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META-ANALYSIS

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# Obesity and Risk of Thyroid Cancer: Evidence from a Meta-Analysis of 21 Observational Studies

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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**Background:** Several studies have evaluated the association between obesity and thyroid cancer risk. However, the results remain uncertain. In this study, we conducted a meta-analysis to assess the association between obesity and thyroid cancer risk.

**Material/Methods:** Published literature from PubMed, EMBASE, Springer Link, Ovid, Chinese Wanfang Data Knowledge Service Platform, Chinese National Knowledge Infrastructure (CNKI), and Chinese Biology Medicine (CBM) were retrieved before 10 August 2014. We included all studies that reported adjusted risk ratios (RRs), hazard ratios (HRs) or odds ratios (ORs), and 95% confidence intervals (CIs) of thyroid cancer risk.

**Results:** Thirty-two studies (n=12 620 676) were included in this meta-analysis. Obesity was associated with a significantly increased risk of thyroid cancer (adjusted RR=1.33; 95% CI, 1.24–1.42; $I^2$=25%). In the subgroup analysis by study type, increased risk of thyroid cancer was found in cohort studies and case-control studies. In subgroup analysis by sex, both obese men and women were at significantly greater risk of thyroid cancer than non-obese subjects. When stratified by ethnicity, significantly elevated risk was observed in Caucasians and in Asians. In the age subgroup analysis, both young and old populations showed increased thyroid cancer risk. Subgroup analysis on smoking status showed that increased thyroid cancer risks were found in smokers and in non-smokers. In the histology subgroup analyses, increased risks of papillary thyroid cancer, follicular thyroid cancer, and anaplastic thyroid cancer were observed. However, obesity was associated with decreased risk of medullary thyroid cancer.

**Conclusions:** Our results indicate that obesity is associated with an increased thyroid cancer risk, except medullary thyroid cancer.

**MeSH Keywords:** Meta-Analysis • Obesity • Thyroid Neoplasms

**Full-text PDF:** http://www.medscimonit.com/abstract/index/idArt/892035

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## Background

Thyroid cancer is a common endocrine malignancy that has rapidly increased in global incidence in recent decades [1]. In the United States, the 6.6% average annual increase in thyroid cancer incidence between 2000 and 2009 is the highest among all cancers [1]. Although the death rate of thyroid cancer is relatively low, the rate of disease recurrence or persistence is high, which is associated with increased incurability, morbidity, and mortality [2]

The prevalence of obesity has dramatically increased in the last 2 decades [3]. The diagnosis of obesity is often based on body mass index (BMI), calculated as weight in kilograms divided by height in meters squared (kg/m$^2$). The ideal BMI is between 18.5 and 24.9. Being obese is considered as having a BMI of 30.0 or greater [4]. Obesity has long been recognized as a trigger for many diseases, such as hypertension, hypercholesterolemia, diabetes, and insulin resistance. Additionally, during the last decades obesity has been consistently related to the development and progression of different types of cancers. An extensive review published a few years ago estimated that 20% of all cancers might be caused by obesity [5].

The relationship between obesity and risk of thyroid cancer has been studied for more than 10 years. Several studies found obesity to be a risk factor in thyroid cancer, but other studies showed no association between obesity and risk of thyroid cancer. These studies reached conflicting conclusions [6–26]. Two meta-analyses investigated the association between obesity and thyroid cancer risk [27,28], reporting that obesity was associated with thyroid cancer risk. However, recent studies did not confirm this result [23,25,26]. A single study may have insufficient statistical power to detect a slight effect. Furthermore, these 2 meta-analyses did not include all the observational studies. Therefore, in this study we conducted a meta-analysis to assess the association between obesity and thyroid cancer risk.

