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Body Mass Index and Thyroid Cancer Risk: A Pooled Analysis of Half a Million Men and Women in the Asia Cohort Consortium

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Background: Although previous meta-analyses have suggested a dose–response relationship between body mass index (BMI) and thyroid cancer risk, limited evidence has been presented about Asian populations. To assess this association among Asian populations, where underweight is more prevalent than in other regions, a pooled analysis from the Asia Cohort Consortium was conducted.

Methods: Baseline height and weight were measured in five cohorts and self-reported in eight cohorts. Thyroid cancer incidence was ascertained by linkage to local cancer registries. Cohorts were treated as a stratum in the Cox proportional hazard model to estimate the pooled hazard ratios (HRs) and corresponding confidence intervals (CIs) from the estimates for each cohort. All analyses were stratified by sex.

Results: A total of 538,857 men and women from 13 cohorts from mainland China, Korea, Japan, and Singapore were included in the analysis. During a mean of 15.1 years of follow-up, 1132 thyroid cancer cases were ascertained. Using a BMI of 18.5–22.9 kg/m^2 as a reference, an elevated risk of thyroid cancer was observed for groups with a BMI between 25 and 29.9 kg/m^2 (HR: 1.31, [CI: 0.95–1.80]) and a BMI of 30 kg/m^2 and greater (HR: 1.84, [CI: 0.89–3.81]) in men. Thyroid cancer risk was elevated in women with a BMI of 23–24.9 kg/m^2 (HR: 1.26, [CI: 1.07–1.48]). The HRs for 5-U increment of BMI showed a linear association among men (HR: 1.25, [CI 1.10–1.55]) but not among women (HR: 1.07, [CI: 0.97–1.18]). Although the overall

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thyroid cancer risk was lower among underweight men and women, the papillary cancer risk may be elevated among underweight men (HR: 2.24, [CI: 0.75–6.66]).
Conclusion: While higher BMI is associated with an elevated risk of thyroid cancer in both men and women, the association of underweight BMI may differ by sex and histological subtype.

Keywords: body mass index, cohort consortium, obesity, thyroid cancer

Introduction

ALTHOUGH THYROID CANCER is the most commonly diagnosed endocrine cancer, it is a relatively rare cancer that accounts for 4% of all cancer incidence worldwide according to GLOBOCAN 2018 (1). In addition, 60% of all cases occur in Asia (1). The rising incidence of thyroid cancer across all regions of the world during the past two decades (2) with no substantial changes in mortality suggests that the introduction of new diagnostic techniques such as ultrasonography, computed tomography, and magnetic resonance imaging as well as increased access to health care services has increased the detection asymptomatic cases, which are mainly responsible for the increase (3). Nonetheless, parallel increases in the prevalence of obesity and overweight and thyroid cancer incidence suggest a potential role of obesity in thyroid carcinogenesis (4).

Previous meta-analyses on the association between adiposity and thyroid cancer risk have consistently shown a dose–response relationship between body mass index (BMI) and thyroid cancer risk (5–8). Those meta-analyses included a few studies from Asian countries. Prospective studies conducted in Asia generally support a linear association between BMI and thyroid cancer risk in men (9–11); however, the association has not been consistent in findings among women (9,10,12,13).

Taking into account the sex differences in the incidence of thyroid cancer (14) and the stronger association between BMI and thyroid cancer risk among men in previous pooled analysis (8) as well as the Korean Health Insurance database based study (9), analysis stratified by sex is crucial to elucidate the role of obesity and underweight in thyroid cancer development. Further, the association with underweight individuals can be better addressed among the Asian population, where the prevalence of underweight is substantially higher than that in Western countries (15).

To better address the role of adiposity in the etiology of thyroid cancer, we conducted a pooled analysis from the Asia Cohort Consortium, which has approximately half a million participants.

