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Anthropometric Factors and Thyroid Cancer Risk by Histological Subtype: Pooled Analysis of 22 Prospective Studies

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Background: Greater height and body mass index (BMI) have been associated with an increased risk of thyroid cancer, particularly papillary carcinoma, the most common and least aggressive subtype. Few studies have evaluated these associations in relation to other, more aggressive histologic types or thyroid cancer-specific mortality.

Methods: This large pooled analysis of 22 prospective studies (833,176 men and 1,260,871 women) investigated thyroid cancer incidence associated with greater height, BMI at baseline and young adulthood, and adulthood BMI gain (difference between young-adult and baseline BMI), overall and separately by sex and histological subtype using multivariable Cox proportional hazards regression models. Associations with thyroid cancer mortality were investigated in a subset of cohorts (578,922 men and 774,373 women) that contributed cause of death information.

Results: During follow-up, 2996 incident thyroid cancers and 104 thyroid cancer deaths were identified. All anthropometric factors were positively associated with thyroid cancer incidence: hazard ratios (HR) [confidence intervals (CIs)] for height (per 5 cm) = 1.07 [1.04–1.10], BMI (per 5 kg/m^2) = 1.06 [1.02–1.10], waist circumference (per 5 cm) = 1.03 [1.01–1.05], young-adult BMI (per 5 kg/m^2) = 1.13 [1.02–1.25], and adulthood BMI gain (per 5 kg/m^2) = 1.07 [1.00–1.15]. Associations for baseline BMI and waist circumference were attenuated after mutual adjustment. Baseline BMI was more strongly associated with risk in men compared with women ($p = 0.04$). Positive associations were observed for papillary, follicular, and anaplastic, but not medullary, thyroid carcinomas. Similar, but stronger, associations were observed for thyroid cancer mortality.

Conclusion: The results suggest that greater height and excess adiposity throughout adulthood are associated with higher incidence of most major types of thyroid cancer, including the least common but most aggressive form, anaplastic carcinoma, and higher thyroid cancer mortality. Potential underlying biological mechanisms should be explored in future studies.

Introduction

Although thyroid cancer only accounts for approximately 2% of all cancers diagnosed worldwide (1), the incidence of thyroid cancer, particularly papillary thyroid carcinoma, has increased dramatically in many countries over the past few decades (2). This pattern appears to reflect the enhanced ability to detect very small thyroid tumors, but some of the increase may be attributable to changes in the prevalence of lifestyle and environmental risk factors (3). Exposure to ionizing radiation during childhood and adolescence, which is the only established modifiable risk factor, does not appear to have contributed importantly to these trends (4,5). Among other possible contributing factors includes the rising prevalence of obesity (6,7).

Greater body mass index (BMI), a measure of total adiposity, has been associated with an increased risk of thyroid cancer in several observational studies (6,8–14), with some exceptions (15–18). Most of these studies also showed positive associations with greater height. While the underlying biological mechanisms remain speculative, studies utilizing other anthropometric measures or the same measures at different periods during life could provide additional clues. Compared with BMI, waist circumference more directly measures the amount of central adipose tissue, the metabolic consequences of which include insulin resistance and inflammation (19). However, associations of waist circumference with thyroid cancer risk have been examined in only three studies, with conflicting results (14,15,20). BMI specifically in young adulthood has been associated with an increased risk of thyroid cancer in some studies (6,10,11,15) but not others (8,21). Few studies have evaluated associations for specific histological subtypes apart from papillary carcinoma, which is the least aggressive and increasingly predominant subtype.

Individual-level data were compiled from 22 prospective cohort studies from North America, Europe, Australia, and Asia to evaluate height, baseline and young-adult BMI, adulthood BMI gain (difference between young-adult and baseline BMI), and waist circumference comprehensively in relation to risk of thyroid cancer and major histologic subtypes.

Methods

Study population

Cohorts participating in the National Cancer Institute Cohort Consortium were eligible to join a pooled study of anthropometric factors and thyroid cancer risk if the baseline year occurred on or after 1970 and the study ascertained height and weight information (22–43). Table 1 provides a brief description of the included cohorts and their acronyms. Full cohort data were available from 20 cohorts. CSDLH and NLCS used a case-cohort approach, providing data from all incident thyroid cancer cases and a random sample of participants from the full cohort. Height and weight were self-reported in most cohorts, but measured in MCCS, SMHS, SWHS, most of EPIC (89%), and most of SISTER (>99%). Information on waist circumference was ascertained in 15 cohorts (AARP, BCDDP, COSM, CPSII, CSDLH, CTS, EPIC, IWHS, MCCS, NYUWHS, SISTER, SMC, SMHS, SWHS, and WLH), having been measured by someone other than the participant in six of these cohorts (EPIC [89%], MCCS, NYUWHS, SISTER, SMHS, and SWHS), and data on young-adult weight (recalled for ages 17–21 by participants) was assessed in 10 of the cohorts (AARP, AHS, COSM, CPSII, IWHS, MCCS, PLCO, SMC, VITAL, and WLH). Baseline and young-adult BMI was calculated as kg/m^2. BMI gain was defined as baseline BMI minus young-adult BMI. Information on covariates, including education,

