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Body fat distribution, weight change during adulthood, and thyroid cancer risk in the NIH-AARP Diet and Health Study

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Abstract

Body mass index (BMI) has been positively associated with thyroid cancer risk in several studies, but the underlying mechanisms remain unclear. We examined the associations for waist and hip circumference and weight change during adulthood with thyroid cancer risk among 125,347 men and 72,363 women in the NIH-AARP Diet and Health Study who completed a second mailed questionnaire in 1996–97. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated separately by sex and adjusted for race/ethnicity, education, and smoking status. During follow-up (median=10.1 years), 106 men and 105 women were diagnosed with a first primary thyroid cancer, as identified through linkage to state cancer registries. Having a large waist circumference (above the clinical cutpoint for normal: >102 cm in men and >88 cm in women) was associated with increased risk in both men (HR=1.79, 95% CI: 1.21–2.63) and women (HR=1.54, 95% CI: 1.05–2.26). Having both a large waist and BMI in the obese range (≥30 kg/m^2) approximately doubled the risk of thyroid cancer (HR in men=2.13, 95% CI: 1.18–3.85; HR in women=1.91, 95% CI: 1.31–3.25) compared to having a normal waist circumference/normal BMI (18.5–24.9 kg/m^2). We also observed a positive association for weight gain between ages 18–35 in men (gained ≥10.0 kg versus lost/gained <5 kg, HR=1.49, 95% CI: 0.93–2.39, *P*-trend=0.03), but the association was less pronounced in women. No clear association for weight gain in later life was observed. These results support a potential role for hormonal and metabolic parameters common to central adiposity in thyroid carcinogenesis.

Keywords

thyroid cancer; anthropometry; obesity; prospective study

Thyroid cancer incidence rates increased dramatically in the U.S. over the past three decades. Improvements in the detection and diagnosis of small (≤1 cm), localized papillary thyroid cancers appear to at least partially account for these changes, but the increasing incidence of larger and later stage tumors suggests that environmental factors may also play a role.[1] There was a similarly dramatic increase in the prevalence of obesity during the same time period,[2] which may have, at least partially, contributed to the rising incidence of thyroid cancer. This hypothesis has been supported by recent evidence from case-control[3–6]

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and prospective[7–12] studies finding a positive association between body mass index (BMI) and the risk of thyroid cancer, though some studies found no association.[13–15]

There are certain limitations of using BMI as a measure of obesity, including the inability of this measurement to distinguish lean from fat mass (e.g. muscle) and central versus peripheral fat distribution.[16,17] Without having more detailed measurements of the amount or distribution of body fat besides BMI, it is unclear whether the positive associations observed between BMI and thyroid cancer risk were attributable to excess body fat, overall body size, or some other, related factor. Waist circumference measures have been shown to be more strongly correlated with highly metabolically-active visceral adipose tissue than BMI,[17,18] but to date no published studies have been reported on the association between excess abdominal body fat and thyroid cancer risk. The association between weight change during adulthood, which tends to reflect changes in fat rather than lean mass,[19] and the risk of this disease has been examined in only a few studies, and results have been conflicting likely due to small numbers of cases and lack of consistent definitions for weight change.[5,6,12,13,20]

We examined the association of body fat distribution (as measured by waist circumference, hip circumference, and waist-to-hip ratio) and adulthood weight change with thyroid cancer risk in the NIH-AARP Diet and Health Study, a large prospective study of U.S. men and women. A previous publication showed significant positive associations between BMI and thyroid cancer risk in men, but not women, in this cohort.[7] After three additional years of follow-up, significant positive associations were observed for both men and women.[23]

Methods

Study population

The NIH-AARP Diet and Health Study began in 1995–1996 when health questionnaires were mailed to AARP members between the ages of 50 to 71 years old and residing in one of six U.S. states (CA, FL, LA, NJ, NC, and PA) or two metropolitan areas (Atlanta and Detroit) with population-based cancer registries.[24] Within 6 months from the mailing of the baseline questionnaire, a second questionnaire was sent to men and women who had completed the baseline health questionnaire satisfactorily, had consented to participate in the study and did not have self-reported breast, colorectal, and prostate cancer in the baseline questionnaire and still lived in the study area. The NIH-AARP Diet and Health Study was approved by the Special Studies Institutional Review Board of the U.S. National Cancer Institute.

