

Obesity and Thyroid Cancer Risk among U.S. Men and Women: A Pooled Analysis of Five Prospective Studies

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Abstract

Background: Thyroid cancer incidence has risen dramatically in the United States since the early 1980s. Although the prevalence of obesity has doubled during this time period, the relationship between obesity and thyroid cancer is uncertain.

Methods: We examined the association between body mass index (BMI) and thyroid cancer risk in a pooled analysis of five prospective U.S. studies, including 413,979 women and 434,953 men. Proportional hazards models with attained age as the time metric were adjusted for education, race, marital status, smoking, alcohol intake, and (where appropriate) cohort and sex.

Results: Over follow-up (mean = 10.3 years), 768 women and 388 men were diagnosed with thyroid cancer. The risk of thyroid cancer was greater with increasing BMI [per 5 kg/m²: HR in women, 1.16 (95% CI, 1.08–1.24); HR in men, 1.21 (95% CI, 0.97–1.49)]. There was no significant heterogeneity between studies (both $P > 0.05$). For women and men combined, the HRs for overweight (25.0–29.9 kg/m²) and obesity (≥ 30 kg/m²) compared with normal-weight (18.5–24.9 kg/m²) were 1.20 (95% CI, 1.04–1.38) and 1.53 (95% CI, 1.31–1.79), respectively. We found no significant effect modification by other factors, and the results did not differ significantly by histologic type. A significant positive association for BMI in young adulthood (ages 18–20) with thyroid cancer risk was also observed [per 5-kg/m² increase: HR, 1.18 (95% CI, 1.03–1.35)].

Conclusion: BMI was positively associated with thyroid cancer risk in both men and women.

Impact: Our study provides strong evidence that obesity is an independent risk factor for thyroid cancer. *Cancer Epidemiol Biomarkers Prev*; 20(3); 464–72. ©2011 AACR.

Introduction

Thyroid cancer incidence in U.S. men and women has nearly tripled since 1980 (1), with the most rapid period of increase being between 1997 and 2006 (2). There is evidence that these patterns may represent a true increase, although greater diagnostic scrutiny probably also plays a role (3). Despite much interest in the reasons for the growing number of thyroid cancer diagnoses, there are few widely recognized risk factors for thyroid cancer apart from ionizing radiation in childhood and a medical

history of goiter or thyroid nodules (4), though there is some evidence of a decreased risk with smoking and alcohol consumption (4–6).

During a similar time period, the prevalence of obesity in U.S. adults has doubled, and overweight in children and adolescents has tripled (7). Excess adiposity has been implicated in the etiology of a number of cancer sites (8), but whether it may increase thyroid cancer risk has not yet been established. Of the few epidemiologic studies on this relationship, most included small numbers of incident cases and were retrospective in design and therefore may have been influenced by differential recall and/or postdiagnostic weight change. Although a positive association between obesity and thyroid cancer risk has been observed in women in several case-control (9–11) and prospective (12–15) studies, though not all (16–18), the results are less consistent in men, for whom the thyroid cancer incidence rate is lower (9–14, 16, 18–20). Furthermore, it remains unclear whether the association is modified by other factors or differs according to thyroid cancer subtypes, which are suspected to differ etiologically (4).

We conducted the first pooled analysis of prospective studies for the association between body mass index (BMI) and thyroid cancer risk, which was also one of

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the first to consider a large number of other postulated risk factors as potential effect modifiers and one of the largest prospective investigations of thyroid cancer in men to date.

Methods

Study population

The present study combines data from prospective cohorts from the National Cancer Institute that have accrued 50 or more incident, primary thyroid cancers and have baseline height and weight data. The eligible cohorts are the NIH-AARP Diet and Health Study (NIH-AARP; ref. 21), U.S. Radiologic Technologists Study (USRT; ref. 22), Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO; ref. 23), Agricultural Health Study (AHS; ref. 24), and Breast Cancer Detection and Demonstration Project (BCDDP; ref. 25). All 5 cohorts are based in the United States. The institutional review boards from the National Cancer Institute and all participating institutions approved the use of these data.