Table 1. Description of the Studies Included in the Pooled Analysis of Anthropometric Factors and Thyroid Cancer Risk

Cohort name	Cohort acronym	Geographic location	Study design	Participants		Thyroid cancer cases		Study period	Years of follow-up, mean (SD)	Age at baseline, mean (SD)	Baseline BMI ≥30 (%)
				Men	Women	Men	Women				
NIH-AARP Diet and Health Study (22)	AARP	U.S.	Cohort	304,592	195,251	260	327	1995–2006	9.1 (2.9)	62.0 (5.4)	22
Agricultural Health Study (23)	AHS	U.S.	Cohort	38,383	27,458	33	55	1993–2008	12.7 (2.5)	47.2 (12.4)	22
Breast Cancer Detection Demonstration Project (24)	BCDDP	U.S.	Cohort	—	38,140	—	35	1987–1997	8.2 (1.7)	61.7 (8.0)	13
Cohort of Swedish Men (25)	COSM	Sweden	Cohort	43,500	—	21	—	1998–2008	9.3 (2.5)	60.6 (9.7)	10
Cancer Prevention Study-II (26)	CPSII	U.S.	Cohort	72,589	80,997	87	129	1992–2009	12.2 (3.9)	63.0 (6.4)	15
Canadian Study of Diet, Lifestyle, and Health[a] (27)	CSDLH	Canada	Case-cohort	4100	4268	23	73	1991–2010	9.9 (4.9)	61.2 (13.1)	10
California Teachers Study (28)	CTS	U.S.	Cohort	—	104,442	—	277	1995–2010	12.9 (4.0)	51.9 (13.5)	14
European Prospective Investigation Into Cancer and Nutrition (29)	EPIC	Europe (multiple sites)	Cohort	146,430	341,073	67	540	1991–2010	11.0 (2.8)	51.3 (9.9)	14
Iowa Women's Health Study (30)	IWHS	U.S.	Cohort	—	37,957	—	67	1986–2005	16.4 (5.5)	62.2 (4.2)	19
Melbourne Collaborative Cohort Study (31)	MCCS	Australia	Cohort	15,687	22,335	12	35	1990–2009	14.9 (4.1)	55.1 (8.7)	21
Netherlands Cohort Study[b] (32)	NLCS	Netherlands	Case-cohort	2269	2389	23	52	1986–2003	14.9 (4.3)	61.4 (4.2)	7
New York University Women's Health Study (33)	NYUWHS	U.S.	Cohort	—	13,306	—	48	1985–2007	18.7 (5.2)	50.6 (8.7)	13

(*continued*)

Table 1. (Continued)

Cohort name	Cohort acronym	Geographic location	Study design	Participants		Thyroid cancer cases		Study period	Years of follow-up, mean (SD)	Age at baseline, mean (SD)	Baseline BMI ≥30 (%)
				Men	Women	Men	Women				
Physicians' Health Study (34)	PHS	U.S.	Cohort	28,350	—	51	—	1981–2009	18.1 (8.4)	55.3 (9.7)	6
Prostate, Lung, Colorectal, and Ovarian Cancer Screening Study (35)	PLCO	U.S.	Cohort	71,068	69,990	50	93	1993–2006	8.4 (2.8)	63.1 (5.4)	24
Sister Study (36)	SISTER	U.S.	Cohort	—	48,167	—	81	2003–2012	3.7 (1.3)	55.5 (9.0)	30
Swedish Mammography Cohort (37)	SMC	Sweden	Cohort	—	36,375	—	16	1998–2008	9.7 (2.1)	62.3 (9.2)	11
Shanghai Men's Health Study (38)	SMHS	China	Cohort	61,394	—	26	—	2001–2009	5.4 (1.4)	55.4 (9.7)	3
Shanghai Women's Health Study (39)	SWHS	China	Cohort	—	74,861	—	163	1996–2009	10.8 (1.9)	52.6 (9.1)	5
U.S. Radiologic Technologists Study (40)	USRT	U.S.	Cohort	13,317	49,395	19	119	1994–2006	8.9 (1.5)	47.9 (8.5)	16
VITamins And Lifestyle Study (41)	VITAL	U.S.	Cohort	31,497	31,310	23	69	2000–2009	7.4 (2.0)	60.9 (7.3)	25
Women's Health Study (42)	WHS	U.S.	Cohort	—	38,946	—	101	1993–2010	14.7 (3.9)	54.7 (7.0)	18
Swedish Women's Lifestyle and Health Study (43)	WLH	Sweden	Cohort	—	44,211	—	21	1991–2006	14.8 (1.7)	40.2 (5.8)	6
Overall				**833,176**	**1,260,871**	**695**	**2,301**	**1981–2012**	**10.4 (4.0)**	**56.7 (10.3)**	**17**

[a]Subcohort selected from a full cohort of 34,291 men and 39,618 women.
[b]Subcohort selected from a full cohort of 58,279 men and 62,573 women.

marital status, alcohol consumption, smoking, physical activity level, and history of benign thyroid disease were self-reported. These data were formatted uniformly across studies using standard units and category cut points prior to analysis. Each study received approval from its respective Institutional Review Board.