## Material and Methods

### Publication search

We searched PubMed, EMBASE, Springer Link, Ovid, Chinese Wanfang Data Knowledge Service Platform, Chinese National Knowledge Infrastructure (CNKI), and Chinese Biology Medicine (CBM) databases up to 10 August 2014. References from relevant articles were manually checked for further studies. Combination of the following terms were applied: 'thyroid cancer' OR 'thyroid neoplasms'; 'obesity' OR 'BMI' OR 'body mass index'.

### Inclusion criteria and data extraction

We included articles if they met all the following criteria: (1) evaluation of obesity and thyroid cancer risk, (2) using a case-control or cohort design, (3) adjusted risk ratios (RRs), hazard ratios (HRs), or odds ratios (ORs) with 95% confidence intervals (CIs) were reported.

Data were extracted by 2 authors independently. If they encountered conflicting evaluations, agreement was reached following a discussion; if they could not reached agreement, another author was consulted to resolve the debate. The following information was extracted from each study: first author, year of publication, study type, ethnicity, age, sex, years of follow-up, sample size, number of cases, covariates, adjusted OR/HR/OR, and the corresponding 95% CI of thyroid cancer risk.

### Statistical analysis

For thyroid cancer risk, we calculated summary RRs and 95% CIs for obesity versus normal weight. The random effects model was utilized. HRs and ORs were regarded as equivalent to RRs. Statistical heterogeneity among studies was evaluated using the Q and $I^2$ statistics. For the $I^2$ metric, we considered low, moderate, and high $I^2$ values to be 25%, 50%, and 75%, respectively. We did subgroup analyses according to study type, sex, race, pneumonia type, age, smoking status, and histology. Cumulative meta-analysis was also performed. Sensitivity analysis was conducted by excluding 1 study at a time to explore whether the results were driven by 1 large study or by a study with an extreme result. Publication bias was investigated with funnel plots. Egger's test was also used to assess publication bias [29].

All statistical analyses were performed with STATA software (version 12.0, Stata Corporation, College Station, TX, USA). A threshold of $P<0.1$ was used to decide whether heterogeneity was present. In other cases, $P$ values were 2-sided, with a significance level of 0.05.

## Results

### Study characteristics

The process of identifying relevant studies is shown in Figure 1. The initial search produced 359 studies. After exclusion of duplicates and irrelevant studies, 107 potentially eligible studies were selected. After detailed evaluations, 21 studies were selected for final meta-analysis [6–26]. A manual search of reference lists from these studies did not yield any new eligible study. Eleven studies reported 2 cohorts, and finally 32 studies (n=12 620 676) were included in this meta-analysis. There

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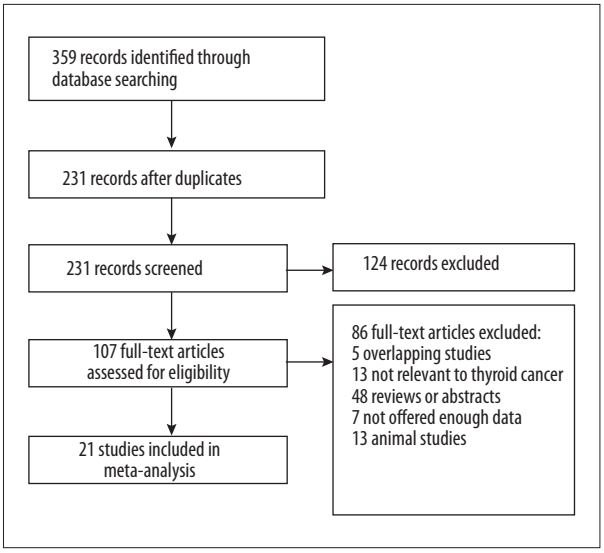


**Figure 1.** Flow diagram of meta-analysis literature search results.

were 24 cohort studies and 8 case-control studies. Table 1 summarizes the main characteristics of these included studies.