Out of 334,907 participants who satisfactorily completed the second questionnaire, we excluded, in this order, participants who were proxy respondents (n=10,383), reported having poor health in the baseline questionnaire (n=4,383), had a diagnosis of cancer other than non-melanoma skin cancer at the time of completion of the second questionnaire (n=18,809), were identified as having had incident cancer during follow-up through death records only (n=936), did not accrue any follow-up time (n=18), had missing data on waist or hip circumference (n=84,501), current height (n=1,653), current weight (n=2,032), or weight at ages 18, 35, 50 (n=13,710), or had extreme or implausible values of waist or hip circumference (<52 cm or ≥190 cm, n=149) or current BMI (<15 or >50 kg/m^2, n=623). The analytic cohort included the remaining 197,710 participants (125,347 men and 72,363 women).

Exposure assessment

The baseline questionnaire elicited information on general demographics, including age, sex, race/ethnicity, marital status, and education, as well as smoking, current height and weight,

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physical activity, medical history, and reproductive and hormonal factors. Some additional variables utilized in this analysis were ascertained from the risk factor questionnaire, completed approximately one year after the baseline questionnaire: self-reported height at age 18, self-reported weight at ages 18, 35, and 50, and self-reported waist and hip circumferences. Participants were asked to record their waist and hip measurements to the nearest 0.25 inch while standing, and to avoid measuring over bulky clothing. The waist was defined as "one inch above navel even if this is not your natural waistline," and the hip was defined as "the largest spot".

Identification of cancer cases

Incident, first primary thyroid cancers (*International Classification of Disease for Oncology*, Third Edition [ICD-O-3] codes C73)[25] were identified through December 31, 2006 by probabilistic linkage of the NIH-AARP cohort membership with state cancer registries and the National Death Index.[26] The state cancer registries are estimated to be at least 90% complete within two years of cancer incidence and are certified by the North American Association of Central Cancer Registries (NAACCR) for meeting the highest standard of data quality. A validation study of cancer endpoint ascertainment among a subset of the cohort (n=12,000), comparing state cancer registry data to self-report and subsequent medical record confirmation of incident cancers in this group, showed that 89% of all cancer cases identified through the cancer registries were valid.[26]

Statistical analysis

Cox proportional hazards regression models were used to calculate hazard ratios for thyroid cancer according to waist and hip circumference, ratio of waist to hip circumference, and weight change over adulthood, separately in men and women. All models used age as the underlying time metric and were adjusted for race/ethnicity (Caucasian, other, missing), education (not a college graduate, college graduate, or missing), and smoking status (never, former, current, missing), which are potential risk factors for thyroid cancer.[27] In models of adulthood weight change, we also adjusted for weight at the beginning of the weight-change interval. Additional adjustment for alcohol intake (number of drinks consumed per week), hormone therapy use (current, former, never, unknown), dietary intake of fish, fruits, dark green leafy vegetables (number of servings per day), and physical activity of at least 20 minutes over the past 12 months (number of times per month) had little influence on the relative risk estimates, so these variables were not retained in the multivariate models. None of the models were found to be in violation of the proportional hazards assumption. To test for trend, we modeled the median values for each category as continuous variables and evaluated this coefficient using the Wald test. Statistical significance for interactions between any two factors was tested using the likelihood ratio test comparing a model with the cross-product term to one without.

Waist and hip circumference, as well as the ratio of waist to hip circumference, were categorized into sex-specific quartiles. We defined "large waist circumference" as >102 cm for men and >88 cm for women, according to clinical guidelines.[28] Weight change during different periods of adulthood (young [ages 18–35]; middle [ages 35–50]; older [ages 50-current age]; and overall [ages 18-current age]) were categorized into the following, potentially clinically-useful, groups: lost ≥5 kg, no change (<5 kg gained or lost), gained 5–9.9 kg, gained ≥10 kg.

As secondary analyses, we examined the associations of body surface area (BSA) and height with thyroid cancer risk. BSA was calculated using Boyd's formula.[29]

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To evaluate the possible impact of excluding participants with missing data on waist and hip circumference, we used the multiple imputation method in which we regressed these measures on a number of other individual-level variables, including age, sex, BMI, smoking status, and physical activity level.[30] Imputed estimates and variance from ten imputed datasets were combined to obtain the final estimated HRs and 95% CIs.

Additionally, we evaluated the joint effect of current BMI (categorized as 18.5–24.9, 25–29.9, and ≥30 kg/m^2, using WHO criteria for normal weight, overweight, and obese)[31] and waist circumference (>102 cm in men; >88 cm in women) on thyroid cancer risk in men and women, using the joint category of normal-weight (18.5–24.9 kg/m^2) and normal waist circumference (≤102 cm in men; ≤88 cm in women) as the reference group.

