with attained age as the time scale. Models adjusted for attained education level, self-reported race and ethnicity, healthcare utilization, benign thyroid disorders, and smoking status. Tests of trend were performed by modeling categorical variables as ordinal variables. Test for non-linearity of the association between BMI and thyroid cancer risk, conducted by adding a quadratic term to a model with continuous BMI, did not reach statistical significance (p = 0.35). The proportional hazard assumption was tested in each model using Schoenfeld residuals, and no violations were found. A Nelson-Aalen cumulative hazard estimates curve is also provided (Supplementary Fig. S1). The main exposure variables were BMI (continuous and categorical), waist circumference (continuous and categorical), waist-to-hip ratio (categorical), ABSI (categorical), metabolic syndrome, dyslipidemia, hypertension, diabetes type-2 (yes/no), diabetes type-2 treated with metformin (yes/no/no diabetes), PCOS, and primary hypothyroidism. Because metformin use was reported by only 5.7% (n = 60) of women with PCOS and without diabetes, we did not separately assess PCOS treated or not treated with metformin. Sensitivity analyses included 1) assessing the impact of removing healthcare use from the models and 2) excluding women who reported a baseline history of metabolic conditions or 3) thyroid nodules. We also evaluated the impact of mutual adjustment of anthropometric factors and obesity-associated metabolic conditions. Subjects with missing covariate data (described in Table 1) were excluded on a model-specific basis. Covariate-specific estimands are provided in Supplementary Table S1.

We also evaluated the joint association of obesity (BMI ≥30 kg/m^2) or abdominal obesity (waist circumference ≥88 cm) and history of "any obesity-related metabolic condition," defined as one or more of the following conditions: dyslipidemia, hypertension, diabetes type-2, or PCOS, using as the reference category the absence of both obesity (or clinical abdominal obesity) and any of the above-mentioned conditions. Metabolic syndrome was not included in "any obesity-related metabolic condition" as it is defined as a cluster of risk factors including abdominal obesity. Multiplicative interactions between excess adiposity and presence of any medical condition were tested by adding a cross-product term to the model.

To evaluate the potential for detection bias, we modelled associations of BMI or waist circumference (continuous) with thyroid cancer risk after excluding subjects with any obesity-related metabolic condition (hypertension, dyslipidemia, diabetes, PCOS, hypothyroidism; n = 28,142) or self-reported benign thyroid nodules (n = 3473) at baseline. To test for effect modification by menopausal status, we modelled associations of BMI and waist circumference (continuous) stratified by baseline self-reported menopausal status.

In a sensitivity analysis, we restricted the outcome to medically confirmed papillary, follicular, anaplastic thyroid cancer (n = 179), which are histological types derived from follicular thyroid cells, as opposed to parafollicular thyroid cells (medullary). We also performed an analysis restricted to non-Hispanic White women; there was limited statistical power to evaluate associations for women of other racial/ethnic groups.

All analyses were conducted using Stata version 17.0. Graphs were made using R version 4.1.2.

Role of funding sources

The funders of the study reviewed the final version of the manuscript but had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Among the included 47,739 women, median (25th-75th percentiles) follow-up was 12.5 (11.3–14.1) years. Median (25th, 75th percentiles) baseline age was 55.4 (48.9–62.1) years and median (25th, 75th percentiles) age at the end of follow-up was 67.7 (61.1–74.3) years. During follow up, 259 thyroid cancer cases were reported. Of the cases for whom we had pathology reports (n = 189, 80%), 168 (65%) were papillary (International Classification of Disease for Oncology [ICDO], 3rd edition, codes: 8260, 8265, 8340, 8341), 10 were follicular (ICDO codes: 8290, 8330, 8331, 8335), 5 medullary (ICDO codes 8510, 8010), 1 anaplastic (ICOD code: 8021) and 5 other or unspecified types (ICDO codes: 8000, 8346, 8347, 9084).