To be eligible for this pooling study, participants had to have responded to a baseline questionnaire, be followed for cancer incidence, have no history of cancer other than nonmelanoma skin cancer at baseline, and have a diagnosis date for any cancer diagnosed during follow-up. A total of 889,026 participants met these criteria. We further excluded men and women with missing ($n = 37,181$) or extreme ($<15 \text{ kg/m}^2$ or $>50 \text{ kg/m}^2$) BMI ($n = 2,913$). The final study population included 848,932 participants (434,953 men and 413,979 women).

Exposure assessment and data standardization

Participants from each cohort completed a self-administered baseline questionnaire eliciting information on general demographics (e.g., age, sex, race/ethnicity, education, marital status), lifestyle factors (e.g., cigarette smoking, alcohol intake, physical activity), and personal medical history. Anthropometric data were self-reported in all cohorts except BCDDP, in which trained medical staff measured participants' height and weight.

The level of detail on covariates differed across the cohorts. Therefore, we coded height, weight, BMI, education, race, marital status, smoking status, alcohol intake, and physical activity, using standardized definitions and categories. In addition, confounding by some known or potential risk factors for thyroid cancer, such as radiation exposure, and a medical history of benign thyroid conditions was evaluated in the USRT cohort, which had all the relevant data.

Outcome assessment

Participants were followed from the date of completion of the baseline questionnaire to the date of any cancer diagnosis other than nonmelanoma skin cancer, death, or last date of follow-up, whichever came first. Incident cancer information was obtained through different sources in each cohort: self-report (USRT, PLCO,

BCDDP), cancer registry linkage (NIH-AARP, USRT, AHS, BCDDP), death certificates (USRT, PLCO, BCDDP), and/or the National Death Index (NIH-AARP, USRT, BCDDP). Participants were considered to be cases if they were diagnosed with a malignant first primary thyroid neoplasm during follow-up. Using information from medical and pathology records and cancer registry linkage, thyroid cancers were classified by papillary (8050, 8052, 8130, 8260, 8340, 8341, 8342, 8343, 8344, 8450, 8452) and follicular (8290, 8330, 8331, 8332, 8335), medullary (8345, 8346, 8510), and anaplastic (8021) histologic types according to the International Classification of Diseases for Oncology, Third Edition, morphology codes.

Statistical analysis

Study-specific HR and 95% CIs for thyroid cancer were calculated using Cox proportional hazards models with attained age as the underlying time metric. BMI was modeled both continuously and categorically using indicator variables. All multivariable models were stratified by sex and adjusted for education (up to high school degree, post-high school up to college degree, postcollege, missing), race (white, black, American Indian/Alaskan Native, Asian/Pacific Islander, other, missing), marital status (married/living together, divorced/separated, widowed, single/never married, missing), cigarette smoking (never, former, current, missing), and usual alcohol intake during the previous 12 months (none, <1 drink/wk, 1–6 drinks/wk, ≥ 7 drinks/wk, missing). To test for log-linear trends, the median values of each BMI category were modeled continuously, and the Wald test was used to assess statistical significance. The HRs were then pooled using random effects models (26). Heterogeneity in the HRs between studies was assessed using the Q statistic and the I^2 index (27).

Because there was no statistically significant heterogeneity across studies, data from all 5 cohorts were combined into 1 aggregate data set to conduct additional analyses. BMI was modeled using higher-order (up to cubic) effects to further evaluate the shape of the association between BMI and thyroid cancer risk; the fit of these models to those using log-linear values of BMI were compared using the likelihood ratio test. To evaluate effect modification, models were stratified by categories of potential thyroid cancer risk factors including baseline age, birth cohort, education, smoking status, alcohol intake, and physical activity level; cross-product terms were included in the models and compared with models without this term, using the likelihood ratio test. We also separately assessed the associations by histologic type and evaluated the differences using the Mantel–Haenszel test for heterogeneity.

We conducted several sensitivity analyses. To assess the potential for confounding by ionizing radiation exposure or a medical history of benign thyroid conditions, both of which are established thyroid cancer risk factors (4), we included these factors in models of BMI and thyroid cancer risk in USRT, the only study in which these data

were available. Although evidence linking physical inactivity and diabetes to thyroid cancer risk is limited (14,18, 28), we additionally adjusted for physical activity level and a medical history of diabetes in a subset of the cohort without missing data to evaluate the potential for confounding or mediation, respectively, by these exposures. We also excluded the first 2 years of follow-up to evaluate the potential bias associated with including participants with preclinical thyroid cancer at baseline whose weight may have changed as a result of the disease.