Because the etiology of thyroid cancer may differ by histology,[27] we examined these associations separately for papillary thyroid cancers (ICD-O-3 codes 8050, 8660, 8340, 8341, 8343, 8344, and 8350),[25] which accounted for 76% of all incident thyroid cancers in this study.

All *P*-values presented are two-sided, and *P*-values <0.05 were considered statistically significant. Analyses were carried out using Stata 11 (StataCorp, College Station, TX).

Results

At the time of completion of the risk factor questionnaire, the median age was 63.8 years (range: 51.3–72.1) in men and 63.1 years (range: 51.3–71.9) in women. Eighteen percent of men and women were obese (BMI ≥30 kg/m^2). A large waist circumference (>102 cm in men and >88 cm in women) was observed in 29.6% of men and 35.6% of women. Over a median 10.1 years of follow-up, 211 participants (106 men and 105 women) were diagnosed with a first primary thyroid cancer.

Men and women with large waist circumferences were more likely to have greater hip circumferences, waist-to-hip ratios, and BMI compared to individuals with normal waist circumferences (Table 1). Individuals with large waist circumferences were also less likely to be college graduates and more likely to be former smokers. Age at the time of completion of the risk factor questionnaire and the proportion of different race/ethnicity groups were similar between men and women with large and normal waist circumferences.

The anthropometric variables were highly correlated with one another. For instance, the Spearman rho between current BMI and waist circumference was 0.75 in men and 0.78 in women. Between waist and hip circumference, the Spearman rho was 0.76 in men and 0.77 in women. Between BSA and current BMI, the Spearman rho was 0.78 in men and 0.84 in women. There was a weak correlation of height with waist (Spearman rho=0.23 in men and 0.10 in women) and hip (Spearman rho=0.29 in men and 0.17 in women) circumferences and total adult weight change (Spearman rho=0.13 in men and 0.10 in women).

A significant positive, dose-response association was observed for waist circumference and thyroid cancer in men (4^{th} versus 1^{st} quartile: HR=2.20, 95% CI: 1.23–3.95, *P*-trend=0.007; Table 2). In women, a lower risk was observed in the 2^{nd} compared to the 1^{st} quartile, with risk subsequently increasing in the 3^{rd} and 4^{th} quartiles (*P*-trend=0.13). However, having a clinically-defined large (>102 cm in men; >88 cm in women), compared to normal, waist circumference was associated with a significantly increased risk of thyroid cancer in both men (HR=1.79, 95% CI: 1.21–2.63) and women (HR=1.54, 95% CI: 1.05–2.26). Hip circumference was also positively associated with thyroid cancer in men (*P*-trend=0.01), but this association was less apparent in women (*P*-trend=0.24). Waist-to-hip ratio was not significantly associated with risk in either men or women (*P*-trend=0.19 in men and 0.25 in

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women). There were no significant interactions by sex for any of these anthropometric factors (*P*-interaction>0.05). The results for men were slightly stronger after restricting the outcome to papillary thyroid cancer (Table 2).

We also examined the joint effects of current BMI and waist circumference on thyroid cancer risk, separately in men and women (Table 3). Compared to normal weight (18.5–24.9 kg/m^2) and normal waist circumference (≤102 cm in men; ≤88 cm in women), being obese and having a large waist circumference (>102 cm in men;>88 cm in women) was associated with a 2.13-fold (95% CI: 1.18–3.85) and 1.91-fold (95% CI: 1.13–3.25) increased risk of thyroid cancer in men and women, respectively. In men, we observed that a large waist circumference was associated with an increased risk of the disease within each category of BMI.

Weight gain between ages 18 to 35 was significantly positively associated with thyroid cancer risk in men (*P*-trend=0.03, Table 4). Compared to men who lost or gained <5 kg between ages 18 to 35, men who gained 5–9.9 kg or ≥10 kg had an HR of 1.14 (95% CI: 0.68–1.92) and 1.49 (95% CI: 0.93–2.39), respectively, while men who lost ≥5 kg had an HR of 0.27 (95% CI: 0.03–2.19). Weight gain at later ages was not significantly associated with thyroid cancer risk in men. The associations for weight gain and thyroid cancer risk were weaker in women compared to men, but there were no significant interactions by sex for any of the weight change variables (*P*-interaction>0.05). None of these associations were substantially different after restricting to papillary thyroid cancers (Table 4).

We observed positive associations for BSA which were similar in strength to those for current BMI in both men and women (Appendix Table). After mutual adjustment, both factors were non-significantly associated with thyroid cancer risk (Appendix Table); this finding was likely due to the high correlation between these two measures (Spearman rho=0.78 in men and 0.84 in women). We did not observe a statistically significant association between height (per 5 cm) and thyroid cancer risk in either men (HR=1.06, 95% CI: 0.94–1.20) or women (HR=0.99, 95% CI: 0.86–1.15). Additional adjustment for height did not change any of the results for the other anthropometric variables examined in this analysis, including waist circumference and adult weight change (data not shown).