Table 1 describes the baseline cohort characteristics by BMI status. Most participants were non-Hispanic

Total N	Baseline BMI categories					
	<25 kg/m^2		≥25–<30 kg/m^2		≥30 kg/m^2	
	18,502		15,082		14,154	
	N	%	N	%	N	%
Age at baseline						
≥35–<45 years	2996	(16.2)	1697	(11.2)	1631	(11.5)
≥45–<55 years	6648	(35.9)	4978	(33.0)	5012	(35.4)
≥55–<65 years	5991	(32.4)	5514	(36.6)	5241	(37.0)
≥65 years	2868	(15.5)	2893	(19.2)	2270	(16.1)
Race/Ethnicity						
Non-Hispanic white	16,470	(89.0)	12,395	(82.2)	10,780	(76.1)
Hispanic (all races)	737	(4.0)	895	(5.9)	746	(5.3)
Non-Hispanic Black	705	(3.8)	1341	(8.9)	2188	(15.5)
Non-Hispanic Asian/Pacific Islander	201	(1.1)	88	(0.6)	32	(0.2)
Non-Hispanic American Indian	24	(0.1)	24	(0.2)	37	(0.3)
Non-Hispanic other/unknown race	361	(2.0)	333	(2.2)	367	(2.6)
Missing	5	(0.03)	6	(0.04)	4	(0.03)
Any baseline metabolic disorder[a]	8415	(46)	9403	(63)	10,672	(77)
Missing	229	(1.2)	135	(0.9)	89	(0.6)
Any self-reported thyroid disease (primary or secondary)	3112	(16.8)	3071	(20.4)	3280	(23.2)
Missing	0	(0)	0	(0)	0	(0)
Self-reported thyroid nodules	1215	(6.6)	1148	(7.6)	1110	(7.8)
Missing	0	(0)	0	(0)	0	(0)
Attained self-reported education						
Less high school	141	(0.8)	189	(1.3)	235	(1.7)
High school diploma/GED/some college without degree	4976	(26.9)	5403	(35.8)	5575	(39.4)
Bachelor's degree or associate/tech degree	8089	(43.7)	6082	(40.3)	5561	(39.3)
Master/Doctoral degree	5292	(28.6)	3405	(22.6)	2779	(19.6)
Missing	5	(0.03)	3	(0.02)	4	(0.06)
Smoking status						
Never smoked	10,822	(58.5)	8343	(55.3)	7867	(55.6)
Past smoker	6260	(33.8)	5429	(36.0)	5157	(36.5)
Current smoker	1416	(7.7)	1307	(8.7)	1122	(7.9)
Missing	5	(0.03)	3	(0.02)	8	(0.06)
Utilization of healthcare in the year before study entry:						
No dental or physical exam	423	(2.3)	435	(2.9)	630	(4.5)
At least one dental or physical exam	5017	(27.1)	4725	(31.3)	4885	(34.5)
At least one dental or physical exam and both breast and cervical cancer screening	2959	(16.0)	2189	(14.5)	2127	(15.0)
Both dental and physical exam and both breast and cervical cancer screening	9879	(53.4)	7551	(50.1)	6304	(44.5)
Missing	225	(1.2)	182	(1.2)	208	(1.5)

BMI, Body mass index; N, Number. [a]Defined has not having any of these conditions: self-reported dyslipidemia, self-reported use of anti-cholesterol medications, measured systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg, self-reported use of antihypertensive medications, self-reported diabetes type-2, self-reported polycystic ovary syndrome, or self-reported primary hypothyroidism.

Table 1: **Characteristics of the cohort participants by body mass index.**

white (83%). Compared to women with BMI <25 kg/m^2, those with BMI ≥30 kg/m^2 were more likely to be non-Hispanic Black (15% versus 4%) and less likely to have had a post-college education (20% versus 29%) or to have reported routine cancer screenings in the year before study entry (89% versus 93%). Smoking status was comparable across BMI categories.

BMI (per-5 kg/m^2) was positively associated with thyroid cancer (HR = 1.25, 95% CI = 1.14–1.37) (Fig. 1). This association was unchanged in models unadjusted for healthcare use (HR = 1.24, 95% CI = 1.14–1.36) (Fig. 1). Similar results were observed among those without any baseline metabolic conditions (HR = 1.31, 95% CI = 1.08–1.58) and in those without baseline thyroid nodules (HR = 1.27; 95% CI 1.15–1.40). Waist circumference was also associated with thyroid cancer (per-5 cm, HR = 1.11, 95% CI = 1.06–1.15). Similar to the results for BMI, this association did not differ in