Data on weight at young adulthood (18–20 years) were available from the baseline questionnaire in the PLCO and AHS cohorts and from a follow-up questionnaire in the NIH-AARP cohort (collected between 1996 and 1997). We prospectively examined BMI at young adulthood in relation to thyroid cancer risk within this subset ($n = 521$ cases).

All analyses were conducted using Stata software (version 9.2). All statistical tests were 2-sided and were considered statistically significant if $P < 0.05$.

Results

The mean age of subjects in the entire groups of cohorts ($n = 848,932$) was 58 years at baseline, with 51% of the participants being male, and 20% being obese (≥ 30 kg/m²; Table 1). There were different entry and exit dates for each of the cohorts within the period from 1979 to 2009, during which 1,156 participants (388 male and 768 female) were diagnosed with a first primary thyroid cancer. There were 132 thyroid cancer cases with missing information on histology. Of the 1,024 thyroid cancer cases with complete histologic information, 810 (79%) were papillary, 164 (16%) were follicular, 34 (3%) were medullary, and 16 (2%) were anaplastic.

Among women, but not men, BMI was positively associated with baseline age (Table 2). Compared with their normal-weight (18.5–24.9 kg/m²) counterparts, obese (≥ 30 kg/m²) participants were less likely to be current smokers and have a post-high school education. The proportions of women who were white, married, and reported drinking alcohol were lower in the obese compared with normal-weight category.

When BMI was modeled continuously (per 5 kg/m², Fig. 1), significant positive associations were observed in men from 2 of 4 cohorts (NIH-AARP and PLCO) and, in women, 4 of 5 cohorts (NIH-AARP, USRT, PLCO, and BCDDP). The pooled HR for thyroid cancer was 1.21 (95% CI, 0.97–1.49) in men and 1.16 in women (95% CI, 1.08–1.24); results were not significantly different by sex (P -interaction = 0.34). When we excluded the first 2 years of follow-up, the pooled HR became slightly stronger and statistically significant in men [HR, 1.30 (95% CI, 1.15–1.47)] but remained the same for women [HR, 1.17 (95% CI, 1.08–1.27)]. Despite a slightly stronger pooled HR in men compared with women, there was a nonsignificant inverse association among men in the AHS cohort [HR, 0.69 (95% CI, 0.41–1.15)]. For approximately 31% of the AHS cohort, missing or extreme BMI values were assigned using data from a 5-year follow-up questionnaire, and to a lesser extent drivers' license information on height and weight. However, exclusion of these individuals did not materially alter the HR for men in the AHS cohort, and in women, the positive association became slightly stronger.

In the aggregate data set (which combined men and women in the 5 cohorts), the relationship between BMI and thyroid cancer was approximately log-linear [per 5 kg/m²: HR, 1.17 (95% CI, 1.10–1.24; Fig. 2); the inclusion of high-order terms did not significantly improve the data fit ($P > 0.05$). We also examined the association using broader BMI categories, which correspond to the WHO criteria for normal-weight (18.5–24.9 kg/m²), overweight (25.0–29.9 kg/m²), and obesity (≥ 30 kg/m²; ref. 29). Compared with normal-weight, the HRs for overweight and obesity were 1.20 (95% CI, 1.04–1.38) and 1.53 (95% CI, 1.31–1.79).

We observed no significant heterogeneity in the association between BMI (per 5 kg/m²) and thyroid cancer risk by baseline age, birth cohort, education level, smoking status, alcohol intake, or physical activity level (Fig. 3). Although not significantly different, the results were stronger among never smokers [HR, 1.21 (95% CI, 1.11–1.31)] compared to former or current smokers. The results were stronger for papillary ($n = 810$ cases) compared with follicular thyroid cancer ($n = 164$ cases), but

Table 1. General characteristics of the five cohorts included in the pooled analysis