Materials and Methods

Details for the Asia Cohort Consortium have been previously described (16). The consortium consisted of 44 participating cohorts from 10 Asian countries as a collaboration seeking to understand the relationship between genetics, environmental exposures, and the etiology of diseases, including cancer, through the establishment of a cohort of at least one million healthy people (https://www.asiacohort.org/index.html). For the current study, 20 cohorts from 6 countries were included. Among cohort participants, the following exclusions were applied: no information on sex or age; missing information on BMI or BMI lower than 12 or higher than 50; and diagnosed with cancer before enrollment. Seven cohorts with no incident thyroid cancer cases during follow-up were excluded from the final analysis. Details of the exclusions are presented in Supplementary Table S1.

Most cohorts were population-based studies except for Korea National Cancer Center cohort (KNCC), which is a hospital screening center-based study. The BMI was calculated by the measured (four cohorts) or self-reported (eight cohorts) height and weight. Height and weight from one cohort (Radiation Effects Research Foundation [RERF]) were assessed by both actual measurement at examination and self-report in the mailed survey. The BMI was categorized into five categories: <18.5, 18.5–22.9, 23.0–24.9, 25–29.9, and ≥30 according to the WHO proposal for the classification of BMI among adult Asians (17). In an additional analysis, BMI categories 25–29.9 and ≥30 were combined and represented as BMI ≥25. Smoking and alcohol consumption habits were collected at baseline surveys and categorized into never or ever.

Cancer incidence was ascertained by linkage to local cancer registries. Each cohort received approval from its respective institutional review board. The current study protocol was approved by the executive committee of the Asia Cohort Consortium and by the ethical committee of the National Cancer Center Japan (no. 2014-041).

A Cox proportional hazards model was used to estimate the hazard ratios (HRs) and corresponding confidence intervals [CIs] for thyroid cancer occurrence by different BMI groups using 18.5–22.9 as the reference category. The HRs for 5 U increment of BMI were also calculated. Further stratified analysis was performed by methods of height and weight ascertainment (actual measurement vs. self-report). Age was used as a time scale in the analysis, and participants were followed from the date of the baseline survey to the date of thyroid cancer incidence, death, or the end of the follow-up of each cohort, whichever came first. Cohort-specific and pooled HRs were estimated for men and women separately. Cohorts were treated as a stratum in the pooled analysis.

Information on histological types of thyroid cancer was available for nine cohorts (six Japanese, two Korean, and one Singaporean), and additional analysis by histological type was conducted. Sensitivity analyses were done, excluding one cohort at a time to determine whether the results were being driven by any one influential cohort.

We used the regression modeling strategies (rms) package (18) in R to evaluate the nonlinear association between BMI and thyroid cancer risk. The BMI was treated as a continuous variable by using a restricted cubic spline function with four knots at the quintiles. The plots of nonlinear associations between BMI and thyroid cancer risk present

HRs and corresponding CIs compared with the BMI of 21 kg/m^2 with adjustment for smoking and alcohol consumption. Cohorts were treated as a stratum in analyses for nonlinear association.

Results

Table 1 shows the distribution of the main variables among the participating cohorts. A total of 538,857 men and women from 13 cohorts from mainland China, Korea, Japan, and Singapore were included in the analysis. During a mean of 15.1 years of follow-up, 1132 thyroid cancer cases were ascertained. Among them, 226 cases (20%) occurred among men (Supplementary Table S2 and S3).

When the BMI range 18.5–22.9 kg/m^2 was used as a reference, none of the BMI categories showed statistically significant risk estimates in men (Table 2). While when BMI was treated as a continuous variable, the linear association was significant for all participants (HR: 1.25 for 5-U increment, [CI: 1.01–1.55]). In terms of individual cohorts, the Shanghai Men's Health Study (HR: 1.45, [CI: 1.02–2.08]) and the Miyagi cohort (HR: 2.32, [CI: 1.08–4.98]) showed significant linear association. As there were only 8 thyroid cancer cases in the BMI ≥30 category among men (Supplementary Table S2), we combined the BMI ≥30 with the BMI 25–29.9 category and found that the HRs of the resulting combined categories did not show much difference when compared with the HRs of BMI 25–29.9 alone (Supplementary Table S4).