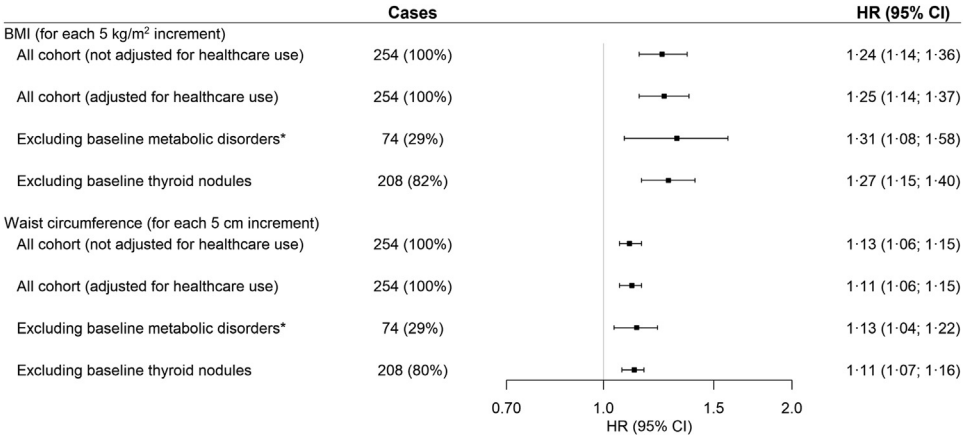

Fig. 1: **Hazard ratios and confidence intervals for thyroid cancer associated with body mass index and waist circumference.** CI, Confidence interval; HR, Hazard ratio; PCOS, Polycystic ovary syndrome. *Obesity-related metabolic conditions were defined as presence of any of the following: Self-reported dyslipidemia, diabetes type-2, PCOS, use anti-cholesterol or antihypertensive medication, or measured systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg.

models unadjusted for healthcare use or after restricting to women without baseline obesity-associated metabolic conditions or thyroid nodules.

Compared to BMI <25 kg/m^2, obesity was associated with a 54% higher incidence of thyroid cancer (HR = 1.54, 95% CI = 1.14–2.07) (Table 2). High waist circumference (≥88 versus <80 cm, HR = 1.67, 95% CI 1.25–2.22), waist-to-hip ratio (≥0.85 versus <0.85, HR = 1.49, 95% CI 1.14–1.94), and ABSI (highest versus lowest quartile, HR = 1.48, 95% CI 1.02–2.13) were also associated with thyroid cancer (Table 2). Similar results were obtained when restricting the analysis to non-Hispanic white women (Supplementary Table S2), after excluding women with a baseline history of thyroid nodules (Supplementary Table S3), and for pre- and post-menopausal women (Supplementary Table S4). Although based on a smaller number of cases, risk estimates were comparable when including only medically confirmed cases of papillary, follicular, or anaplastic histologic types of thyroid cancer

	Cases	Basic model[a]		Fully adjusted model[a]	
		HR	95% CI	HR	95% CI
BMI					
<25 kg/m^2	91	1 (ref)		1 (Ref)	
≥25–<30 kg/m^2	70	1.00	0.73–1.37	1.01	0.74–1.38
≥30 kg/m^2	93	**1.52**	**1.13–2.05**	**1.54**	**1.14–2.07**
Waist circumference					
<80 cm	82	1 (Ref)		1 (Ref)	
≥80–<88 cm	45	1.05	0.73–1.52	1.06	0.73–1.53
≥88 cm	127	**1.65**	**1.24–2.19**	**1.67**	**1.25–2.22**
Waist-to-hip ratio					
<0.85	166	1 (Ref)		1 (Ref)	
≥0.85	85	**1.48**	**1.13–1.93**	**1.49**	**1.14–1.94**
ABSI categories[b]					
First Quartile	51	1 (Ref)		1 (Ref)	
Second Quartile	60	1.19	0.82–1.74	1.19	0.82–1.73
Third Quartile	75	**1.53**	**1.07–2.19**	**1.54**	**1.08–2.20**
Fourth Quartile	68	**1.47**	**1.01–2.12**	**1.48**	**1.02–2.13**

ABSI, A body shape index; BMI, Body mass index; CI, Confidence interval; HR, Hazard ratio. [a]Basic model is adjusted for: attained education, race/ethnicity, smoking, history of thyroid disorders. Fully adjusted model is adjusted for: attained education, race/ethnicity, smoking, history of thyroid disorders, healthcare use. [b]ABSI is calculated as the ratio between the waist circumference (in m) and the product between the BMI$^{2/3}$ and height$^{1/2}$ (in m), multiplied by 1000. Cut points are: first quartile <69.8, second quartile ≥69.8 to <73.5, third quartile = ≥73.5 to <77.4, fourth quartile ≥77.4.