### Quantitative data synthesis

The evaluations of the association between obesity and thyroid cancer risk are summarized in Table 2. Obesity was associated with a significantly increased risk of thyroid cancer when compared with normal weight (adjusted RR=1.33; 95% CI, 1.24–1.42; $I^2$=25%; Figure 2). In the subgroup analysis by study type, increased risk of thyroid cancer was found in cohort studies (RR=1.29; 95% CI, 1.20–1.37; $I^2$=21%) and case-control studies (OR=1.76; 95% CI, 1.36–2.28; $I^2$=0%), respectively. In the subgroup analysis according to sex, both obese men (RR=1.26; 95% CI, 1.13–1.40; $I^2$=9%) and women (RR=1.43; 95% CI, 1.25–1.64; $I^2$=33%) were significantly at risk of thyroid cancer. When stratified by ethnicity, significantly elevated risk was observed in Caucasians (RR=1.26; 95% CI, 1.18–1.33; $I^2$=9%) and in Asians (RR=1.54; 95% CI, 1.27–1.86; $I^2$=16%). In the age subgroup analysis, both young (RR=1.23; 95% CI, 1.13–1.34; $I^2$=0%) and old populations (RR=1.28; 95% CI, 1.11–1.46; $I^2$=32%) showed increased thyroid cancer risk. Subgroup analysis on smoking status showed that increased thyroid cancer risks were found in smokers (RR=1.10; 95% CI, 1.02–1.20; $I^2$=0%) and in non-smokers (RR=1.20; 95% CI, 1.11–1.28; $I^2$=0%). In the histology subgroup analyses, increased risks of papillary thyroid cancer (RR=1.26; 95% CI, 1.15–1.39; $I^2$=35%), follicular thyroid cancer (RR=1.29; 95% CI, 1.08–1.53; $I^2$=33%), and anaplastic thyroid cancer (RR=1.93; 95% CI, 1.23–3.03; $I^2$=0%) were observed. However, obesity was associated with decreased risk of medullary thyroid cancer (RR=0.50; 95% CI, 0.27–0.97; $I^2$=1%).

As shown in Figure 3, significant associations were evident with each addition of more data over time. The results showed that the pooled ORs tended to be stable. A single study involved in the meta-analysis was deleted each time to reflect the influence of the individual data set on the pooled ORs, and the corresponding pooled ORs were not materially altered (Figure 4).

Funnel plot analysis was performed to assess the publication bias of studies. The shape of the funnel plot showed asymmetry (Figure 5). Egger's test found evidence of publication bias ($P$<0.01).

## Discussion

The present meta-analysis, including 12 620 676 subjects from 32 observational studies, explored the association between obesity and thyroid cancer risk. We found that obesity was significantly associated with increased thyroid cancer risk. This result remained significant in various types of studies, such as cohort studies and case-control studies. In addition, obesity was significantly associated with thyroid cancer risk in males and females. Subgroup analyses stratified by ethnicity showed that obese Asians had higher thyroid cancer risk than Caucasians, but it is possible that random error may account for this difference. In fact, only 6 studies investigated the association between obesity and thyroid cancer risk in Asians. Thus, more studies with Asians are needed to validate this result. In addition, Price et al. [30] found that dynamic patterns of change for thyroid hormones were not different in Asian and Western Caucasian women. In the subgroup analysis by age, we found obesity exhibited increased thyroid cancer risk in young and old subjects. Actually, when we limited the meta-analysis to studies that controlled for age, a significant association between obesity and thyroid cancer risk remained (RR=1.30; 95% CI, 1.22–1.40; $I^2$=22%). This result indicates that the role of obesity was not selective by age. Cigarette smoking is a pro-inflammatory stimulus and an important risk factor for cancer. Several studies explored the interaction between obesity and smoking habits. Our results showed that both smokers and non-smokers had increased thyroid cancer risk. Furthermore, we investigated the association between obesity and different types of thyroid cancer. Obese subjects showed increased risks of papillary thyroid cancer, follicular thyroid cancer, and anaplastic thyroid cancer. Interestingly, there was an inverse association between obesity and medullary thyroid cancer risk. This result indicates that obesity may have a different effect on the pathogenesis and occurrence of thyroid cancer in different histologies. However, why obesity could influence the different histological types of thyroid cancer is still uncertain. Clearly, more studies are needed to elucidate the differential effect of obesity in the various thyroid cancer types.