From a total of 2,281,345 eligible study participants, participants without follow-up time ($n = 19{,}953$), whose age at study exit was implausible (>110 years; $n = 65$), who were <18 or >85 years of age at baseline ($n = 7286$), who reported having had a previous diagnosis of cancer at baseline ($n = 102{,}116$), and anyone with missing data on height or weight ($n = 55{,}703$) were excluded. Participants with BMI values of <15 kg/m^2 ($n = 1717$) and ≥60 kg/m^2 ($n = 458$) were also excluded. The final sample consisted of 2,094,047 individuals (833,176 men and 1,260,871 women) from 22 prospective cohort studies.

Thyroid cancer follow-up

Participants were followed from baseline questionnaire completion date to any first primary cancer diagnosis other than non-melanoma skin cancer, loss-to-follow-up, death, or cohort-specific administrative end date, whichever occurred first. Cancer diagnoses were identified through linkages to local, state, or national cancer registries (AARP, AHS, COSM, CSDLH, CTS, IWHS, MCCS, NLCS, SMC, WLH, and VITAL), self-report verified through medical record confirmation (PHS, PLCO, SISTER, USRT, and WHS), or a combination of approaches (BCDDP, CPSII, EPIC, NYUWHS, SMHS, and SWHS). Participants were classified as cases if the first primary cancer diagnosed during follow-up was malignant thyroid cancer (International Classification of Disease for Oncology, Third Edition [ICD-O-3], topography code C73 or the equivalent). Histological subtypes of thyroid cancer were further classified using ICD-3 morphology codes or the equivalent (papillary: 8050, 8260, 8340–8344, 8350, 8450–8460; follicular: 8290, 8330–8335; medullary: 8345, 8510–8513; anaplastic: 8020–8035) (44).

While not an original objective of the current study, anthropometric factors in relation to thyroid cancer mortality were also evaluated among the subset of the cohorts that additionally provided information on cause of death (AARP, AHS, BCDDP, COSM, CPSII, CTS, IWHS, MCCS, NYUWHS, PHS, PLCO, SMC, USRT, VITAL, WHS, and WLH), including 1,353,295 study subjects (578,922 men and 774,373 women). Thyroid cancer deaths were defined using ICD-9 code 193 and ICD-10 code C73.

Statistical analysis

Cohort- and sex-specific hazard ratios (HRs) and confidence intervals (CIs) were estimated using Cox proportional hazards regression models with attained age in years as the underlying time metric and adjusted for known or potential thyroid cancer risk factors, including race/ethnicity (white, black, Asian, other), smoking status (never, former, current), education (high school or less, some college/post-high school training, college graduate), marital status (married/living together, divorced/separated, widowed, single/never married), physical activity level (cohort-specific tertiles), and alcohol intake (0–9, 10–19, ≥20 g of ethanol per day). Data from the CSDLH and NLCS cohorts were analyzed separately using a case-cohort approach (45). Between-study heterogeneity was evaluated using the I^2 index, with a value of 0% indicating none and higher values indicating increasing heterogeneity (46). Full-cohort data from 20 prospective studies were then aggregated to estimate pooled multivariable-adjusted HRs and CIs in models additionally stratified by cohort, with anthropometric factors modeled categorically and continuously. No evidence of non-linear relationships was found between any of the exposures examined in relation to thyroid cancer incidence or mortality based on restricted cubic spline models with automatic stepwise selection of up to four knots. *p*-Values for log-linear relationships were based on Wald tests corresponding to continuous values of the exposure. The aggregate data were also used to evaluate effect modification, specifically by sex, geographical area, race/ethnicity, age at the time of report for height and weight, and age at thyroid cancer diagnosis, and smoking status, and to examine associations by histology. Interaction tests were conducted by comparing the fit of a model including a cross-product term between the exposure and effect modifier to one without using the likelihood ratio test. To evaluate effect modification by age at diagnosis, exposures were treated as time varying by splitting person-time for each participant by category of attained age and evaluating the fit of a model with the cross-product term between exposure and attained age category to one without. No evidence of violation of the proportional hazards assumption was observed.