Table 2: **Association between baseline indicators of excess adiposity and thyroid cancer risk.**

(Supplementary Table S5). Associations of BMI and waist circumference with thyroid cancer were similar in models adjusted for obesity-associated metabolic conditions (Supplementary Table S6).

Obesity-related metabolic conditions, including metabolic syndrome, dyslipidemia, borderline diabetes, hypertension, and PCOS, were each associated with thyroid cancer, with HRs ranging from 1.46 for dyslipidemia and 2.10 for PCOS (Table 3). Additional adjustment for BMI (on a continuous scale) attenuated these estimates, although dyslipidemia (HR = 1.35, 95% CI 1.04–1.75) and PCOS (HR = 1.86, 95% CI 1.06–3.28) remained associated with increased thyroid cancer risk. Compared to women without diabetes, neither diabetes type-2 treated with metformin nor diabetes type-2 not treated with metformin was not associated with thyroid cancer risk (Table 3). The HR for diabetes type-2 treated with metformin versus not treated with metformin was 1.37 (95% CI 0.49–3.84), based on 11 and 6 thyroid cancer cases in these categories, respectively (data not shown in tables). Results did not change after excluding participants with baseline history of thyroid nodules (Supplementary Table S3). Self-reported primary hypothyroidism was not associated with thyroid cancer in the full cohort (HR = 1.08, 95% CI 0.77–1.50); however, in models excluding women with thyroid nodules at baseline, primary hypothyroidism was associated with reduced thyroid cancer (HR = 0.57, 95% CI 0.35–0.93).

In Fig. 2, we reported the combined associations of BMI (≥30 versus <30 kg/m^2) with the presence of any obesity-related metabolic condition (e.g., dyslipidemia, hypertension, diabetes type-2, or PCOS). Compared with no obesity/no metabolic condition, thyroid cancer was 75% higher in women with no obesity but with any metabolic conditions, 90% higher in women with obesity but with no metabolic condition, and more than

Obesity-related metabolic conditions	Cases	Fully adjusted model 1[a]		Fully adjusted model 2[a]	
		HR	95% CI	HR	95% CI
Metabolic syndrome[b]					
No	187	1 (Ref)		1 (Ref)	
Yes	63	**1.67**	**1.24–2.25**	1.32	0.96–1.81
Self-reported dyslipidemia or use of anti-cholesterol medication					
No	144	1 (Ref)		1 (Ref)	
Yes	110	**1.46**	**1.13–1.90**	**1.35**	**1.04–1.75**
Self-reported borderline diabetes or diabetes type 2[c]					
No	220	1 (Ref)		1 (Ref)	
Borderline diabetes	12	**2.06**	**1.15–3.69**	1.70	0.94–3.06
Diabetes	17	1.53	0.93–2.54	1.17	0.70–1.96
Self-reported diabetes type 2 and use of metformin					
No diabetes	232	1 (Ref)			
Diabetes treated with metformin	11	1.68	0.91–3.10	1.22	0.66–2.29
Diabetes not treated with metformin	6	1.22	0.54–2.77	0.98	0.43–2.23
Blood pressure measurement and self-reported use of anti-hypertensive medication					
Systolic/Diastolic blood pressure <140/90 and without use of antihypertensive treatment	149	1 (Ref)		1 (Ref)	
Systolic/Diastolic blood pressure <140/90 with antihypertensive treatment	88	**1.49**	**1.12–1.96**	1.28	0.96–1.71
Systolic/Diastolic blood pressure ≥140/90 with or without antihypertensive treatment	16	1.50	0.88–2.53	1.18	0.69–2.02
Self-reported polycystic ovary syndrome					
No	239	1 (Ref)		1 (Ref)	
Yes	13	**2.10**	**1.20–3.67**	**1.86**	**1.06–3.28**
Primary hypothyroidism[d]					
No	209	1 (Ref)		1 (Ref)	
Yes	43	1.08	0.77–1.50	1.00	0.72–1.40