There were several potential explanations for why obese individuals may have higher risk of thyroid cancer. First, there

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**Table 1.** Characteristics of the case-control studies included in this meta-analysis.

| First author | Year | Study type | Race | Age | Gender | Years of follow-up | Sample size | No. of Case | Covariate |
|---|---|---|---|---|---|---|---|---|---|
| Samanic 1 | 2004 | Cohort | Caucasian | 52 | Men | 11 | 3668486 | 875 | Age and calendar year |
| Samanic 2 | 2004 | Cohort | African | 47 | Men | 12 | 832214 | 169 | Age and calendar year |
| Oh | 2005 | Cohort | Asian | ≥20 | Men | 10 | 781283 | 223 | Age, smoking status, average amount of alcohol consumed per day, frequency of regular exercise for more than 30 minutes during a week, family history of cancer, and residency area at baseline |
| Rapp | 2005 | Cohort | Caucasian | 42 | Women | 9.9 | 78484 | 61 | Smoking, occupational group at baseline |
| Engeland 1 | 2006 | Cohort | Caucasian | 62 | Men | 23 | 963523 | 778 | Age, year of birth, height |
| Engeland 2 | 2006 | Cohort | Caucasian | 58 | Women | 23 | 1037424 | 2268 | Age, year of birth, height |
| Samanic | 2006 | Cohort | Caucasian | 34 | Men | 19 | 362552 | 171 | Age, calendar year, smoking status, and relative to normal weight subjects |
| Guignard 1 | 2007 | Case-control | Caucasian | NA | Men | NA | 58 | 39 | Age, year of reference, and ethnic group |
| Guignard 2 | 2007 | Case-control | Caucasian | NA | Women | NA | 354 | 293 | Age, year of reference, ethnic group, number of full-term pregnancies, miscarriages, and irregular menstruations |
| Suzuki 1 | 2008 | Case-control | Asian | 20–79 | Men | NA | 210 | 42 | Smoking habit, drinking habit, regular exercise, family history of thyroid cancer, past history of thyroid diseases, total non-alcohol energy intake |
| Suzuki 2 | 2008 | Case-control | Asian | 20–79 | Women | NA | 655 | 131 | Smoking habit, drinking habit, regular exercise, family history of thyroid cancer, past history of thyroid diseases, total non-alcohol energy intake, menopausal status, age at menarche, parity, hormone-replacement therapy |
| Song | 2008 | Cohort | Asian | 56 | Women | 9 | 170481 | 367 | Age, height, smoking status, alcohol intake, physical exercise, and pay level at study entry |
| Brindel 1 | 2008 | Case-control | Caucasian | <56 | Men | NA | 33 | 18 | Height, ethnicity, educational level, smoking, interviewer, radiation to head or neck for diagnosis before 15 years old |
| Brindel 2 | 2008 | Case-control | Caucasian | <56 | Women | NA | 255 | 160 | Height, ethnicity, educational level, smoking, interviewer, radiation to head or neck for diagnosis before 15 years old, and also for the number of full-term pregnancies and menopausal status among women |
| Leitzmann | 2009 | Cohort | Caucasian | 62 | Women | 8 | 484326 | 352 | Age, sex, physical activity, race, education, smoking status, current alcohol use; and oral contraceptive use among women |

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**Table 1 continued.** Characteristics of the case-control studies included in this meta-analysis.