Cohort	No. of participants	No. of cases	Study period	No. of years of follow-up, mean (SD)	Age at baseline, mean (SD)	Male (%)	BMI ≥ 30 (%)
NIH-AARP Diet and Health Study (ref. 21)	498,957	583	1995–2006	9.1 (2.9)	62.0 (5.4)	61	22
USRT study (ref. 22)	89,529	275	1983–2006	15.9 (5.3)	40.4 (11.1)	23	9
PLCO study (ref. 23)	139,131	168	1993–2009	9.6 (3.2)	62.6 (5.3)	50	24
AHS (ref. 24)	67,925	67	1993–2005	9.9 (1.9)	46.9 (12.6)	58	21
BCDDP (ref. 25)	53,390	63	1979–1999	15.3 (2.8)	55.4 (8.8)	0	10
Total	848,932	1,156	1979–2009	10.3 (4.0)	58.2 (10.4)	51	20

Table 2. Age-adjusted means and percentages of select baseline characteristics according to BMI category in the aggregate data set of the five cohorts

	BMI, kg/m ²			
	15.0–18.4	18.5–24.9	25.0–29.9	30.0–49.9
<i>Men (no. participants)</i>	2,101	125,239	214,697	92,916
BMI, kg/m ²	17.4	23.2	27.2	33.2
Baseline age	61.3	59.8	60.1	59.6
Education (% beyond high school)	75.0	76.2	71.7	67.3
Smoking status				
Never	32.4	35.9	32.5	29.5
Former	41.7	45.8	53.6	57.9
Current	22.3	15.3	10.8	9.2
Missing	3.6	2.9	3.1	3.4
Alcohol intake (% nondrinker)	27.3	21.6	20.7	23.6
Marital status (% married)	76.3	82.4	86.1	84.9
Race (% white)	89.1	91.6	92.8	92.5
<i>Women (no. participants)</i>	7,644	206,578	121,950	77,807
BMI, kg/m ²	17.7	22.3	27.2	34.4
Baseline age	51.1	54.2	58.7	59.0
Education (% beyond high school)	69.1	67.5	61.9	60.0
Smoking status				
Never	43.7	48.6	50.5	51.2
Former	24.3	31.2	32.6	34.8
Current	26.3	16.0	13.1	10.4
Missing	5.7	4.2	3.7	3.5
Alcohol intake (% non-drinker)	31.7	27.1	31.0	37.3
Marital status (% married)	56.1	63.6	63.5	57.6
Race (% white)	91.0	92.8	90.2	87.6

this difference was also not statistically significant, likely due to the smaller number of follicular tumors (*P-heterogeneity* = 0.27). We also separately examined the associations between BMI (per 5 kg/m²) and medullary [*n* = 34 cases, HR, 0.87 (95% CI, 0.59–1.28)] and anaplastic [*n* = 16 cases, HR, 1.45 (95% CI, 0.95–2.22)] cancers, though the relative risk estimates were unstable due to small numbers. The differences in the results for the 4 histologic types were not significant (*P-heterogeneity* = 0.23). When we restricted the results to Caucasians (*n* = 1,075 cases), the HR was 1.19 (95% CI, 1.12–1.26).

Additional adjustment for physical activity level and medical history of diabetes had little influence on the results (Supplementary Table). Adjustment for other factors available only from the USRT cohort, including personal and medical exposure to radiation and medical history of benign thyroid conditions also did not change the results (Supplementary Table).

The strength of the association for BMI in young adulthood [18–20 years; per 5-kg/m² increase: HR, 1.18 (95% CI, 1.03–1.35)] was very similar to that of baseline BMI [per 5-kg/m² increase: HR, 1.17 (95% CI, 1.11–1.24)]. However, mutual adjustment for baseline BMI slightly attenuated the association for young adulthood BMI [HR,

1.08 (95% CI, 0.93–1.25)], whereas that of baseline BMI remained similar [HR, 1.14 (95% CI, 1.04–1.25)].

We additionally examined the association between height (per 5 cm) and thyroid cancer risk in men and women, separately, and found a significant positive association in women [HR, 1.06 (95% CI, 1.00–1.12)] but no association in men [HR, 1.01 (95% CI, 0.94–1.08)]. We observed significant heterogeneity between studies in men (*P-heterogeneity* = 0.01), but the results were less heterogeneous after the exclusion of the AHS cohort [HR, 1.03 (95% CI, 0.96–1.11), *P-heterogeneity* = 0.34].