Results

A general description of the studies is shown in Table 1. During an average of 10.4 years of follow-up, 2996 first primary thyroid cancer cases were identified (695 men and 2,301 women). Of these, 2182 (73%) were classified as papillary, 418 (14%) as follicular, 100 (3%) as medullary, and 53 (2%) as anaplastic. The mean age at baseline was 57 years, and the mean age at thyroid cancer diagnosis during follow-up was 62 years (range 25–92 years).

In the subset of cohorts that contributed cause of death information, 104 thyroid cancer deaths were identified (53 men and 51 women).

Study- and sex-specific HRs and CIs for continuous values of height (per 5 cm increase), baseline BMI (per 5 kg/m^2 increase), waist circumference (per 5 cm increase), young-adult BMI (per 5 kg/m^2 increase), and BMI gain (per 5 kg/m^2 increase) are shown in Supplementary Figures S1–S5 (Supplementary Data are available online at www.liebertpub.com/thy). Significant between-cohort differences were observed for the associations for baseline BMI ($I^2 = 41.1\%$) and young-adult BMI in women ($I^2 = 59.0\%$) and waist circumference in men ($I^2 = 58.9\%$). Heterogeneity remained after individually excluding the two largest cohorts, AARP and EPIC.

Pooled results

In the aggregate data set of 20 cohorts, increases in risk of thyroid cancer were observed for greater values (on a continuous scale, per 5 cm or 5 kg/m^2) of height (HR = 1.07 [CI 1.04–1.10]), baseline BMI (HR = 1.06 [CI 1.02–1.10]), waist circumference (HR = 1.03 [CI 1.01–1.05]), young-adult BMI (HR = 1.13 [CI 1.02–1.25]), and adulthood BMI gain

Table 2. Hazard Ratios and Confidence Intervals for Thyroid Cancer According to Anthropometric Factors

	Men			*Women*			*Total*		
	No. cases	*HR*[a]	*CI*	*No. cases*	*HR*[a]	*CI*	*No. cases*	*HR*[a]	*CI*
Height (cm)[b,c]									
M 122–169/W 122–149	67	0.87	0.64–1.18	32	0.73	0.50–1.07	99	0.79	0.63–1.00
M 170–174/W 150–154	119	1.00	Reference	174	1.00	Reference	305	1.00	Reference
M 175–179/W 155–159	192	1.18	0.94–1.48	335	**1.23**	**1.03–1.48**	557	**1.21**	**1.05–1.40**
M 180–184/W 160–164	158	1.07	0.84–1.37	564	**1.21**	**1.02–1.44**	790	**1.20**	**1.05–1.37**
M 185–189/W 165–169	68	1.02	0.76–1.39	488	**1.24**	**1.04–1.48**	598	**1.19**	**1.03–1.38**
M 190–244/W 170–244	35	1.35	0.92–1.98	388	**1.41**	**1.17–1.69**	452	**1.38**	**1.18–1.61**
Per 5 cm	*639*	*1.05*	*1.00–1.11*	*1981*	***1.08***	***1.04–1.12***	*2801*	***1.07***	***1.04–1.10***
Baseline BMI (kg/m^2)[d]									
15.0–18.4	2	0.66	0.16–2.67	29	0.86	0.59–1.24	32	0.78	0.55–1.10
18.5–24.9	191	1.00	Reference	995	1.00	Reference	1313	1.00	Reference
25.0–29.9	327	**1.23**	**1.02–1.47**	615	1.02	0.93–1.14	980	1.05	0.96–1.14
30.0–59.9	129	**1.35**	**1.07–1.71**	356	1.05	0.92–1.19	500	1.09	0.98–1.22
Per 5 kg/m^2	*649*	***1.17***[g]	***1.06–1.28***	*1995*	*1.04*[g]	*1.00–1.09*	*2825*	***1.06***	***1.02–1.10***
Waist circumference (cm)[e]									
M 52–79/W 52–69	15	1.31	0.73–2.36	185	0.97	0.80–1.16	200	0.99	0.84–1.18
M 80–89/W 70–79	59	1.00	Reference	357	1.00	Reference	416	1.00	Reference
M 90–99/W 80–89	114	1.18	0.85–1.62	292	1.06	0.91–1.24	406	1.08	0.94–1.24
M 100–109/W 90–99	70	1.26	0.88–1.81	171	**1.25**	**1.04–1.51**	243	**1.25**	**1.06–1.48**
M 110–189/W100–189	37	1.50	0.98–2.30	94	1.13	0.90–1.44	132	1.22	1.00–1.49
Per 5 cm	*295*	*1.04*	*0.98–1.10*	*1099*	***1.02***	***1.00–1.05***	*1397*	***1.03***	***1.01–1.05***
Young-adult BMI (kg/m^2)[d]									
15.0–18.4	32	1.04	0.71–1.52	113	1.21	0.98–1.50	145	1.17	0.97–1.40
18.5–22.4	159	1.00	Reference	360	1.00	Reference	519	1.00	Reference
22.5–24.9	96	1.28	0.99–1.65	82	1.01	0.79–1.28	178	1.13	0.95–1.34
25.0–59.9	66	1.34	1.00–1.80	62	**1.50**	**1.14–1.96**	128	**1.40**	**1.15–1.70**
Per 5 kg/m^2	*353*	***1.18***	***1.01–1.40***	*617*	*1.10*	*0.96–1.25*	*970*	***1.13***	***1.02–1.25***
Adulthood BMI gain (kg/m^2)[f]									
<0	20	0.79	0.49–1.29	56	1.11	0.82–1.50	76	1.01	0.79–1.30
0–4.9	156	1.00	Reference	245	1.00	Reference	401	1.00	Reference
5.0–9.9	143	**1.30**	**1.03–1.65**	223	**1.20**	**1.00–1.44**	366	**1.23**	**1.06–1.42**
≥10.0	34	1.27	0.86–1.86	93	1.09	0.85–1.39	127	1.13	0.92–1.39
Per 5 kg/m^2	*353*	***1.23***	***1.07–1.41***	*617*	*1.02*	*0.94–1.11*	*970*	*1.07*	*1.00–1.15*