| First author | Year | Study type | Race | Age | Gender | Years of follow-up | Sample size | No. of Case | Covariate |
|---|---|---|---|---|---|---|---|---|---|
| Meinhold 1 | 2009 | Cohort | Caucasian | 43 | Men | 23 | 21207 | 40 | Birth year, smoking status, body mass index, number of personal radiographs to the head or neck, cumulative occupational radiation dose, and medical history of benign thyroid conditions |
| Meinhold 2 | 2009 | Cohort | Caucasian | 39 | Women | 23 | 69506 | 242 | Birth year, smoking status, body mass index, number of personal radiographs to the head or neck, cumulative occupational radiation dose, and medical history of benign thyroid conditions |
| Clavel-Chapelon | 2010 | Cohort | Caucasian | 49 | Women | 13 | 91909 | 317 | Age, stratified on year of birth, history of goiter or thyroid nodules, smoking status, iodine |
| Clero | 2010 | Case-control | Caucasian | 18–78 | Mixed* | NA | 776 | 554 | Ethnicity, educational level, smoking, radiation to head or neck for diagnosis before 15 years old, and alsofor the number of full-term pregnancies among women |
| Almquist 1 | 2011 | Cohort | Caucasian | 43 | Men | 12 | 289866 | 133 | Age, smoking |
| Almquist 2 | 2011 | Cohort | Caucasian | 44 | Women | 12 | 288834 | 255 | Age, smoking |
| Kitahara | 2011 | Cohort | Caucasian | 58 | Mixed* | 10 | 848932 | 1156 | Education, race, marital status, smoking, alcohol intake, sex |
| Kabat | 2012 | Cohort | Caucasian | 44 | Women | 11 | 144319 | 294 | Age, education, pack-years of smoking, alcohol intake, history of benign thyroid disease |
| Marcello | 2012 | Case-control | Caucasian | 34 | Mixed | NA | 103 | 115 | Age, gender, and ethnicity |
| Rinaldi 1 | 2012 | Cohort | Caucasian | 52 | Men | 6 | 150000 | 58 | Center, age, smoking |
| Rinaldi 2 | 2012 | Cohort | Caucasian | 51 | Women | 6 | 370000 | 508 | Center, age, smoking |
| Han 1 | 2013 | Cohort | Asian | 51 | Men | 1 | 9275 | 127 | Age, smoking status, and TSH levels |
| Han 2 | 2013 | Cohort | Asian | 50 | Women | 1 | 8138 | 140 | Age, smoking status, and TSH levels |
| Farfel 1 | 2014 | Cohort | Caucasian | 16–19 | Men | 48 | 1145865 | 437 | Year of birth, country of origin, and years of schooling |
| Farfel 2 | 2014 | Cohort | Caucasian | 16–19 | Women | 16 | 478445 | 323 | Year of birth, country of origin, and years of schooling |
| Kitahara 1 | 2014 | Cohort | Caucasian | 7–13 | Men | 39 | 162632 | 64 | Birth cohort |
| Kitahara 2 | 2014 | Cohort | Caucasian | 7–13 | Women | 39 | 158453 | 171 | Birth cohort |

* Information of gender can be extracted. TSH – thyroid stimulating hormone; NA – not available.

is a clinical association between higher serum thyroid-stimulating hormone (TSH) levels and increased risk of malignancy in human thyroid nodules and advanced stage of the disease [31,32]. Some cross-sectional studies in euthyroid subjects demonstrated a positive association between serum TSH and BMI [33]. Second, leptin levels were higher in thyroid cancer patients compared to healthy subjects in a case-control study [34]. Leptin was also shown to enhance migration of PTC cells [35]. Third, insulin resistance, a common metabolic perturbation in obesity, may play a role in thyroid tumor growth, with

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**Table 2.** Main result and subgroup analyses of this meta-analysis.