Discussion

Because thyroid cancer is a relatively rare cancer, it is difficult to investigate potential risk factors, such as obesity, within individual prospective studies. Our pooled analysis is the largest prospective study on this topic to date that has individual-level data on other key exposures, including cigarette smoking, alcohol intake, physical activity, medical history of diabetes, and included a large number of incident thyroid cancers in men, for whom the disease is less common. Overall, we

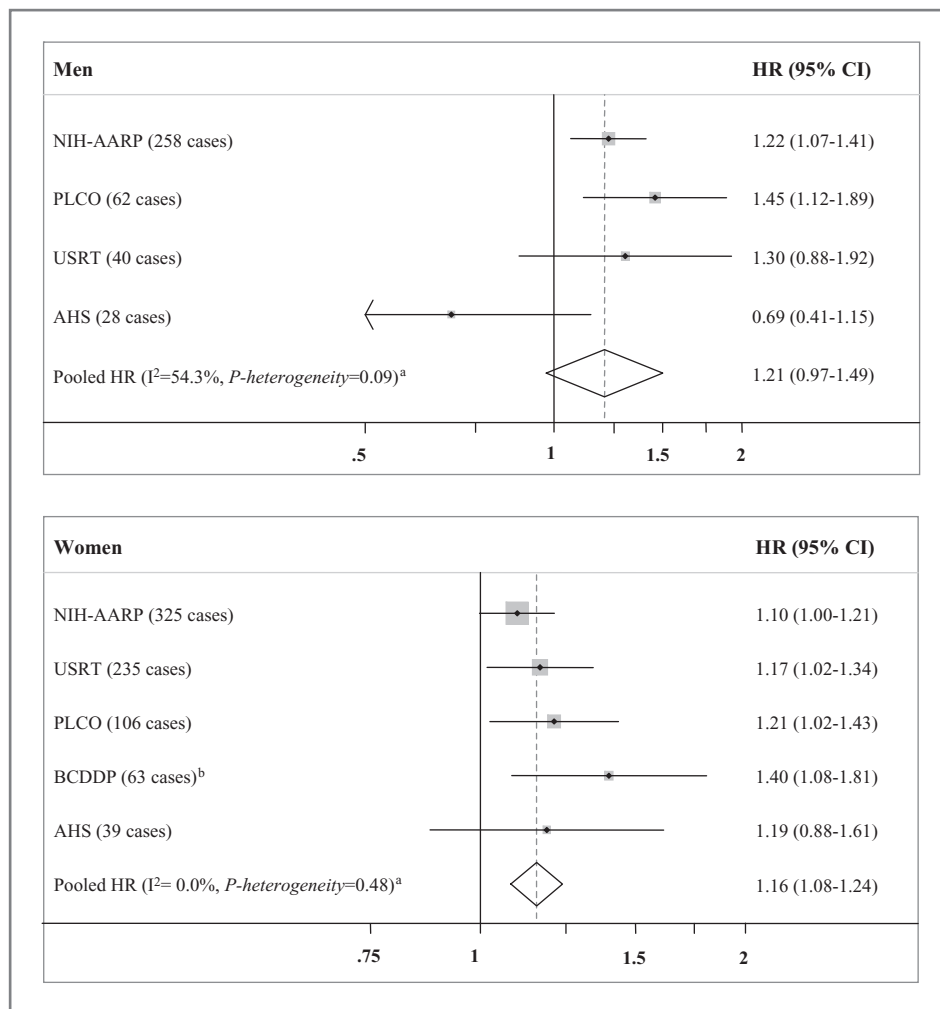


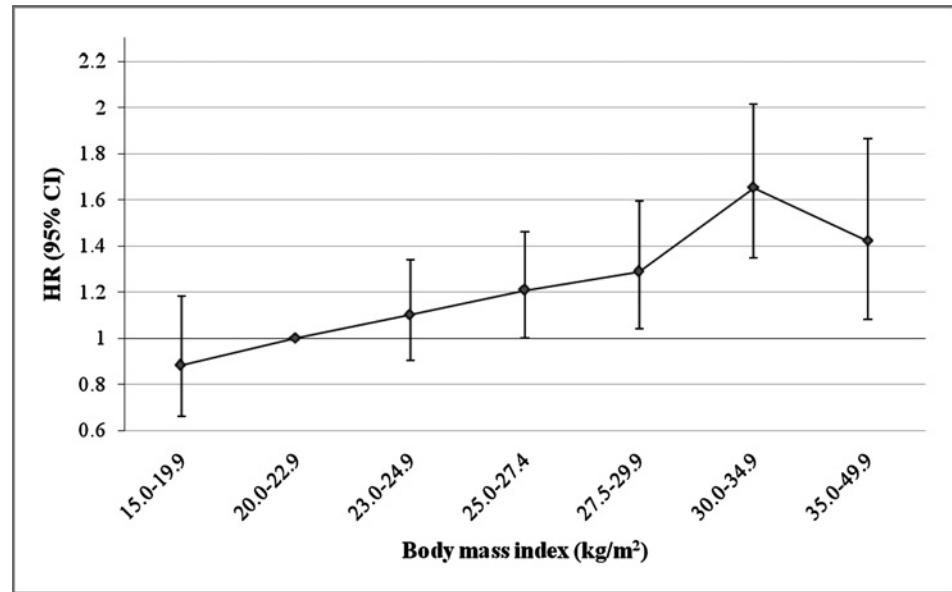
Figure 1. Multivariable-adjusted HRs (adjusted for education, race, marital status, cigarette smoking, and alcohol intake) and 95% CIs for BMI (per 5 kg/m²) and thyroid cancer risk by sex: pooled analysis of the five cohorts. Squares and horizontal lines correspond to the study-specific HRs and 95% CIs, respectively. The size of a square reflects the study-specific weight, and the diamond represents the pooled HR and 95% CI. The vertical dotted line represents the pooled HR. The abbreviations of the studies are same as in Table 1.^a, calculated using a random effects model.^b, height and weight were measured directly.

observed a positive association between BMI and thyroid cancer risk, which was generally consistent across the 5 prospective studies.

Results from previous prospective and case-control studies on the association between obesity and thyroid cancer risk have generally been more inconsistent in men than women. A pooled analysis of 12 case-control studies from the United States, Europe, and Asia (2,056 female and 417 male cases) found a significant, but weak, positive association between BMI and thyroid cancer risk in women [highest vs. lowest tertile: RR, 1.2 (95% CI, 1.0–1.4)] but not men; however, there was significant heterogeneity by study, with the positive association for women being largely driven by 2 U.S. studies (9). A large prospective Norwegian study (2,268 female and 778 male cases) also found a moderate positive association between BMI and thyroid cancer in women but not men, but the results were unadjusted for smoking and