Statistically significant ($p < 0.05$) values are shown in bold.
[a]Adjusted for age (used as time metric), sex, alcohol intake, physical activity level, race/ethnicity, marital status, education, and smoking status, and stratified by cohort.
[b]Additionally adjusted for baseline BMI (per 5 kg/m^2).
[c]Restricted to height values between 122 and 244 cm.
[d]Restricted to BMI values between 15.0 and 59.9 kg/m^2.
[e]Restricted to waist circumference values between 52 and 189 cm.
[f]Additionally adjusted for young-adult BMI (per 5 kg/m^2).
[g]$p = 0.04$.
HR, hazard ratio; CI, confidence ratio; BMI, body mass index.

(HR = 1.07 [CI 1.00–1.15]; Table 2). The risk of thyroid cancer generally increased across categories of baseline height, BMI, and waist circumference, as well as young-adult BMI. An adult BMI gain of 5.0–9.9 kg/m^2 was associated with a statistically significant 23% increased risk [CI 6–42%] compared with a BMI gain of 0–4.9 kg/m^2, but the risk for a BMI gain of ≥10 kg/m^2 was not significantly different from unity. Positive associations for height, baseline BMI, waist circumference, and young-adult BMI were observed in both men and women. The association for baseline BMI was significantly stronger for men versus women ($p = 0.04$). The association for adulthood BMI gain was restricted to men (HR for men = 1.23 [CI 1.07–1.41]), but not significantly modified by sex ($p = 0.12$).

The HRs for BMI (per 5 kg/m^2 increase) were attenuated after restricting the analysis to subjects with measured values, although the sample size was substantially reduced (based on 743 cases, HR = 1.01 [CI 0.93–1.10]); this attenuation was restricted to men (HR = 0.76 [CI 0.57–1.03]; HR for women = 1.03 [CI 0.95–1.13]). The HRs for height (per 5 cm) did not materially change (data not shown). As observed previously (14), the HRs for height and BMI in EPIC did not materially change after excluding self-reported values (data not shown). Adjusting for history of benign thyroid conditions from the subset of studies with this information yielded similar results (data not shown). HRs and CIs for height in models unadjusted for BMI were similar to adjusted models in the overall study population, in men, and in women:

Table 3. Sex-Specific Hazard Ratios and Confidence Intervals for Thyroid Cancer and Histological Subtypes According to Anthropometric Factors