| Characteristics | No. of studies | Test of association | | | | Model | Heterogeneity | | |
|---|---|---|---|---|---|---|---|---|---|
| | | RR (95% CI)* | | Z | P Value | | $I^2$ | P Value | $I^2$ (%) |
| All studies | 32 | 1.33 | (1.24–1.42) | 7.94 | <0.00001 | R | 41.26 | 0.10 | 25 |
| Study type | | | | | | | | | |
| Cohort study | 24 | 1.29 | (1.20–1.37) | 7.52 | <0.00001 | R | 28.95 | 0.18 | 21 |
| Case-control study | 8 | 1.76 | (1.36–2.28) | 4.33 | <0.0001 | R | 4.78 | 0.69 | 0 |
| Gender | | | | | | | | | |
| Male | 13 | 1.26 | (1.13–1.40) | 4.19 | <0.0001 | R | 6.41 | 0.89 | 0 |
| Female | 13 | 1.43 | (1.25–1.64) | 5.20 | <0.00001 | R | 14.97 | 0.13 | 33 |
| Race | | | | | | | | | |
| Asian | 6 | 1.54 | (1.27–1.86) | 4.41 | <0.0001 | R | 5.97 | 0.31 | 16 |
| Caucasian | 25 | 1.26 | (1.18–1.33) | 7.53 | <0.00001 | R | 26.34 | 0.34 | 9 |
| Age | | | | | | | | | |
| ≤50 years | 6 | 1.23 | (1.13–1.34) | 4.84 | <0.00001 | R | 2.25 | 0.81 | 0 |
| >50 years | 6 | 1.28 | (1.11–1.46) | 3.44 | 0.0006 | R | 5.89 | 0.21 | 32 |
| Smoking status | | | | | | | | | |
| Smoker | 3 | 1.10 | (1.02–1.20) | 2.41 | 0.02 | R | 0.11 | 0.95 | 0 |
| Non-smoker | 4 | 1.20 | (1.11–1.28) | 4.95 | <0.00001 | R | 0.93 | 0.82 | 0 |
| Histology | | | | | | | | | |
| Papillary thyroid cancer | 9 | 1.26 | (1.15–1.39) | 4.73 | <0.00001 | R | 12.34 | 0.14 | 35 |
| Follicular thyroid cancer | 6 | 1.29 | (1.08–1.53) | 7.45 | 0.005 | R | 7.45 | 0.19 | 33 |
| Medullary thyroid cancer | 3 | 0.50 | (0.27–0.91) | 2.25 | 0.02 | R | 2.01 | 0.37 | 1 |
| Anaplastic thyroid cancer | 3 | 1.93 | (1.23–3.03) | 2.85 | 0.004 | R | 1.97 | 0.37 | 0 |

* The multivariable-adjusted RRs with 95% CIs were pooled. RR – risk ratio; CI – confidence intervals; R – random effects model.

insulin directly binding to insulin receptors or stimulating insulin-like growth factor, estrogen, or other hormones, such as TSH, to enhance the proliferation of thyroid cancer cells [36].

Obesity is a major public health problem worldwide and its prevalence continues to increase [37,38]. The incidence of thyroid cancer has also been increasing in many countries [39,40]. Studies on the positive association between obesity and thyroid cancer will have important implications in the future, because obesity is a modifiable risk factor [41–45]. Future studies on the effects of weight gain or weight loss on altering risk for thyroid cancer are essential.

Our result was consistent with 2 previous meta-analyses [27,28]. We also found a significant association between obesity and thyroid cancer risk. However, our study had some advantages. First, it was the first study of interactions between age, histology, and smoking status specificities and obesity. Second, the methodological issues for meta-analyses, such as one-way sensitivity analysis and cumulative meta-analysis, were well investigated. Third, this meta-analysis included 32 studies (n=12 620 676) and thus was more conclusive and more powerful than previous studies.