other factors (13). In a large prospective study of Korean men, there was a strong dose-response association after adjustment for cigarette smoking, alcohol intake, physical activity, family history of cancer, and urban versus rural residency [≥ 30 vs. 18.4–22.9 kg/m²: RR, 2.23 (95% CI, 1.40–3.55); P -trend < 0.001; ref. 19]; however, results were not presented for women. Our results were consistent with those from a meta-analysis of prospective studies from the United States, Europe, and Korea not included in the current analysis (refs. 12, 13, 17, 19, 20; per 5-kg/m² increase: pooled RR for women = 1.14, 95% CI, 1.06–1.23; pooled RR for men = 1.33, 95% CI, 1.04–1.70); however, there was significant heterogeneity between studies in men ($I^2 = 77.4\%$, P -heterogeneity = 0.004; ref. 30). The inconsistent results between men and women in previous studies are likely due to smaller number of cases in men or lack of control for important covariates. Failure to adjust for smoking status, for

Figure 2. Multivariable-adjusted HRs (adjusted for sex, education, race, marital status, cigarette smoking, alcohol intake, and cohort) and 95% CIs for BMI categories and thyroid cancer risk: aggregate analysis of the five cohorts.



instance, may positively bias the association between BMI and risk of thyroid cancer as current smoking is associated with lower BMI levels and has been linked to a reduced risk of thyroid cancer (4,14). When we restricted to never smokers, we found that the association between BMI and thyroid cancer was slightly stronger than the association in the pooled analysis overall, which suggests that the BMI–thyroid cancer association is independent of cigarette smoking.

