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Original Article

Meta-analysis in the association between obesity and risk of thyroid cancer

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Abstract: Although many epidemiologic studies have investigated obesity and thyroid cancer risk, definite conclusions cannot be drawn. To clarify the effects of obesity on the risk of thyroid cancer, a meta-analysis was performed. Related studies were identified from PubMed, Springer Link, Ovid, Chinese Wanfang Data Knowledge Service Platform, Chinese National Knowledge Infrastructure (CNKI), and Chinese Biology Medicine (CBM) till 16 Aug 2014. Pooled RRs and 95% CIs were used to assess the strength of the associations. A total of 16 studies including 12616154 subjects were involved in this meta-analysis. A significantly elevated thyroid cancer risk was found in overall analysis (RR = 1.29, 95% CI 1.20-1.37, $P < 0.00001$). In the gender subgroup analyses, a statistically significant association was found in male patients (RR = 1.35, 95% CI 1.16-1.58, $P = 0.0001$) and in female patients (RR = 1.29, 95% CI 1.19-1.40, $P < 0.00001$). When we limited the meta-analysis to studies that controlled for age (RR = 1.34, 95% CI 1.24-1.44, $P < 0.00001$), smoke (RR = 1.36, 95% CI 1.22-1.52, $P < 0.00001$), alcohol use (RR = 1.40, 95% CI 1.15-1.71, $P = 0.0009$), and history of benign thyroid disease (RR = 1.51, 95% CI 1.24-1.83, $P < 0.0001$), a significant association between obesity and thyroid cancer risk remained. This meta-analysis provides the evidence that obesity may contribute to the thyroid cancer development.

Keywords: Thyroid cancer, BMI, obesity, association, meta-analysis

Introduction

Obesity is due to excessive fat accumulation that may impair health resulting from social behaviour and environmental and genetic factors [1]. During the last 20 years, obesity has rapidly become a global pandemic health problem: catastrophic data come from America and from Europe where ~35% and ~20% of the population, respectively, are obese [2]. Globally, the World Health Organization (WHO) has predicted that, in 2015, ~2.3 billion of adults will be overweight; 700 million will be obese, while ~200 million of school aged children will be obese/overweight (http://www.IASO.org/).

Thyroid cancer is the most common endocrine cancer, traditionally classified into two major groups based on morphologic and clinical features: differentiated carcinoma and undifferentiated carcinoma [3]. The worldwide incidence of thyroid cancer has been rapidly increasing over the last three decades [4]. Dieringer et al. found that obesity was significantly associated with larger thyroid cancer size and marginally significantly associated with advanced thyroid cancer stage [5]. In addition, Kim et al. showed that a higher body mass index (BMI) was associated with more aggressive tumor features, such as lymph node metastasis, lymphatic invasion, and tumor multiplicity [6]. Therefore, obesity might have a critical role in the thyroid cancer development.

A series of studies have investigated the association between the obesity and thyroid cancer susceptibility, but provided controversial or inconclusive results [7-22]. Thus, we performed this meta-analysis to assess the relationship of obesity with risk of thyroid cancer.

Materials and methods

Publication search

We searched databases containing PubMed, Springer Link, Ovid, Chinese Wanfang Data Knowledge Service Platform, Chinese National