Overall, thyroid cancer risk was elevated in women with a BMI of 23–24.9 kg/m^2 (HR: 1.26, [CI: 1.07–1.48]) but no clear association was found in the linear trend (HR: 1.07, [CI: 0.97–1.18]) (Table 3). Among individual cohorts, Takayama cohort showed a significant linear association (HR: 2.3, [CI: 1.34–3.97]). In the stratified analysis by height and weight ascertainment methods, a higher risk of thyroid cancer was observed in BMI ≥25 (HR: 1.32, [CI 1.05–1.67]) and 5-U increment (HR: 1.20, [CI 1.03–1.39]) in cohorts with self-reported values (Table 3 and Supplementary Table S5).

Figure 1 shows nonlinear associations between BMI as a continuous factor and thyroid cancer risk by using a restricted cubic spline function stratified by sex. In women, the plot of the nonlinear association between BMI and thyroid cancer risk indicated a reverse U-shaped association and showed a peak in HRs for thyroid cancer risk at close to a BMI of 24 kg/m^2.

Among the 9 cohorts in which histology was available, 468 out of 569 (85.4%) cases were papillary thyroid cancer (Supplementary Tables S6 and S7). Although in the overall analyses underweight BMI was not found to be associated with thyroid cancer risk in both men and women, an additional analysis revealed that linear association disappeared due to elevated risk among underweight men when papillary cancer was used as the outcome (HR: 2.22, [CI: 0.75–6.60]) (Supplementary Table S8 and Supplementary Fig. S1). Nonsignificant elevated risks were observed for three Japanese cohorts—Japan Public Health Center-based Prospective Study (JPHC) 1 and 2, and RERF cohort, which had papillary cancer cases in their underweight category. Among women, results were similar to those for all outcomes (Supplementary Table S9 and Supplementary Fig. S1).

In the sensitivity analysis, it was observed that excluding one cohort at a time showed results that were very similar with overall results among men (Supplementary Table S10). However, the results for women were substantially influenced by Shanghai Women's Health Study (SWHS), which has the largest number of thyroid cancer cases (Supplementary Table S11). When the SWHS was excluded, more clear linear association was observed (HR: 1.16, [CI 1.03–1.31]).

Discussion

The current pooled analysis of 13 cohorts from 4 Asian countries supports previous findings on the linear association between BMI and thyroid cancer risk among men. The linear association was less clear among women than men. These findings suggest a potential role of obesity in thyroid cancer risk that may differ by gender. Subgroup analysis suggested that the role of underweight may differ by histological types among men.

The International Agency for Research on Cancer (IARC) working group reassessed the epidemiologic evidence on body fatness and cancer and included thyroid cancer as a cancer site with sufficient evidence in humans (19). The previous pooled analysis based on 22 prospective studies applied a dose–response model between body fatness and thyroid cancer risk (8). A stronger association between obesity and thyroid cancer risk among men than among women is consistent with the previous pooled analysis (8).

Papillary cancer is the most common histology (14,20), and previous studies have shown that the strengths of the associations vary by histologic types; however, the direction of the association has been reported to be similar across histologic types (21). In a pooled analysis of cohorts, baseline BMI was associated with a nonsignificantly elevated risk of papillary thyroid cancer only among men (8). Although caution is needed due to the small numbers of papillary cancers among men in the current study, underweight men were at increased risk of papillary cancers; the reverse of that is seen for underweight men and overall thyroid cancer risk.

This result suggests that underweight has a potentially different association with thyroid cancer risk by histologic types. For underweight individuals, previous studies generally support a dose–response association between BMI and thyroid cancer risk (22). Considering that none of the cohorts included in the current study contributed to the previous meta-analysis (22) and only two Shanghai studies were included in the pooled analysis (8), the role of underweight in thyroid cancer risk needs to be explored in larger prospective studies.