CI, Confidence interval; HR, Hazard ratio. [a]Fully adjusted model 1 is adjusted for: attained education, race/ethnicity, smoking, history of thyroid disorders, healthcare use. Fully adjusted model 2 is adjusted for: attained education, race/ethnicity, smoking, history of thyroid disorders, healthcare use, BMI (continuous). [b]Defined as waist circumference ≥80 cm and at least two among: 1) Self-reported dyslipidemia or use anti-cholesterol medication; 2) Self-reported borderline diabetes or diabetes type 2; 3) Blood pressure ≥140 or diastolic blood pressure ≥90 mmHg or self-reported use of anti-hypertensive medication. [c]Subjects likely having type-1 diabetes, defined as self-reported diagnosis of diabetes type-1 (as free text option) or diabetes before age 20 or between age 20–35 and start of insulin treatment ≤12 months from diagnosis (n = 130), were excluded from this analysis. Also, we excluded subjects likely having secondary diabetes, defined as report of hemochromatosis, liver cirrhosis, hyperthyroidism, PCOS (n = 19), or gestational diabetes (n = 25) ≤12 months from diabetes diagnosis date. [d]Model not adjusted for history of benign thyroid disorders. We excluded from this model 544 subjects reporting a diagnosis of hyperthyroidism before or at the same age as hypothyroidism and 106 subjects reporting hypothyroidism following thyroidectomy or use of amiodarone, lithium, interferon, sodium-potassium iodine, or other iodine-based medications, as likely have secondary hyperthyroidism.

Table 3: **Association between obesity-related metabolic conditions and thyroid cancer risk.**

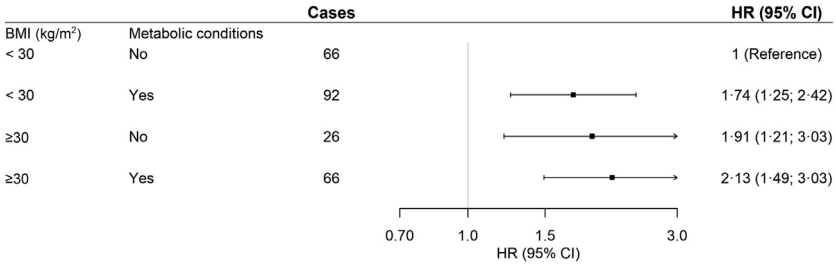

Fig. 2: **Joint association of BMI with obesity-related metabolic conditions (dyslipidemia, hypertension, diabetes type-2, and PCOS).*** CI, Confidence interval; HR, Hazard ratio; PCOS, Polycystic ovary syndrome. Models were adjusted for attained education, race, smoking, history of thyroid disorders, and healthcare use. No significant interaction was observed (p-interaction = 0.11). *Obesity-related metabolic conditions were defined as presence of any of the following: Self-reported dyslipidemia, diabetes type-2, PCOS, use anti-cholesterol or antihypertensive medication, or measured systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg.

doubled in women with obesity and metabolic condition (HR = 2.13, 95% CI 1.49–3.03) (p-interaction = 0.11, suggestive of a sub-multiplicative interaction). Similar risk estimates were obtained in models evaluating the joint association of waist circumference and presence of metabolic conditions (Fig. 3).

Discussion

Obesity and abdominal obesity, as well as several obesity-related metabolic conditions, were positively associated with thyroid cancer in this large U.S nationwide cohort of women. The positive associations were unaffected after adjusting for frequency of routine healthcare visits and breast and cervical cancer screenings or after excluding women with a baseline history of thyroid nodules, suggesting that detection bias is unlikely to explain these observations.

Consistent with previous studies,[4,5] we found that BMI, waist circumference, and waist-to-hip ratio were associated with higher incidence of thyroid cancer. To our knowledge, our study is the first to examine the association between ABSI and thyroid cancer risk, reporting an increase of thyroid cancer risk with higher ABSI score. ABSI is considered an indicator of abdominal obesity independent of BMI.[17] Measures of abdominal obesity (waist circumference, waist-to-hip ratio, ABSI) are more strongly predictive of metabolic abnormalities compared with BMI. Such abnormalities also characterize metabolic syndrome, dyslipidemia, and PCOS, which also were associated with thyroid cancer risk in this study. Metabolic syndrome or obesity accompanied by at least one metabolic abnormality (hyperglycemia, hypertension, dyslipidemia, insulin resistance) has been associated with thyroid cancer risk in some cohort studies,[11,22] but not others.[23] There is limited evidence regarding an association between dyslipidemia or PCOS with thyroid cancer risk.[12,23] PCOS has been associated with increased risk of other types of cancer, particularly endometrial, ovarian, and breast cancer, possibly mediated by mechanisms involving chronic hyperinsulinemia or progesterone deficiency.[7,24] thyroid cancer risk has been associated with history of infertility and ovarian cysts, which are characteristic of PCOS.[25,26]