Table 1. Characteristics of the studies

First author/Year	Age	Male (%)	No. of subjects	Adjustment of covariants
Samanic a/2004	52	100	3668486	Age, calendar year
Samanic b/2004	47	100	832214	Age, calendar year
0h/2005	≥20	100	781283	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, residency area at baseline
Rapp/2005	42	0	78484	Smoking, occupational group at baseline
Engeland a/2006	62	100	963523	Age, year of birth, height
Engeland b/2006	58	0	1037424	Age, year of birth, height
Samanic/2006	34	100	362552	Age, calendar year, smoking status, and relative to normal weight subjects
Song/2008	56	0	170481	Age, height, smoking status, alcohol intake, physical exercise, pay level at study entry
Leitzmann/2009	62	0	484326	Age, sex, physical activity, race, education, smoking status, current alcohol use; oral contraceptive use among women
Meinhold a/2009	43	100	21207	Birth year, smoking status, body mass index, number of personal radiographs to the head or neck, cumulative occupational radiation dose, medical history of benign thyroid conditions
Meinhold b/2009	39	0	69506	Birth year, smoking status, body mass index, number of personal radiographs to the head or neck, cumulative occupational radiation dose, medical history of benign thyroid conditions
Clavel-Chapelon/2010	49	0	91909	Age, stratified on year of birth, history of goiter or thyroid nodules, smoking status, iodine
Almquist a/2011	43	100	289866	Age, smoking
Almquist b/2011	44	0	288834	Age, smoking
Kitahara/2011	58	74	848932	Education, race, marital status, smoking, alcohol intake, sex
Kabat/2012	44	0	144319	Age, education, pack-years of smoking, alcohol intake, history of benign thyroid disease
Rinaldi a/2012	52	100	150000	Center, age, smoking
Rinaldi b/2012	51	0	370000	Center, age, smoking
Han a/2013	51	100	9275	Age, smoking status, TSH levels
Han b/2013	50	0	8138	Age, smoking status, TSH levels
Farfel a/2014	16-19	100	1145865	Year of birth, country of origin, years of schooling
Farfel b/2014	16-19	0	478445	Year of birth, country of origin, years of schooling
Kitahara a/2014	7-13	100	162632	Birth cohort
Kitahara b/2014	7-13	0	158453	Birth cohort

Knowledge Infrastructure (CNKI), and Chinese Biology Medicine (CBM) up to 16 Aug 2014, using the following Mesh terms: ("thyroid Neoplasms" [MeSH] or "thyroid cancer" or "thyroid tumor" or "thyroid carcinoma" or "carcinoma of thyroid") and ("obesity" or "body mass index"). The references from retrieved articles were also searched.

Inclusion criteria and data extraction

Studies included in this meta-analysis have to meet the following criteria: (1) case-control study or cohort study studying on association between obesity and risk of thyroid cancer; (2) all patients with the diagnosis of thyroid cancer confirmed by pathological or histological examination; (3) sufficient published data about sample size, risk ratio (RR), and their 95% confidence interval (CI). Studies were excluded when they were: (1) not case-control study or cohort study; (2) duplicate of previous publication; (3) based on incomplete data; (4) meta-analyses, letters, reviews, or editorial articles.

Data were independently extracted by two reviewers using a standardized data extraction form. Discrepancies were resolved by discussion and if consensus was not achieved the decision was made by all the reviewers. The title and abstract of all potentially relevant articles were screened to determine their relevance. Full articles were also scrutinized if the title and abstract were ambiguous. The following information was collected from each study: authors, year of publication, age, sex, sample size, covariants.

Statistical analysis

Statistical analysis was conducted by using STATA statistical package (version 11, STATA,

Table 2. Main results of this meta-analysis

	No. of studies	RR (95% CI)	*P* Value	I^2 (%)	$P_{heterogeneity}$
Overall	24	1.29 (1.20-1.37)	< 0.00001	21	0.18
Man	11	1.35 (1.16-1.58)	0.0001	23	0.23
Women	12	1.29 (1.19-1.40)	< 0.00001	0	0.77
Adjusted for					
Age	18	1.34 (1.24-1.44)	< 0.00001	3	0.42
Smoke	16	1.36 (1.22-1.52)	< 0.00001	37	0.07
Alcohol use	5	1.40 (1.15-1.71)	0.0009	64	0.02
History of benign thyroid disease	4	1.51 (1.24-1.83)	< 0.0001	0	0.75