A plausible explanation that obesity leads to elevated thyroid cancer risk has not been clearly demonstrated. Insulin resistance, altered adipocytokine profiles, inflammation, and their vicious cycle have been suggested as biological mechanisms for the role of obesity in increasing thyroid cancer risk (23). The endocrine and inflammatory roles of adipose tissue have been demonstrated by adipocytokines (especially low serum adiponectin), the behavior of which is modified by central obesity and leads to insulin resistance (23).

In addition, it has been suggested that the thyrotropin has mitogenic effects and high levels of this hormone have been observed among overweight and obese individuals (24). Moreover, it has been reported that thyroid cancer patients showed higher serum tumor necrosis factor-alpha (TNF-α)

Table 1. Characteristics of the Study Participants Included in the Analysis of Body Mass Index and Thyroid Cancer Risk from the Asia Cohort Consortium

Country and cohort	N	*Study period*	*Follow-up period, years, mean (SE)*	*Age at enrollment, years, mean (SE)*	*Body mass index at study entry kg/m^2, mean (SE)*	*Method of height and weight ascertainment*	*% who had ever smoked at study entry*	*% who had ever drank alcohol at study entry*	*No. of thyroid cancer*
China									
SCS	18,099	1986 to 1989	21.4 (0.06)	55.3 (0.04)	22.2 (0.02)	Self-report	57.3	42.6	16
SMHS	61,425	2001 to 2006	9.5 (0.01)	55.4 (0.04)	23.7 (0.01)	Actual measurement	69.6	33.7	78
SWHS	73,329	1996 to 2000	14.9 (0.01)	52.5 (0.03)	24.0 (0.01)	Actual measurement	2.8	2.3	306
Korea									
KMCC	18,666	1993 to 2005	13.8 (0.03)	53.6 (0.11)	23.6 (0.02)	Actual measurement	36.4	41.6	87
KNCC	8606	2007 to 2015	4.3 (0.02)	52.7 (0.09)	23.7 (0.03)	Actual measurement	33.5	59.5	47
Japan									
JPHC1	41,823	1990 to 1992	21.0 (0.02)	49.5 (0.03)	23.6 (0.01)	Self-report	40.3	50.1	135
JPHC2	54,476	1992 to 1995	17.7 (0.02)	54.2 (0.04)	23.5 (0.01)	Self-report	40.0	49.2	105
Miyagi	44,338	1990	16.2 (0.02)	51.9 (0.04)	23.6 (0.01)	Self-report	42.7	52.6	102
Ohsaki	46,060	1995	10.8 (0.02)	60.0 (0.05)	23.5 (0.01)	Self-report	42.1	50.8	40
RERF	49,578	1963 to 1993	21.9 (0.05)	52.2 (0.06)	21.9 (0.02)	Actual measurement/ self-report	42.8	40.2	67
Takayama	29,027	1992	13.7 (0.02)	55.2 (0.07)	22.2 (0.02)	Self-report	46.3	—	29
3 Pref Aichi	32,129	1985	11.6 (0.03)	56.1 (0.06)	22.1 (0.02)	Self-report	47.2	59.4	21
Singapore									
SCHS	61,301	1993 to 1999	14.0 (0.02)	56.4 (0.03)	23.1 (0.01)	Self-report	30.6	19.0	99
Total	538,857	1963 to 2015	15.1 (0.01)	54.3 (0.01)	23.2 (0.004)		39.0	34.9	1132

JPHC, Japan Public Health Center-based Prospective Study; KMCC, Korean Multicenter Cancer Cohort; KNCC, Korea National Cancer Center cohort; RERF, Radiation Effects Research Foundation; SCS, Shanghai Cohort Study; SCHS, Singapore Chinese Health Study; SMHS, Shanghai Men's Health Study; SWHS, Shanghai Women's Health Study.