We also observed a significant positive association between BMI in young adulthood (ages 18–20) and thyroid cancer risk [HR, 1.18 (95% CI, 1.03–1.35)]. This finding, as well as the lack of effect modification by baseline age on the relationship between baseline BMI and thyroid cancer risk, suggests that obesity during any stage of adulthood may predispose individuals to thyroid cancer. Although no association between early adulthood BMI and thyroid cancer was observed in a pooled analysis of case–control studies (9), a recent case–control study in French Polynesia showed a significantly increased risk of thyroid cancer in both women and men with a high BMI at age 18 (11).

Several case–control and prospective studies have observed positive associations between height and thyroid cancer risk in both men and women (9,11,13,16,31). For reasons that are currently unclear, in our pooled analysis, we observed positive associations in women but not men. There may be genes or early environmental exposures, such as nutrition, that contribute both to skeletal growth and also to the risk of thyroid cancer (31). Future investigations of such factors are warranted.

There were some limitations of our study, however. The number of thyroid cancer diagnoses may have been underestimated due to the reliance on self-report in some

of the studies, but given that thyroid cancer is rarely fatal this number is expected to be small. We lacked information on tumor size, which would be useful in distinguishing between tumors found incidentally with those that have potentially greater clinical significance. It is unclear whether small, clinically insignificant tumors are more or less likely to be detected in obese compared to normal-weight individuals, though it is possible that this type of bias may have affected our results. Measurement error in height and weight may have attenuated our results because all but one of the cohorts (BCDDP) had self-reported measures, which is evidenced by the slightly stronger association we observed for BCDDP compared with the other 4 cohorts. Even greater measurement error in the estimation of BMI in young adulthood may be expected due to the long period of time between young adulthood and age at self-report; this may partly account for the inconsistency in previous studies (9,11). We cannot rule out the possibility of residual confounding by some measured and unmeasured factors. For example, residual confounding or misclassification of physical activity may have occurred, as it was defined differently across the cohorts and probably reported with some inaccuracy by the participants. Also, we only had information on exposure to ionizing radiation and history of benign thyroid diseases in the USRT cohort, although adjustment for these factors did not change the results for this particular study.

Potential biological mechanisms linking obesity and thyroid cancer risk are not well understood. Thyroid stimulating hormone (TSH), which promotes the secretion of thyroid hormones to regulate resting energy expenditure (32), may play a role in human thyroid cancer etiology. It has been shown to influence the growth