We conducted a number of sensitivity analyses. We excluded the first year of follow-up, which resulted in 24 fewer cases, to assess whether the inclusion of individuals who may have preclinical disease-related weight loss or weight gain at study entry had any influence on our results. We excluded current smokers (n=19 cases) to reduce the possibility for residual confounding by current cigarette smoking, which was inversely associated with body fat in this cohort and may be inversely associated with thyroid cancer risk.[11] We also excluded potentially premenopausal women (e.g. those who did not clearly indicate at baseline that their periods had stopped due to natural menopause, surgery, radiation, or chemotherapy, n=5 cases) because post-menopausal women have been shown to have greater adiposity, specifically greater visceral adipose tissue, and reduced insulin sensitivity compared to premenopausal women.[18] None of these changes had any substantial influence on the relative risk estimates. However, slightly stronger associations for waist circumference (large vs normal) and thyroid cancer risk were observed in women over the age of 60 (HR=1.88, 95% CI: 1.16–3.04) and women who never used menopausal hormone therapy (HR=1.72, 95% CI: 0.93–3.16) compared to ever users, though these differences were not statistically significant (*P*-interaction=0.18 and 0.54, respectively). We also found little difference in the results when we used the multiple imputation method to evaluate the possible influence of excluding participants with missing values of waist and hip circumference.

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Discussion

Although a number of case-control[3–6] and prospective[7–12] studies have found that high BMI, a measure of overall adiposity, is associated with an increased risk of thyroid cancer, to our knowledge, this was the first study to investigate the association between central adiposity and thyroid cancer risk. We found that having a waist circumference above the clinical cutpoint for normal (>102 cm in men and >88 cm in women) was associated with a significant increased risk in both men and women, but a dose-response association between waist circumference and thyroid cancer risk was only evident in men. Among men, having a large waist circumference increased the risk of thyroid cancer within BMI categories of normal-weight, overweight, and obese. We also found that, compared to having a stable weight, weight gain of 10 kg or greater from ages 18 to 35 was associated with a significant increased risk of thyroid cancer in men. In general, all of these associations were less pronounced in women compared to men.

Sex differences in the association between BMI and thyroid cancer have been observed in other studies, though they are generally not consistent between case-control studies finding stronger associations in women[3,4,6] and prospective studies finding stronger associations in men.[23,32] Our finding of a slightly stronger association for waist circumference and weight change with thyroid cancer risk in men compared to women, though not statistically significant, is consistent with the prospective studies on BMI and thyroid cancer risk.

The current study, which utilized self-reported data on waist and hip circumferences and weight at various periods during adulthood, provides some additional information on the potential mechanisms underlying the associations between BMI and thyroid cancer risk. For instance, the associations for waist and hip circumference and weight change were less pronounced in women compared to men. This finding may be partly explained by the slightly different hormone profiles and metabolic consequences of excess body fat in men and women. Despite having less overall body fat, as they age, men have an increased propensity to deposit fat centrally and accumulate a greater amount of visceral adipose tissue, both being strongly related to adverse metabolic conditions, including dyslipidemia and insulin resistance.[18] In women, the accumulation of visceral adipose tissue with age is strongly associated with unfavorable changes in plasma lipids, but it contributes to decreased insulin sensitivity only after the age of 60.[33] Our finding of a slightly stronger association between waist circumference and thyroid cancer risk in women older than 60 compared to those ages 60 and younger, together with evidence from prospective studies showing strong dose-response associations of fasting serum glucose levels and triglycerides with thyroid cancer risk,[34,35] supports the involvement of insulin resistance or associated lipid abnormalities in thyroid cancer development.

Other biological mechanisms may be involved which are generally more consistent with an association of overall, as opposed to central, adiposity and thyroid cancer risk. For instance, leptin may promote thyroid cancer cell growth through enhanced pituitary production of thyroid stimulating hormone (TSH).[36] TSH is a known thyroid growth factor which has been shown to regulate the growth and differentiation of thyroid cells in rodents,[37] and higher concentrations have been found in thyroid surgery patients with differentiated thyroid cancer compared to patients with benign thyroid disease.[38] Alternatively, estrogen could play a role in the association between overall body fatness and thyroid cancer risk among older men and postmenopausal women, as the conversion of androstenedione to estrone in adipose tissue is the main source of estrogen in these populations,[39] and, in laboratory studies, 17β-estradiol has been shown to be a potent growth-promoter of benign and malignant thyroid tumor cells.[40,41] There remains a need, however, for large prospective

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studies directly examining the association of these obesity-related hormones with thyroid cancer risk.