Table 2. Hazard Ratios and Corresponding Confidence Intervals of the Association Between Body Mass Index and Thyroid Cancer Risk Among Men

	Body mass index, kg/m^2					
	<18.5	*18.5–22.9*	*23.0–24.9*	*25–29.9*	*≥30*	*Per 5 kg/m^2 increments*
All participants	0.64 [0.28–1.46]	Reference	0.93 [0.66–1.31]	1.31 [0.95–1.80]	1.84 [0.89–3.81]	1.25 [1.01–1.55]
China						
SCS	—	Reference	1.69 [0.48–5.99]	3.17 [1.02–9.86]	—	1.95 [0.93–4.10]
SMHS	0.35 [0.05–2.55]	Reference	0.84 [0.45–1.58]	1.47 [0.88–2.47]	1.71 [0.52–5.65]	1.45 [1.02–2.08]
Korea						
KMCC	—	Reference	2.50 [0.42–15.04]	3.44 [0.62–19.04]	—	1.98 [0.69–5.67]
Japan						
JPHC1	3.26 [0.73–14.64]	Reference	0.70 [0.26–1.88]	0.52 [0.17–1.61]	1.67 [0.22–12.87]	0.56 [0.26–1.20]
JPHC2	1.47 [0.19–11.52]	Reference	0.92 [0.33–2.54]	2.07 [0.89–4.82]	2.29 [0.29–18.04]	1.55 [0.85–2.84]
Miyagi	—	Reference	1.99 [0.44–8.89]	2.82 [0.67–11.86]	13.22 [2.18–80.09]	2.32 [1.08–4.98]
Ohsaki	—	Reference	0.65 [0.12–3.34]	0.38 [0.04–3.26]	—	0.76 [0.22–2.68]
RERF	1.20 [0.13–10.79]	Reference	1.95 [0.35–10.88]	—	—	1.04 [0.29–3.70]
Takayama	—	Reference	—	0.48 [0.06–3.96]	—	0.21 [0.04–1.03]
3 Pref Aichi	—	Reference	1.04 [0.09–11.50]	1.70 [0.15–18.80]	—	1.83 [0.36–9.31]
Singapore						
SCHS	0.52 [0.07–4.00]	Reference	0.52 [0.17–1.58]	0.70 [0.23–2.14]	—	0.73 [0.36–1.47]
Method of height and weight ascertainment						
Actual measurement[a]	0.34 [0.05–2.50]	Reference	1.13 [0.65–1.96]	1.54 [0.94–2.53]	2.06 [0.72–5.92]	1.09 [0.80–1.47]
Self-report[b]	0.73 [0.26–2.01]	Reference	0.79 [0.50–1.25]	1.19 [0.78–1.82]	1.75 [0.63–4.83]	1.09 [0.80–1.47]

Adjusted for the status of smoking (ever, never, and unknown) and alcohol drinking (ever, never, and unknown).
[a]SMHS, KMCC, and KNCC cohorts.
[b]SCS, SCHS, and all Japanese cohorts.

Table 3. Hazard Ratios and Corresponding Confidence Intervals of the Association Between Body Mass Index and Thyroid Cancer Risk Among Women