Results from one-way sensitivity analysis and cumulative meta-analysis suggest the high stability and reliability of our results. Heterogeneity and publication bias can be important influences on the results of meta-analyses. In our study no significant heterogeneity was observed. Additionally, funnel plots and Egger's tests were used to find potential publication bias. The results indicated that there was significant publication bias. Thus, our results should be interpreted with caution

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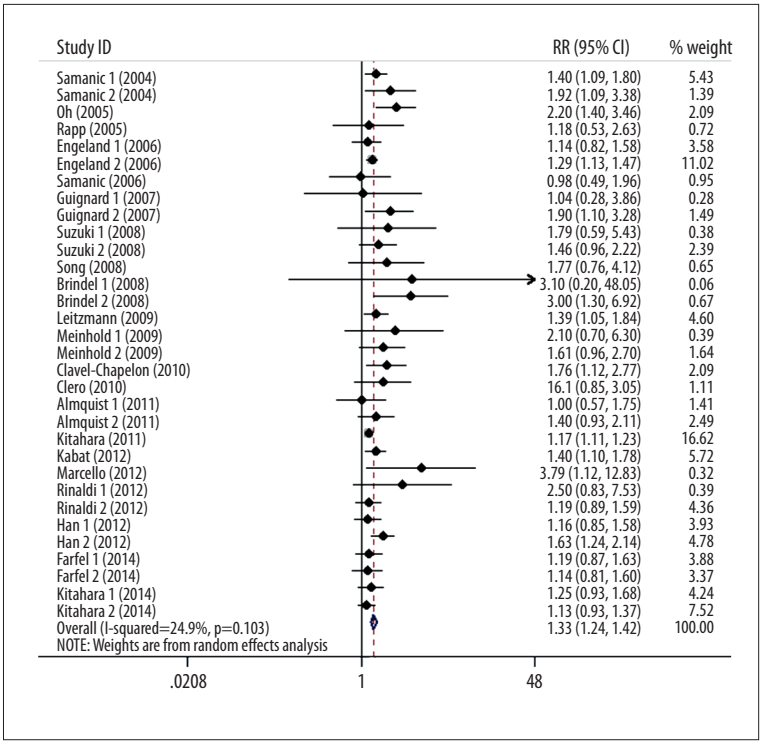


**Figure 2.** Forest plot for the association between obesity and thyroid cancer risk.

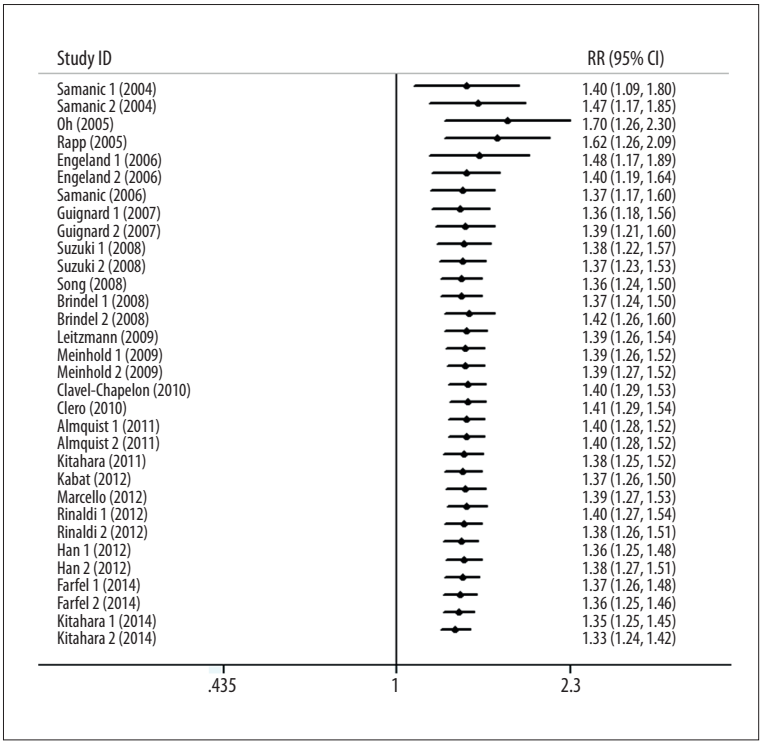


**Figure 3.** Cumulative meta-analysis for the association between obesity and thyroid cancer risk.

and more studies are needed to confirm the effect of obesity on thyroid cancer risk.