All associations of obesity-related metabolic conditions and thyroid cancer were attenuated to some extent after adjustment for BMI, suggesting at least a partial mediating influence of excess adiposity. We also observed a suggestive sub-multiplicative interaction between obesity and metabolic syndrome on thyroid

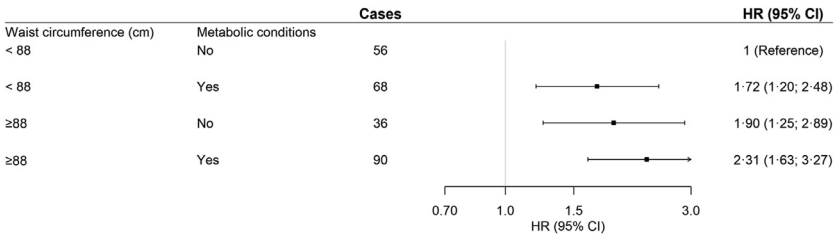

Fig. 3: **Joint association of waist circumference with obesity-related metabolic conditions (dyslipidemia, hypertension, diabetes type-2, and PCOS).*** CI, Confidence interval; HR, Hazard ratio; PCOS, Polycystic ovary syndrome. Models were adjusted for attained education, race, smoking, history of thyroid disorders, and healthcare use. No significant interaction was observed (p-interaction = 0.19). *Obesity-related metabolic conditions were defined as presence of any of the following: Self-reported dyslipidemia, diabetes type-2, PCOS, use anti-cholesterol or antihypertensive medication, or measured systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg.

cancerrisk, consistent with a previous report,[27] which may indicate a common underlying biological mechanism. Thus far, proposed biological mechanisms linking obesity with thyroid cancer include insulin resistance, hyper-estrogenic status, chronic inflammation, and elevated circulating TSH (characteristic of subclinical and overt, untreated hypothyroidism).[8]

In the current study, hypothyroidism was not associated with thyroid cancer overall, and was inversely associated with thyroid cancer among women without a baseline history of thyroid nodules. Hypothyroidism is associated with weight gain mostly because of salt and water accumulation rather than fat accumulation.[19] Thus, it is not surprising that our findings for hypothyroidism differed from those of the other obesity-related metabolic conditions, as the latter may more directly capture the effects of adiposity. Our observed association for hypothyroidism and thyroid cancer risk may not provide direct evidence about the influence of elevated TSH on thyroid cancer risk because our study was only equipped to capture individuals with diagnosed hypothyroidism, and those treated for this condition would go on to achieve lower, or normalized, circulating levels of TSH.[8] Our study was also not equipped to capture subclinical or untreated hypothyroidism, nor could we evaluate high or increasing TSH levels over time, which have been linked with obesity and weight gain even in the normal (euthyroid) range of thyroid function.[28] Consistent with our results, an inverse association between pre-diagnostic circulating TSH levels and thyroid cancer risk was reported in a large prospective study.[29]

Free fatty acids released from adipose tissue, especially abdominal visceral adipose tissue, induce insulin resistance and hyperinsulinemia.[7] Insulin resistance is the main feature of metabolic syndrome, as abdominal obesity associated with hyperglycemia, hypertension, or dyslipidemia are signs of an hyperinsulinemic state.[21] Chronic hyperinsulinemia is also common in women with PCOS.[9] Hyperinsulinemia may promote tumorigenesis directly in preneoplastic cells expressing insulin receptors or by promoting the release of insulin-like growth-factor, which promote cell proliferations.[7] Our results indicating that abdominal obesity, metabolic syndrome, dyslipidemia, and PCOS are associated with higher thyroid cancer risk support the hypothesized role of hyperinsulinemia in thyroid carcinogenesis. Metformin is an insulin-sensitizing treatment currently approved for type-2 diabetes, but is also used off-label for other metabolic conditions including PCOS.[30] Metformin has shown antineoplastic action in pre-clinical studies and has been associated with reduced thyroid cancer risk in some epidemiological studies.[13] However, we did not find clear evidence of a protective association of metformin among women with a history of diabetes in this study.