Thyroid volume has also been proposed as an alternative mechanism mediating the association between obesity and thyroid cancer due to its positive association with body size measures, including BMI and BSA.[42] In a recent pooled case-control study in French Polynesia and New Caledonia, a positive association was observed between BSA and thyroid cancer in women that was independent of BMI.[42] Although we also found a positive association for BSA, it was not more strongly associated with thyroid cancer risk compared to current BMI. However, in our study these measures were highly correlated (Spearman rho=0.8).

Risk factors may vary with age given the relatively young age distribution of thyroid cancer diagnoses (median age at diagnosis is approximately 50 years) and the higher proportion of papillary thyroid cancers and cancers diagnosed in women at younger compared to older ages.[27,43] In this cohort of older adults, we were unable to examine the associations of body fat distribution and weight change with thyroid cancers diagnosed before the age of 50. Therefore it is currently unclear whether the results from this study are generalizable to younger populations. Height, which is dependent on genes and early-life nutritional status, may be one anthropometric measure which is more strongly associated with thyroid cancer diagnosed at younger ages, as a positive association has been observed in several studies,[3,5,6,10,44] but not in the current study.

This study relies on self-reported data, including self-administered waist and hip measurements and self-reported weight at different ages. There is a possibility that, for instance, women were less likely to accurately report their weight and waist or hip circumference measurements than men, thus leading to greater attenuation in the results for women compared to men. This hypothesis is supported by a previous validation study in the U.S., which found a lower correlation between self-reported and technician-measured waist and hip circumference in women compared to men after adjusting for age and BMI.[45] However, the associations of central adiposity with renal cell carcinoma, pancreatic cancer, and total mortality were similar or stronger for women compared to men in this cohort,[46–48] suggesting that measurement error probably may not fully account for the sex differences observed in this study. Finally, without more specific tumor characteristic data, including tumor size, we cannot rule out the possibility that our results were due to increased surveillance of overweight or obese patients for thyroid disease. Nonetheless, detection bias did not appear to be a strong explanation for the positive association observed between obesity and thyroid cancer risk in New Caledonia, which found similar results for BMI irrespective of tumor size.[4]

This study had several important strengths. The relatively large number of thyroid cancer cases in this study allowed for reasonably precise estimates of risk in both men and women, which is notable considering that thyroid cancer is much rarer in men compared to women.[27] The prospective design of the study eliminated the potential for differential recall bias between cases and non-cases of thyroid cancer and also reduced the possibility that the self-reported anthropometric measures were affected by weight loss from preclinical thyroid cancer at study entry. We also had comprehensive data on other factors potentially related to thyroid cancer risk, including socioeconomic status indicators (e.g. education and race), cigarette smoking, alcohol intake, menopausal hormone therapy use, physical activity, and diet.

The high prevalence of overweight and obesity and increasing incidence of thyroid cancer have both become important public health concerns in the U.S.,[1,2] and several previous

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studies have suggested that there may be a link.[3–12] Our results, including the positive associations we observed for waist circumference and, particularly in men, weight gain during young adulthood, provide some additional clues about the etiology of thyroid cancer, which is a malignancy with few known modifiable risk factors.[27] Whether the positive association for central adiposity may be driven by the adverse metabolic effects of visceral adipose tissue, which tends in be higher in men,[18] warrants further investigation. These findings may also be useful for clinicians by providing yet another reason for maintaining a healthy body weight and avoiding weight gain, especially excess abdominal fat. However it may be still too early to recommend monitoring overweight or obese adults for thyroid cancer, as it remains unclear whether the positive associations between obesity and thyroid cancer observed in this and previous studies are attributable to more or less aggressive tumor types.

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Novelty

To our knowledge, this was the first prospective study to examine the association between waist circumference and the risk of thyroid cancer and one of the first and most comprehensive studies to examine the associations for weight change during different periods in adulthood and the risk of this disease.

Impact

Our study showed that having a large waist circumference increased the risk of thyroid cancer, and in men this association persisted in each category of BMI, which suggests a potential role for hormonal and metabolic parameters common to central adiposity in thyroid carcinogenesis. We also found that weight gain in early adulthood may increase the risk of thyroid cancer, especially in men.