	Papillary			*Follicular*			*Medullary*			*Anaplastic*		
	No. cases	*HR*[a]	*CI*	*No. cases*	*HR*[a]	*CI*	*No. cases*	*HR*[a]	*CI*	*No. cases*	*HR*[a]	*CI*
Men												
Height (per 5 cm)[b,c]	396	1.02	0.95–1.10	131	1.09	0.97–1.23	29	1.16	0.90–1.50	19	1.11	0.81–1.51
Baseline BMI (per 5 kg/m^2)[d]	402	**1.15**	**1.02–1.29**	132	1.17	0.95–1.44	31	1.25[g]	0.80–1.93	19	0.85[h]	0.45–1.63
Waist circumference (per 5 cm)[e]	198	1.04	0.97–1.11	62	1.02	0.90–1.15	12	0.99	0.74–1.32	7	0.80	0.53–1.20
Young-adult BMI (per 5 kg/m^2)[d]	238	**1.27**	**1.05–1.54**	81	0.90	0.61–1.31	12	1.17	0.47–2.94	12	1.33	0.56–3.17
Adulthood BMI gain (per 5 kg/m^2)[f]	238	**1.24**	**1.05–1.46**	81	1.24	0.92–1.66	12	0.97	0.43–2.22	12	1.12	0.51–2.46
Women												
Height (per 5 cm)[b,c]	1663	**1.08**	**1.04–1.12**	248	**1.15**	**1.04–1.26**	61	0.95	0.78–1.16	23	1.21	0.89–1.66
Baseline BMI (per 5 kg/m^2)[d]	1676	1.01	0.96–1.06	249	1.13	1.00–1.28	61	0.65[g]	0.47–0.91	23	**1.66**[h]	**1.23–2.23**
Waist circumference (per 5 cm)[e]	802	1.01	0.98–1.04	139	1.07	1.00–1.15	35	0.84	0.71–0.99	9	1.22	0.96–1.56
Young-adult BMI (per 5 kg/m^2)[d]	481	1.10	0.95–1.27	100	1.15	0.84–1.59	16	0.58	0.20–1.70	7	1.43	0.51–4.04
Adulthood BMI gain (per 5 kg/m^2)[f]	481	1.03	0.94–1.14	100	1.01	0.81–1.25	16	0.41	0.19–0.86	7	2.13	1.20–3.78
Total[i]												
Height (per 5 cm)[b,c]	2059	**1.07**	**1.03–1.10**	379	**1.13**	**1.04–1.21**	90	1.02	0.87–1.20	42	1.17	0.94–1.46
Baseline BMI (per 5 kg/m^2)[d]	2078	1.03	0.98–1.08	381	**1.14**	**1.02–1.26**	92	0.80	0.62–1.03	42	**1.43**	**1.09–1.89**
Waist circumference (per 5 cm)[e]	1000	1.01	0.98–1.04	201	1.06	1.00–1.13	47	0.87	0.76–1.01	16	1.07	0.86–1.32
Young-adult BMI (per 5 kg/m^2)[d]	719	**1.16**	**1.03–1.30**	181	1.03	0.80–1.32	28	0.86	0.44–1.69	19	1.38	0.71–2.67
Adulthood BMI gain (per 5 kg/m^2)[f]	719	1.08	0.99–1.17	181	1.09	0.92–1.30	28	0.59	0.34–1.00	19	**1.60**	**1.01–2.54**

Statistically significant values ($p < 0.05$) are shown in bold.

[a]Adjusted for age (used as time metric), alcohol intake (0–9, 10–19, or ≥20 g of ethanol per day), physical activity level (cohort-specific tertiles), race/ethnicity (white, black, Asian, other), marital status (married/living together, divorced/separated, widowed, single/never married), education (high school or less, some college/post-high school training, college graduate), and smoking status (never, former, current), and stratified by cohort.

[b]Additionally adjusted for baseline BMI (per 5 kg/m^2).

[c]Restricted to height values between 122 and 244 cm.

[d]Restricted to BMI values between 15.0 and 59.9 kg/m^2.

[e]Restricted to waist circumference values between 52 and 189 cm.

[f]Additionally adjusted for young-adult BMI (per 5 kg/m^2).

[g]$p = 0.02$.

[h]$p = 0.03$.

[i]Additionally adjusted for sex.

HR = 1.07 [CI 1.04–1.10], HR = 1.05 [CI 0.99–1.11], and HR = 1.07 [CI 1.04–1.11], respectively.

HRs for waist circumference (per 5 cm increase) and BMI (per 5 kg/m^2 increase) were both attenuated after mutual adjustment (HR for waist = 1.02 [CI 0.98–1.06]; HR for BMI = 1.01 [CI 0.92–1.12]; similar findings were observed by sex (data not shown). No consistent pattern in the association between waist circumference (per 5 cm increase) and thyroid cancer was observed in models stratified by baseline BMI: HRs [CIs] for BMI <25.0, 25.0–29.9, and ≥30 kg/m^2 were 1.01 [0.96–1.07], 1.05 [0.99–1.12], and 1.02 [0.96–1.08], respectively.

Results from models of waist-to-hip ratio, available for 50.7% of the entire sample, suggested a non-significant linear association with thyroid cancer risk (data not shown in tables). The HRs [CIs] per 0.1 difference were 1.05 [0.97–1.14] overall, 1.06 [0.88–1.28] for men, and 1.05 [0.96–1.14] for women. These results are consistent with results from models of waist circumference.

It was found that the positive association for adulthood BMI gain (per 5 kg/m^2) was restricted to participants whose young-adult BMI was 18.5–22.4 (HR = 1.16 [CI 1.05–1.29]). HRs [CIs] per 5 kg/m^2 of BMI gain within the categories of young-adult BMI <18.5, 22.5–24.9, and ≥25 kg/m^2 were 0.95 [0.76–1.19], 1.02 [0.86–1.21], and 0.99 [0.84–1.16], respectively.