	Body mass index, kg/m^2					
	<18.5	*18.5–22.9*	*23.0–24.9*	*25–29.9*	*≥30*	*Per 5-U increment*
All participants	0.79 [0.53–1.16]	Reference	1.26 [1.07–1.48]	1.08 [0.91–1.28]	1.07 [0.75–1.53]	1.07 [0.97–1.18]
China						
SWHS	0.59 [0.26–1.34]	Reference	1.25 [0.95–1.64]	0.81 [0.60–1.08]	0.75 [0.40–1.40]	0.90 [0.76–1.07]
Korea						
KMCC	1.39 [0.32–5.96]	Reference	1.86 [1.03–3.35]	1.29 [0.71–2.34]	1.69 [0.63–4.54]	1.12 [0.80–1.56]
KNCC	—	Reference	1.80 [0.88–3.72]	1.60 [0.72–3.57]	2.40 [0.55–10.48]	1.48 [0.96–2.26]
Japan						
JPHC1	1.04 [0.32–3.34]	Reference	1.06 [0.66–1.72]	1.22 [0.77–1.93]	1.68 [0.66–4.23]	1.27 [0.95–1.70]
JPHC2	0.69 [0.16–2.86]	Reference	0.98 [0.55–1.73]	1.06 [0.61–1.85]	0.40 [0.06–2.95]	0.86 [0.59–1.24]
Miyagi	0.94 [0.23–3.94]	Reference	1.26 [0.75–2.11]	1.14 [0.68–1.90]	0.39 [0.05–2.82]	1.07 [0.77–1.50]
Ohsaki	—	Reference	2.42 [1.00–5.84]	1.81 [0.73–4.51]	—	1.36 [0.82–2.24]
RERF	0.91 [0.42–1.96]	Reference	0.90 [0.45–1.82]	0.43 [0.15–1.20]	1.39 [0.33–5.78]	0.88 [0.60–1.28]
Takayama	0.89 [0.11–7.08]	Reference	1.66 [0.55–4.98]	2.99 [0.99–9.08]	14.54 [3.10–68.21]	2.30 [1.34–3.97]
3 Pref Aichi	0.68 [0.08–5.52]	Reference	1.02 [0.27–3.83]	1.42 [0.38–5.36]	10.38 [2.19–49.21]	1.80 [1.00–3.26]
Singapore						
SCHS	0.79 [0.24–2.60]	Reference	1.09 [0.62–1.91]	1.86 [1.05–3.30]	0.88 [0.21–3.72]	1.21 [0.88–1.68]
Method of height and weight ascertainment						
Actual measurement[a]	0.65 [0.32–1.33]	Reference	1.38 [1.10–1.74]	0.93 [0.73–1.20]	0.99 [0.61–1.62]	0.99 [0.85–1.14]
Self-report[b]	0.78 [0.43–1.41]	Reference	1.19 [0.94–1.52]	1.35 [1.06–1.71]	1.15 [0.65–2.02]	1.20 [1.03–1.39]

Adjusted for the status of smoking (ever, never, and unknown) and alcohol drinking (ever, never, and unknown).
[a]SWHS, KMCC, and KNCC cohorts.
[b]SCHS and all Japanese cohorts.