Several limitations need to be addressed. First, the number of published studies was not sufficient for a comprehensive analysis, particularly for Africans. Second, all the studies included in this meta-analysis used a case-control or cohort design, which are susceptible to recall and selection biases. Third, because this meta-analysis investigated only obesity, we cannot exclude the possibility that the observed associations may be confounded by other lifestyle factors, such as lower physical activity or dietary factors.

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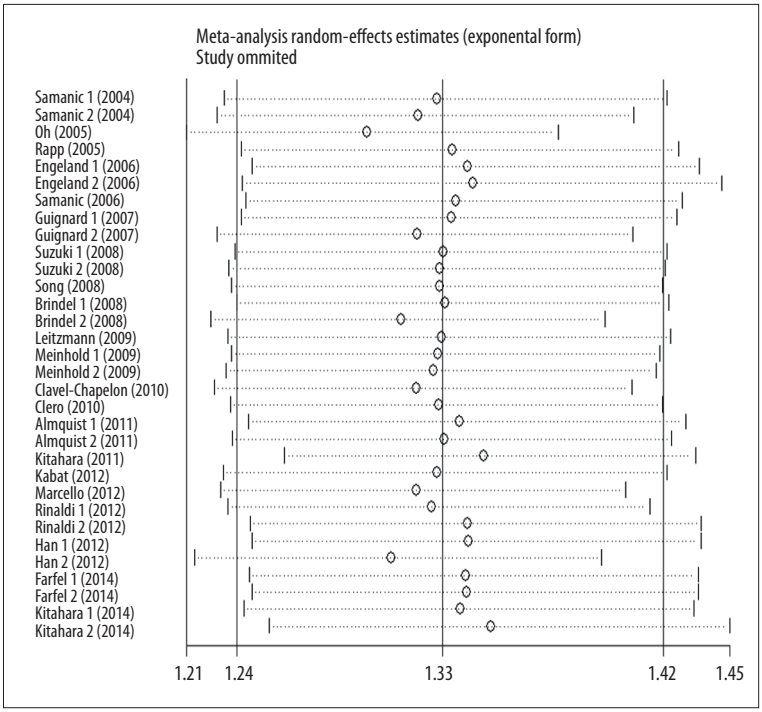


**Figure 4.** Sensitivity analysis for the association between obesity and thyroid cancer risk.

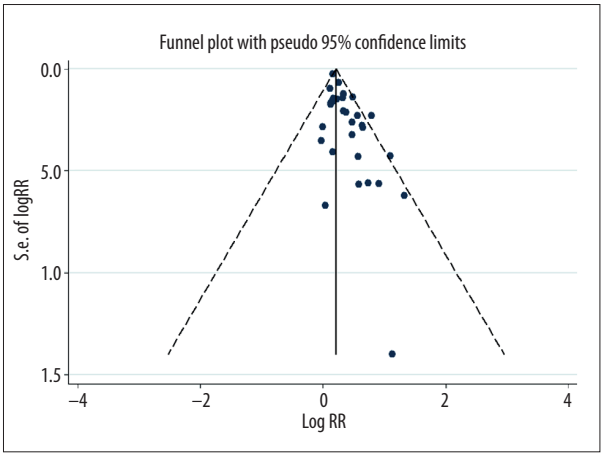


**Figure 5.** Begg's funnel plot for publication bias.

## Conclusions

This meta-analysis found a significant association between obesity and thyroid cancer risk, except medullary thyroid cancer. Further studies in more ethnic groups, especially African, are warranted to validate this result.

### Conflicts of interest

None.

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