The adipose tissue has also an important role in regulating sex steroid levels. In men and postmenopausal women, aromatase activity in adipocytes regulates estrogen synthesis; thus, obesity in men and postmenopausal women has been associated with higher circulating levels of estrogens.[7] Higher circulating estrogen has been linked with mitogenic activity in breast and endometrial tissues.[7] Hyperinsulinemia decreases circulating sex hormone binding protein, thereby increasing bioavailability of testosterone. In premenopausal women, hyperinsulinemia may also promote ovarian androgen synthesis, contributing to higher risk of PCOS. This mechanism has been hypothesized to underlie the association between obesity and premenopausal endometrial cancer.[7] However, we found that the associations between obesity and thyroid cancer did not differ by baseline menopausal status, consistent with previous studies.[31] Nonetheless, the association between PCOS and thyroid cancer is suggestive of a role of insulin and/or androgens in thyroid carcinogenesis.

Strengths of this analysis included the large size of the cohort and long follow-up, which allowed us to detect associations of excess adiposity and associated comorbidities with thyroid cancer risk. Measurements of excess adiposity ascertained by trained personnel allowed for a more precise assessment of total and abdominal adiposity compared to that of most previous studies which relied on self-reported height and weight. Our analysis included a comprehensive evaluation of the potential for detection bias.[2] Although we lacked information on thyroid cancer stage and pathways to thyroid cancer detection, we did not identify evidence that detection bias influenced our results. Participants with obesity did not report more frequent routine medical or dental visits or screening for breast or cervical cancer. On the contrary, regular healthcare utilization and cancer screening was most frequent among women with BMI <25 kg/m^2. Furthermore, the associations of BMI and waist circumference were unchanged after excluding women with a baseline history of obesity-related metabolic conditions or benign thyroid nodules, conditions which may increase the likelihood of incidental thyroid cancerdetection.

Limitations included reliance on self-reported medical and pharmacological history, which may contribute to exposure misclassification and under-ascertainment of sub-clinical diseases. However, because of the prospective nature of this study, exposure misclassification was expected to be non-differential by thyroid cancer status. This type of misclassification generally biases associations toward the null. Studies with clinical records, including imaging, and biomarkers of metabolic diseases are needed to validate the findings from our study and provide additional mechanistic insights. Despite the large size of this cohort, we had limited power to test for interactions between excess adiposity indicators and comorbidities. Also, the number of patients reporting diabetes and use of metformin was insufficient to

disentangle their individual main associations with thyroid cancer risk. As the Sister Study recruited only women with a family history of breast cancer, the results may not be generalizable to men or to women without a family history of breast cancer. Lack of adjustment for childhood radiation exposure (an established risk factor for thyroid cancer) or for iodine deficiency (a probable risk factor for thyroid cancer) is unlikely to introduce confounding in this analysis as those factors are not associated with obesity nor obesity-associated conditions.

In summary, measures of overall and abdominal adiposity, as well as some obesity-related metabolic conditions, were associated with increased thyroid cancer risk in this large U.S. cohort of sisters of women diagnosed with breast cancer. Our results are consistent with the hypothesis that obesity-associated metabolic alterations, including insulin resistance, chronic inflammation, and a hyperestrogenic status may contribute to thyroid carcinogenesis and add to the evidence that the growing prevalence of obesity and obesity-related metabolic conditions may have contributed, in part, to the rising incidence of thyroid cancerworldwide. Nonetheless, thyroid cancer screening in asymptomatic individuals is not currently recommended,[32] and our results cannot be used to infer any benefits of screening in individuals with obesity or obesity-related metabolic conditions.

Contributors

Elisa Pasqual: conceptualization, analysis (including direct access and verification of the underlying data reported in the manuscript), methodology, figures, data interpretation, writing, final decision to submit the study for publication.

Katie O'Brien: study design, data collection, analysis (including direct access and verification of the underlying data reported in the manuscript), data interpretation, writing (review and editing).

Sabina Rinaldi: data interpretation, writing (review and editing).

Dale Sandler: study design, data collection, data interpretation, funding acquisition, writing (review and editing).

Cari Kitahara: conceptualization, analysis, supervision, funding acquisition, writing (review and editing), final decision to submit the study for publication.

Data sharing statement

The Sister Study is overseen by the Institutional Review Board of the National Institute of Health. All participants provided written informed consent. An anonymized dataset for replication of the current analysis may be obtained as described on the Sister Study website under "collaboration & data request" tab.[33] Other study data for collaborative research may be requested. Descriptive statistics, information on data collected, and copies of the questionnaires are also available on the Sister Study website.[20]

Declaration of interests

All authors declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lana.2023.100537.

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