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Table 1

Characteristics of the study participants (medians [IQR] and percentages) by waist circumference category at baseline (1996–7), NIH-AARP Diet and Health Study

	Waist circumference	
	Normal	**Large**†
Men	*n*=88,227	*n*=37,120
Waist circumference (cm)	92.7	109.2
Hip circumference (cm)	99.1	111.1
Waist: hip ratio	0.93	0.99
Age (years)	64 (59–68)	64 (59–67)
Body mass index (kg/m^2)	25 (24–27)	30 (28–33)
Race/ethnicity (%)		
Caucasian	94	96
Other	5	3
Missing	1	1
Education (%)		
College graduate	51	46
Missing	2	2
Smoking status (%)		
Never	33	26
Former	55	63
Current	9	8
Missing	3	3
Women	*n*=46,597	*n*=25,766
Waist circumference (cm)	76.8	96.5
Hip circumference (cm)	99.1	111.8
Waist: hip ratio	0.77	0.87
Age (years)	63 (58–67)	64 (59–67)
Body mass index (kg/m^2)	23 (21–25)	29 (27–33)
Race/ethnicity (%)		
Caucasian	93	92
Other	6	7
Missing	1	1
Education (%)		
College graduate	38	32
Missing	2	2
Smoking status (%)		
Never	46	45
Former	38	42
Current	13	11
Missing	3	3

† >102 cm for men; >88 cm for women

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Table 2

Central adiposity measurements and thyroid cancer risk in men and women, NIH-AARP Diet and Health Study (1996–2006)

	Men				Women			
	All thyroid cancer		Papillary carcinoma		All thyroid cancer		Papillary carcinoma	
	Cases	HR (95% CI) [a]	Cases	HR (95% CI) [a]	Cases	HR (95% CI) [a]	Cases	HR (95% CI) [a]
Waist circumference								
Quartile 1[b]	17	1.00 (Reference)	13	1.00 (Reference)	29	1.00 (Reference)	21	1.00 (Reference)
Quartile 2	29	1.48 (0.81–2.70)	16	1.08 (0.52–2.25)	15	0.57 (0.30–1.06)	12	0.63 (0.31–1.28)
Quartile 3	25	1.71 (0.92–3.17)	16	1.45 (0.69–3.03)	27	0.97 (0.76–2.05)	19	0.96 (0.51–1.79)
Quartile 4	35	2.20 (1.23–3.95)	29	2.43 (1.25–4.70)	34	1.24 (0.76–2.05)	25	1.27 (0.71–2.28)
P-trend*		*0.007*		*0.002*		*0.13*		*0.20*
Per 5 cm	106	1.10 (1.02–1.20)	74	1.13 (1.03–1.24)	105	1.06 (0.99–1.13)	77	1.07 (0.99–1.16)
Normal	61	1.00 (Reference)	38	1.00 (Reference)	57	1.00 (Reference)	43	1.00 (Reference)
Large [c]	45	1.79 (1.21–2.63)	36	2.32 (1.46–3.67)	48	1.54 (1.05–2.26)	34	1.45 (0.92–2.28)
Hip circumference								
Quartile 1[d]	19	1.00 (Reference)	12	1.00 (Reference)	24	1.00 (Reference)	17	1.00 (Reference)
Quartile 2	22	1.23 (0.66–2.28)	13	1.16 (0.53–2.55)	24	1.33 (0.75–2.34)	16	1.22 (0.62–2.42)
Quartile 3	31	1.72 (0.97–3.06)	23	2.04 (1.01–4.12)	28	1.37 (0.80–2.38)	22	1.49 (0.79–2.80)
Quartile 4	34	1.96 (1.11–3.44)	26	2.38 (1.20–4.75)	29	1.41 (0.82–2.43)	22	1.46 (0.77–2.76)
P-trend*		*0.01*		*0.004*		*0.24*		*0.22*
Per 5 cm	106	1.09 (0.99–1.20)	74	1.11 (1.00–1.24)	105	1.03 (0.95–1.12)	77	1.04 (0.95–1.15)
Ratio of waist/hip								
Quartile 1[e]	23	1.00 (Reference)	15	1.00 (Reference)	24	1.00 (Reference)	19	1.00 (Reference)
Quartile 2	23	0.98 (0.55–1.75)	18	1.19 (0.60–2.37)	24	1.03 (0.58–1.81)	17	0.94 (0.49–1.81)
Quartile 3	29	1.24 (0.72–2.15)	19	1.27 (0.64–2.50)	26	1.09 (0.63–1.91)	17	0.94 (0.49–1.81)
Quartile 4	31	1.36 (0.79–2.33)	22	1.51 (0.78–2.92)	31	1.34 (0.78–2.30)	24	1.39 (0.75–2.54)
P-trend*		*0.19*		*0.22*		*0.25*		*0.26*
Per 0.1	106	1.15 (0.91–1.45)	74	1.19 (0.91–1.54)	105	1.21 (0.97–1.50)	77	1.26 (0.98–1.62)