Differences by demographic factors and smoking status. Significant differences were observed for the association of height and thyroid cancer risk by race/ethnicity (stronger for blacks and Asians), baseline age (stronger for younger ages), and age at thyroid cancer diagnosis (stronger for younger ages; Supplementary Table S1). Other differences observed, although not statistically significant, including stronger associations for baseline and young-adult BMI and BMI gain among individuals who were older at baseline, stronger associations for waist circumference in U.S.-based studies and in whites, and stronger associations for BMI gain in Asians than whites or blacks and never smokers (Supplementary Table S1). In women, no significant differences were observed by age at thyroid cancer diagnosis (before versus after age 55, a proxy for age at menopause; data not shown).

Differences by histology. Significant positive associations were observed for papillary carcinoma with height and young-adult BMI, follicular carcinoma with height and baseline BMI, and anaplastic carcinoma with baseline BMI and BMI gain in adulthood (Table 3). Inverse associations for baseline BMI, waist circumference, and BMI gain with risk of medullary carcinoma did not materially change after excluding the first two years of follow-up (data not shown). Sex modified some of the histology-specific associations. Papillary carcinoma was associated with baseline BMI only in men and height only in women, but these differences were not statistically significant ($p = 0.08$ and 0.47, respectively). Inverse associations for medullary carcinoma with baseline BMI, waist circumference, and BMI gain were observed only in women, but this sex difference was significant only for baseline BMI ($p = 0.02$, 0.30, and 0.27, respectively). The association for baseline BMI and anaplastic thyroid cancer was stronger in women versus men ($p = 0.03$). However, the results for medullary and anaplastic thyroid cancer were based on relatively few cases (no more than 92 and 42, respectively, in any given model).

Thyroid cancer mortality. Greater height, baseline BMI, waist circumference, young-adult BMI, and adulthood BMI gain were found to be associated with increased risk of thyroid cancer mortality; results from continuous models (per five-unit increases) of baseline BMI (HR = 1.29 [CI 1.07–1.55]), waist circumference (HR = 1.22 [CI 1.10–1.36]), and young-adult BMI (HR = 1.56 [CI 1.13–2.15]) were statistically significant (Supplementary Table S2). The patterns in risk overall and by sex were similar to those observed for thyroid cancer incidence, but the associations were generally stronger in magnitude. No significant differences were observed by sex.

Discussion

In this comprehensive pooled analysis of 22 prospective cohort studies from North America, Europe, and Asia, it was found that height, baseline BMI, waist circumference, young-adult BMI, and adulthood BMI gain were each positively associated with incidence of total thyroid cancer. These associations were independent of smoking and other factors associated with thyroid cancer risk. The association for baseline BMI was stronger in men compared with women. Some other differences in risk by population subgroup were observed (e.g., stronger associations for baseline BMI in U.S. studies and in whites). Risk patterns were similar for papillary, follicular, and anaplastic carcinoma. None of the anthropometric factors examined were associated with risk of medullary carcinoma, but the confidence intervals were wide. These associations were stronger in magnitude for thyroid cancer mortality compared with incidence.

Compared to most other cancer sites, the associations observed for height (per 5 cm increase) and BMI (per 5 kg/m^2 increase) with incidences of total, papillary, and follicular thyroid cancer were similar in magnitude (47–50). However, the associations of BMI with anaplastic thyroid cancer in women (HR = 1.66) and thyroid cancer mortality in men (HR = 1.47), and men and women combined (HR = 1.29), were stronger and more comparable with cancers that have consistently been linked with obesity, including esophageal adenocarcinoma and endometrial and kidney cancers (50).

Few observational studies have collected information on anthropometric measures other than height and weight. BMI is a widely used measure of adiposity but provides no information on the amount of lean versus fat mass or central versus peripheral body fat (51). Waist circumference and weight gain are more direct measures of central (visceral) adiposity and body fat mass, respectively. The current study found positive associations for waist circumference (but not independent of baseline BMI), young-adult BMI, and adulthood BMI gain with thyroid cancer risk. These results suggest an important role of excess total (as opposed to central) adiposity across the lifespan on thyroid cancer incidence. Prospective studies that directly evaluate pre-diagnostic levels of biomarkers of insulin resistance, inflammation, estrogen, and other metabolic disturbances related to total adiposity may provide some insight regarding possible underlying mechanisms (52–54).

While the likelihood of thyroid nodule detection and thyroid cancer diagnosis could conceivably be greater for individuals with an underlying thyroid condition, the results did not change after adjusting for a history of benign thyroid conditions. In cross-sectional studies, a greater BMI has been associated with higher thyroid cancer prevalence among individuals with screening-detected thyroid nodules (55) and increased tumor aggressiveness among overweight and obese papillary thyroid cancer patients (56,57). In a previous case-control study, greater BMI was associated with risk of thyroid cancers less than and greater than 10 mm in size (9). Taken together, these observations suggest that surveillance biases do not fully account for associations observed between excess adiposity and thyroid cancer in this and other studies.