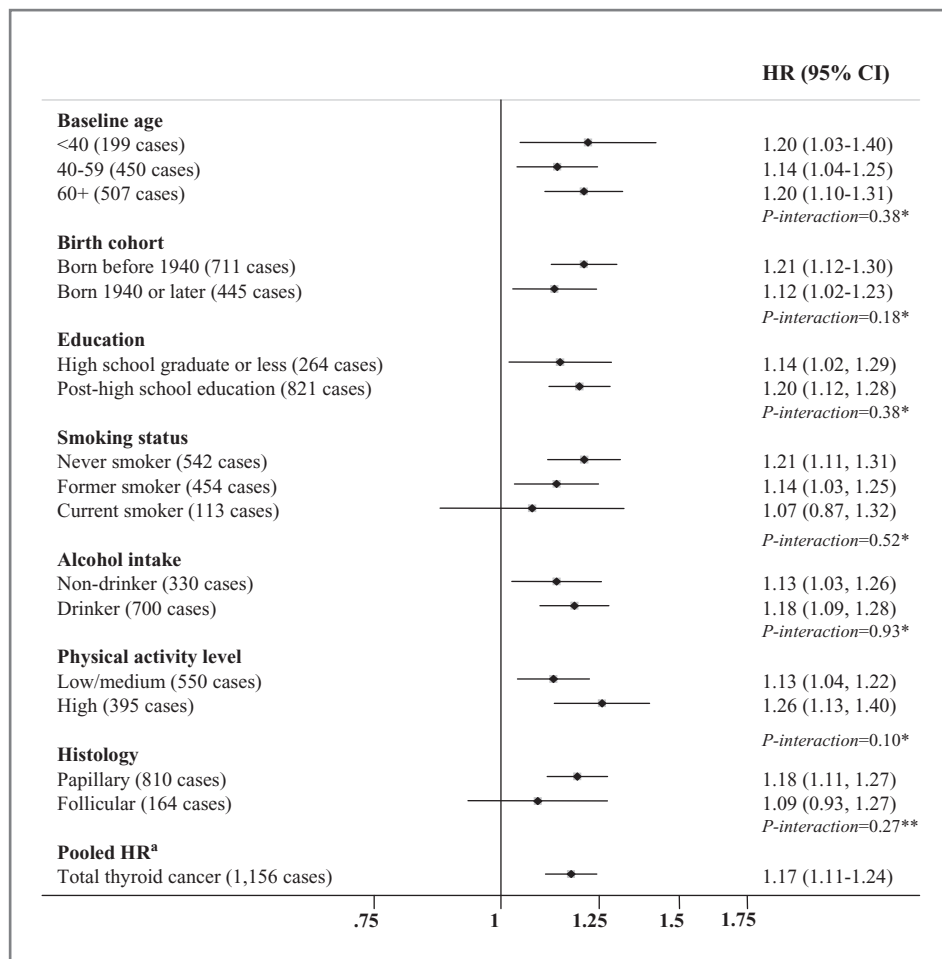


Figure 3. Multivariable-adjusted HRs (adjusted for sex, education, race, marital status, cigarette smoking, alcohol intake, and cohort) and 95% CIs for BMI (per 5 kg/m²) and thyroid cancer risk, stratified by selected risk factors: aggregate analysis of the five cohorts. *, test for interaction calculated using the likelihood ratio test comparing a model with a cross-product term to a model without. **, test for interaction calculated using the Mantel-Haenszel test for heterogeneity.,^a calculated using a random effects model.

and differentiation of thyroid cells in rodents (33), and higher concentrations have been found in thyroid surgery patients with differentiated thyroid cancer compared to patients with benign thyroid disease (34). Although some cross-sectional studies among euthyroid adults have found positive associations between BMI and levels of TSH (35,36), these findings have not been confirmed in others studies (37,38). Alternatively, insulin resistance, a common metabolic perturbation in obesity, may play a role in thyroid tumor growth, with insulin directly binding to insulin receptors or stimulating insulin-like growth factor, estrogen, or other hormones, such as TSH, to enhance the proliferation of thyroid cancer cells (39,40). The few studies that have examined the association of insulin resistance or diabetes with thyroid cancer risk have been inconsistent (14,28); however, additional adjustment for diabetes history did not attenuate the positive association between BMI and thyroid cancer risk observed in our pooled analysis. Because BMI measurements cannot distinguish fat from muscle mass (41), we had expected to observe a stronger association between BMI and thyroid cancer risk among physically inactive

participants, given their presumably lower contributions of muscle to total body mass. Instead, we found that the results were slightly, though nonsignificantly, stronger among active versus less active participants. As some adverse metabolic risk factors, including insulin resistance, are more strongly associated with central adiposity or visceral, as opposed to subcutaneous, adipose tissue (42), future studies with data on distribution and type of adipose tissue may provide additional clues about the etiology of thyroid cancer.

This pooled analysis provides strong support that obesity is an independent risk factor for thyroid cancer in both men and women. The risk estimates we observed for thyroid cancer were consistent with previous studies and were generally stronger than those observed for some other cancers more widely recognized to be obesity-related, including pancreatic, postmenopausal breast, and colon cancer (8,30). This may have considerable public health implications in countries, like the United States, which have experienced dramatic increases in the prevalence of overweight and obesity (7). Therefore, it is plausible that the rise in the number of

thyroid cancer diagnoses in the United States in the last 3 decades may have been at least partially attributable to the growing proportion of overweight and obesity in the population. Further research on the potential mechanisms underlying the BMI–thyroid cancer association may provide additional clues into the etiology of the disease and help identify more specific targets for prevention. Given the available evidence, there appears to be a particular need for prospective studies on central adiposity and obesity-related biomarkers, including markers of thyroid function (serum TSH or free T4) or insulin resistance (fasting serum glucose or insulin), with the risk of this disease.

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