*Calculated using the median quartile values modeled as a continuous variable

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[a] Adjusted for race/ethnicity, education, and smoking status

[b] Quartiles for waist circumference: 52.1–91.0, 91.4–96.5, 97.2–104.1, 104.8–173.4 cm in men; 52.1–75.0, 75.6–82.6, 83.2–92.1, 92.7–169.5 cm in women

[c] >102 cm for men; >88 cm for women

[d] Quartiles for hip circumference: 52.1–97.0, 97.2–101.6, 102.2–108.0, 108.6–175.3 cm in men; 52.1–97.0, 97.2–102.2, 102.9–109.9, 110.5–175.3 cm in women

[e] Quartiles for ratio of waist/hip: 0.5092–0.9054, 0.9055–0.9452, 0.9453–0.9865, 0.9866–2.4667 in men; 0.4194–0.7561, 0.7562–0.8047, 0.8048–0.8611, 0.8612–1.8140 in women

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Table 3

Joint associationof current BMI and waist circumference on thyroid cancer risk in men and women, NIH-AARP Diet and Health Study (1996–2006)

Body mass index category	Waist circumference category	Men		Women	
		Cases	HR (95% CI)[a]	Cases	HR (95% CI)[a]
Normal (18.5–24.9 kg/m^2)	Normal (≤102 cm in men; ≤88 cm in women)	23	1.00 (Reference)	35	1.00 (Reference)
	Large (>102 cm in men; >88 cm in women)	1	1.35 (0.18–10.03)	6	2.03 (0.85–4.83)
Overweight (25.0–29.9 kg/m^2)	Normal (≤102 cm in men; ≤88 cm in women)	35	1.37 (0.81–2.32)	15	1.25 (0.68–2.28)
	Large (>102 cm in men; >88 cm in women)	22	2.19 (1.22–3.94)	19	1.56 (0.89–2.73)
Obese (≥30.0 kg/m^2)	Normal (≤102 cm in men; ≤88 cm in women)	3	1.30 (0.39–4.35)	4	2.52 (0.89–7.11)
	Large (>102 cm in men; >88 cm in women)	22	2.13 (1.18–3.85)	23	1.91 (1.13–3.25)

[a] Adjusted for race/ethnicity, education, and smoking status

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Table 4

Weight change during adulthood and thyroid cancer risk in men and women, NIH-AARP Diet and Health Study (1996–2006)

	Men				Women			
	All thyroid cancer		Papillary carcinoma		All thyroid cancer		Papillary carcinoma	
	Cases	HR (95% CI)	Cases	HR (95% CI)	Cases	HR (95% CI)	Cases	HR (95% CI)
Age 18 to current age[a]								
Lost ≥5 kg	2	0.73 (0.15–3.56)	1	0.36 (0.04–3.38)	2	0.51 (0.12–2.23)	2	0.70 (0.15–3.18)
Lost or gained <5 kg	10	1.00 (Reference)	8	1.00 (Reference)	23	1.00 (Reference)	17	1.00 (Reference)
Gained 5–9.9 kg	14	1.40 (0.62–3.16)	10	1.28 (0.50–3.26)	12	0.62 (0.31–1.25)	6	0.42 (0.16–1.06)
Gained ≥10 kg	80	1.75 (0.89–3.43)	55	1.57 (0.73–3.35)	68	1.08 (0.67–1.74)	52	1.10 (0.63–1.91)
P-trend*		*0.06*		*0.10*		*0.22*		*0.22*
Age 18 to 35[a]								
Lost ≥5 kg	1	0.27 (0.03–2.19)	1	0.34 (0.04–3.01)	7	1.22 (0.53–2.84)	4	0.91 (0.31–2.72)
Lost or gained <5 kg	29	1.00 (Reference)	19	1.00 (Reference)	50	1.00 (Reference)	36	1.00 (Reference)
Gained 5–9.9 kg	29	1.14 (0.68–1.92)	23	1.41 (0.76–2.60)	31	1.32 (0.84–2.07)	22	1.30 (0.76–2.22)
Gained ≥10 kg	47	1.49 (0.93–2.39)	31	1.52 (0.85–2.70)	17	1.28 (0.74–2.24)	15	1.54 (0.84–2.84)
P-trend*		*0.03*		*0.08*		*0.50*		*0.16*
Age 35 to 50[b]								
Lost ≥5 kg	6	0.85 (0.35–2.07)	5	0.96 (0.35–2.62)	3	0.63 (0.19–2.10)	2	0.49 (0.11–2.17)
Lost or gained <5 kg	53	1.00 (Reference)	36	1.00 (Reference)	56	1.00 (Reference)	42	1.00 (Reference)
Gained 5–9.9 kg	23	1.11 (0.68–1.81)	15	1.06 (0.58–1.94)	26	1.15 (0.72–1.84)	21	1.20 (0.71–2.03)
Gained ≥10 kg	24	1.49 (0.91–2.43)	18	1.61 (0.90–2.86)	20	1.12 (0.66–1.90)	12	0.83 (0.43–1.59)
P-trend*		*0.11*		*0.16*		*0.35*		*0.81*
Age 50 to current age[c]								
Lost ≥5 kg	11	1.16 (0.59–2.29)	7	0.96 (0.41–2.26)	5	0.91 (0.35–2.37)	3	0.76 (0.22–2.58)
Lost or gained <5 kg	64	1.00 (Reference)	46	1.00 (Reference)	65	1.00 (Reference)	47	1.00 (Reference)
Gained 5–9.9 kg	16	0.96 (0.55–1.67)	11	0.93 (0.48–1.81)	17	0.85 (0.50–1.46)	14	0.99 (0.54–1.81)
Gained ≥10 kg	15	1.13 (0.64–1.99)	10	1.05 (0.53–2.11)	18	1.02 (0.60–1.74)	13	1.05 (0.56–1.96)
P-trend*		*0.99*		*0.91*		*0.96*		*0.73*