Consistent with most previous studies, adult height was positively associated with thyroid cancer risk in both men and women. Taller height in adolescence has also been associated with risk of thyroid cancer in adulthood (58). This relationship could be explained by higher circulating levels of insulin-like growth factor-I (IGF-I) in taller individuals (59). A higher serum concentration of IGF-I was associated with increased risk of differentiated thyroid cancer in the European Investigation into Cancer and Nutrition cohort (60). Other potential explanations for the positive association for height include the larger size of the thyroid gland (and, thus, greater number of cells with the potential to undergo malignant transformation) and greater likelihood of nodule detection via palpation.

Due to relatively small sample sizes, very few previous studies have shown associations between anthropometric factors and risk of specific histological subtypes of thyroid cancer, apart from papillary thyroid carcinoma, the most common form of thyroid malignancy. A previous large prospective study in Norway showed that baseline BMI was positively associated with risk of total thyroid cancer and papillary, follicular, and anaplastic subtypes, and an inverse association with medullary thyroid cancer (12). An inverse association between BMI and medullary thyroid cancer risk was also reported in a pooled analysis of 14 case-control studies (67 cases) (61). Also consistent with the present results, the Norwegian study showed a stronger association of BMI with follicular and anaplastic compared with papillary thyroid cancer (12).

The incidence of papillary thyroid cancer has increased dramatically in several countries over the past three to four decades (2). The rising prevalence of obesity in these countries has been proposed as one potential explanation (6). While the current results are consistent with this hypothesis, they also suggest that the strength of this association is relatively weak, particularly for women. Several other factors influence thyroid cancer incidence trends, including changing clinical practices with regard to screening and diagnosis and changing prevalence of other thyroid cancer risk factors. Based on results from the current study, it would be expected that increasing rates of obesity would, if anything, have a weak impact on population-level changes in papillary thyroid cancer incidence.

Overall, the present results suggest that greater adiposity and taller height are associated with increased risk of thyroid tumors that arise from the follicular, but not the parafollicular cells of the thyroid (62). Excess weight and weight gain may be particularly important for risk of more aggressive tumors, as suggested by the relatively strong associations observed for BMI and BMI gain with anaplastic thyroid cancer and thyroid cancer mortality. This hypothesis is supported by a recent study examining the effect of an obesity-inducing high-fat diet on thyroid carcinogenesis using a $Thrb^{PV/PV}/Pten^{+/-}$ mouse model, which found that such a diet increased thyroid tumor cell proliferation and induced anaplastic changes, as well as increased serum leptin levels (63). Although anaplastic thyroid cancer is uncommon, median survival after diagnosis is low. Thus, improving our understanding of the etiology of this malignancy is particularly important.

Major strengths of this pooled analysis include the prospective study design, wide variability in the included studies, and the large sample size, which allowed for a detailed investigation by race/ethnicity, smoking, geography, baseline age, and age at diagnosis, as well as histology. To the best of the authors' knowledge, this is the first study evaluating the association between anthropometric factors and thyroid cancer mortality. All of the included studies collected information on potential confounders, including education, smoking, alcohol intake, and physical activity, which allowed us to control for these possible sources of confounding using a standardized approach.

Limitations of this study include the use of mostly self-reported, as opposed to measured, anthropometric factors, and the lack of information on body weight during follow-up. However, measurement error was most likely non-differential by case status, which would have attenuated the associations. Information on thyroid tumor size was lacking, which could have helped distinguish smaller, less aggressive thyroid cancers from those that are clinically relevant. However, in the subset of cohorts for which we received cause of death information, stronger associations for height and excess weight with thyroid cancer mortality were found compared with incidence. These results suggest that biological factors related to taller height and greater adiposity at baseline (generally mid-to-older adulthood) and young adulthood influence the development of more aggressive forms of thyroid cancer. Despite the large sample size, some of the results, particularly in subgroup analyses, may be due to chance. While the large number of studies contributing to the pooled analysis allowed for an evaluation of the consistency of the associations across different study populations, the results should be interpreted cautiously and in consideration of the difference in the range of values of the anthropometric factors across populations and the between-study heterogeneity observed for some factors.

In summary, greater height, excess weight early in life, and, among men, excess weight in mid-to-older adulthood were associated with increased incidence of total thyroid cancer and most major thyroid cancer subtypes, including anaplastic thyroid cancer. Baseline BMI and waist circumference and young-adulthood BMI were more strongly associated with thyroid cancer mortality compared with incidence, providing further support that these factors influence risk of more aggressive or clinically relevant forms of thyroid cancer. Future research is needed to understand the possible underlying biological mechanisms. More broadly, these results support efforts to achieve and maintain a healthy weight throughout life to minimize risks of cancer and other major chronic diseases.

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