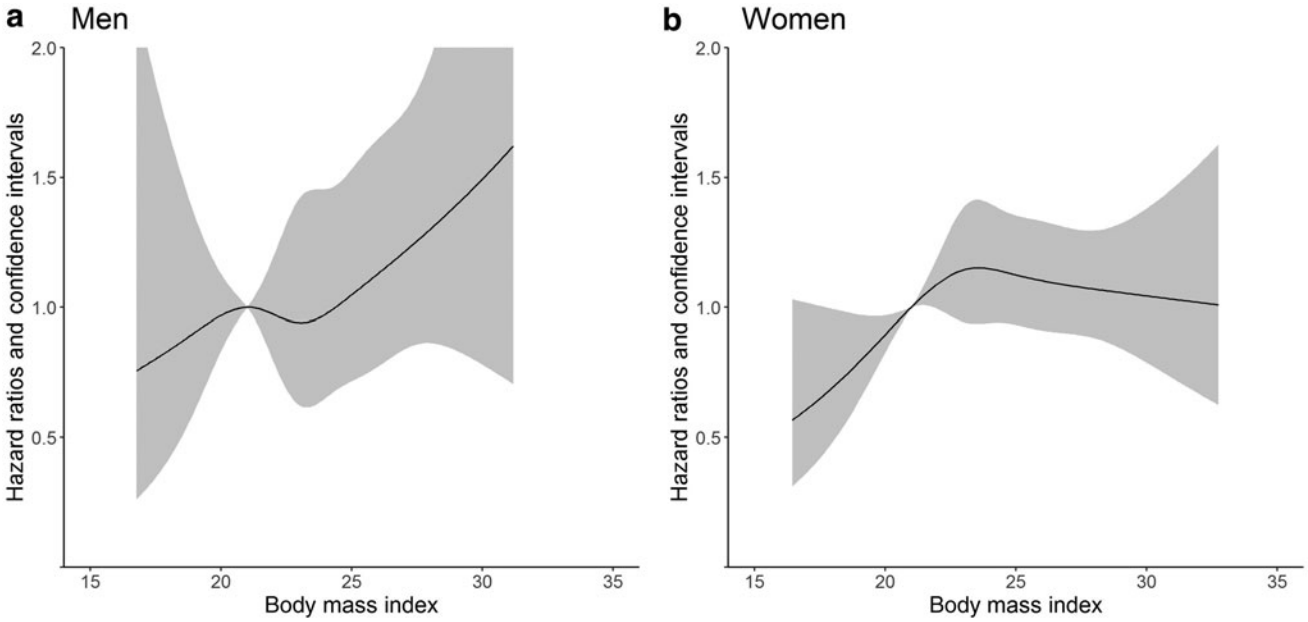

FIG. 1. Nonlinear association between BMI and thyroid cancer risk in the Asia Cohort Consortium; (**a**) men and (**b**) women.

and interleukin-6 (IL-6) and high immunoreactivity of TNF-α, IL-6, and leptin in thyroid tissue (25).

Worldwide observation of female dominance in thyroid cancer incidence (20,26,27) suggests the important role of hormones and reproductive factors in thyroid cancer etiology. Whereas the age-specific incidence of thyroid cancer in men increases with age, that of women peaks during reproductive periods (26,28). Parous women showed a 9% increase in thyroid cancer risk compared with nulliparous women in a meta-analysis of case-control and cohort studies (29). However, other reproductive and hormonal factors, such as breastfeeding, age at menarche or menopause, use of oral contraceptive or hormone replacement therapy, and history of infertility, did not show consistent results in prospective studies (30–32).

Considering the strong influence of estrogen on both thyroid function and adiposity, further studies on reproductive factors and their potential interaction with measures of obesity in thyroid cancer risk should be pursued to elucidate the weak association between obesity measures and thyroid cancer risk among women.

Although rare, an increase in thyroid cancer incidence has been observed in many countries. The most important explanation for the thyroid cancer epidemic is detection among asymptomatic patients (14); the high 5-year relative survival rate ranging from 70% to 100% consistent with a role for overdiagnosis (26,33). However, changes in risk factors should also be considered to explain the epidemic, and the parallel increases in obesity prevalence and thyroid cancer incidence raise the question of the etiological role of obesity in carcinogenesis (34).

The limitations of the current study include the fact that only baseline BMI was available for analysis. Other anthropometric measures, such as waist circumference or adulthood weight gain, could provide further insights into the role of obesity by allowing the exploration of central obesity and obesity throughout life (8). Self-reported height and weight were used to calculate BMI among 8 out of 13 studies. We found that the results from sensitivity analyses and subgroup analyses yielded different results among women.

The sensitivity analyses that excluded the SWHS cohort (which contributed the largest number of thyroid cancer cases and used measured height and weight) showed a statistically significant linear association. It is not clear whether this difference is caused by measurement methods or study population characteristics; however, it is useful to note that the stronger association among women was observed mainly in cohorts with self-reported measures.

Information on thyroid cancer subtypes was available for eight cohorts; therefore, subgroup analysis was available only for papillary cancer due to the limited numbers of cases for other less common subtypes. Lack of information on cancer stage at diagnosis is another limitation, which, if available, could provide insight into the possibility of screening for thyroid cancer. Nonetheless, the strengths of the current study include that this is the largest pooled analysis of prospective studies among Asian populations, which have been underrepresented in previous studies.

Conclusions

In conclusion, a higher BMI is associated with an elevated risk of thyroid cancer in both men and women with a much stronger association among men. The association between underweight and thyroid cancer risk may differ by sex and histological subtype.

Authors' Contributions

Study conception and design by A.S., P.B., M.I., and D.K.; data curation by S.K.A., E.S., M.S.R., and M.R.I.; analyses

by A.S., S.C., and D.J.; draft by A.S.; interpretation of results, critical editing, and article approval by all authors.

Author Disclosure Statement

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Supplementary Material

Supplementary Figure S1
Supplementary Table S1
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