*Calculated using the median category values modeled as a continuous variable

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[a] Adjusted for race/ethnicity, education, smoking status, and weight at age 18

[b] Adjusted for race/ethnicity, education, smoking status, and weight at age 35

[c] Adjusted for race/ethnicity, education, smoking status, and weight at age 50

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Appendix Table

Associations of BMI and BSA with thyroid cancer risk in men and women, NIH-AARP Diet and Health Study (1996–2006)

	Men	Women
	HR (95% CI) [a]	**HR (95% CI)** [a]
BMI		
Quartile 1[b]	1.00 (Reference)	1.00 (Reference)
Quartile 2	1.41 (0.78–2.55)	0.73 (0.40–1.33)
Quartile 3	1.37 (0.75–2.50)	0.98 (0.56–1.71)
Quartile 4	2.06 (1.18–3.62)	1.49 (0.89–2.48)
P-trend*	*0.01*	*0.04*
BSA		
Quartile 1[c]	1.00 (Reference)	1.00 (Reference)
Quartile 2	1.32 (0.73–2.41)	1.48 (0.83–2.66)
Quartile 3	1.55 (0.86–2.79)	1.55 (0.87–2.77)
Quartile 4	2.03 (1.15–3.57)	1.58 (0.88–2.82)
P-trend*	*0.01*	*0.16*
Mutual adjustment: Model 1		
BMI		
Quartile 1[b]	1.00 (Reference)	1.00 (Reference)
Quartile 2	1.27 (0.69–2.35)	0.77 (0.41–1.43)
Quartile 3	1.15 (0.59–2.21)	1.08 (0.56–2.07)
Quartile 4	1.45 (0.66–3.18)	1.79 (0.80–4.01)
BSA as a continuous variable (per m^2)	2.49 (0.62–10.01)	0.64 (0.14–2.91)
Mutual adjustment: Model 2		
BMI as a continuous variable (per kg/m^2)	1.04 (0.97–1.11)	1.02 (0.97–1.09)
BSA		
Quartile 1[c]	1.00 (Reference)	1.00 (Reference)
Quartile 2	1.23 (0.67–2.26)	1.40 (0.77–2.55)
Quartile 3	1.35 (0.71–2.55)	1.38 (0.73–2.62)
Quartile 4	1.52 (0.71–3.25)	1.22 (0.52–2.86)

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[*] Calculated using the median category values modeled as a continuous variable

[a] Adjusted for race/ethnicity, education, and smoking status

[b] Quartiles for BMI: 15.1–24.3, 24.4–26.4, 26.4–28.9, 28.9–50.0 kg/m^2 in men; 15.0–22.4, 22.4–25.0, 25.0–28.4, 28.4–50.0 kg/m^2 in women

[c] Quartiles for BSA: 1.41–1.94, 1.94–2.05, 2.05–2.19, 2.19–3.21 m^2 in men; 1.19–1.66, 1.66–1.77, 1.77–1.91, 1.91–3.02 m^2 in women