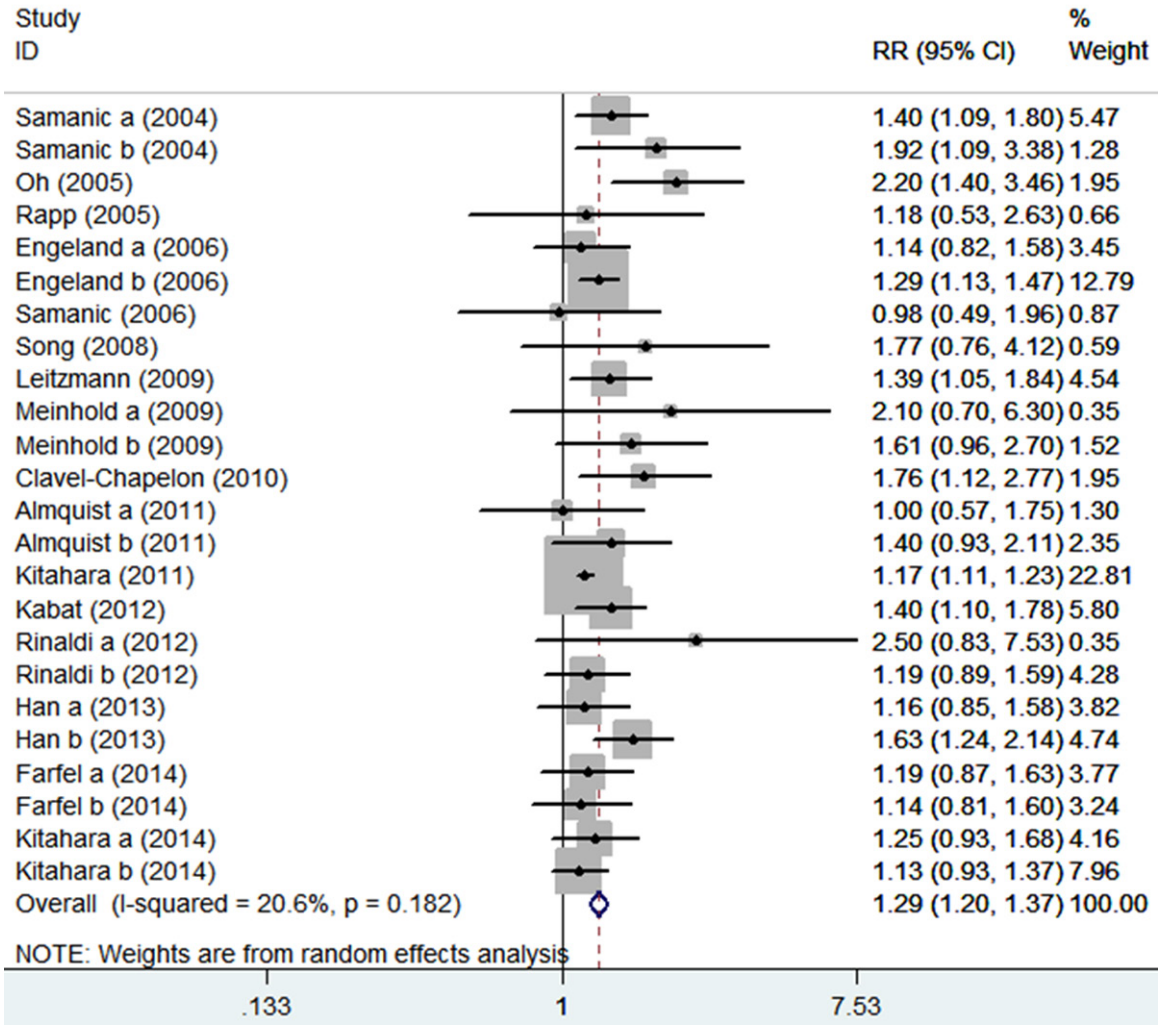

Figure 1. The association between obesity and thyroid cancer risk.

College Station, TX). The association of polymorphisms of obesity and risk of thyroid cancer was estimated by RR with 95% CI. The heterogeneity was tested by the Q-statistics with *P*-values < 0.1, and its possible sources of heterogeneity were assessed by Galbraith plot. Dependent on the results of heterogeneity test among individual studies, the fixed effect model (Mantel-Haenszel) or random effect model (DerSimonian and Laird) was selected to summarize the combined OR and their 95% CI. The significance of the pooled OR was determined

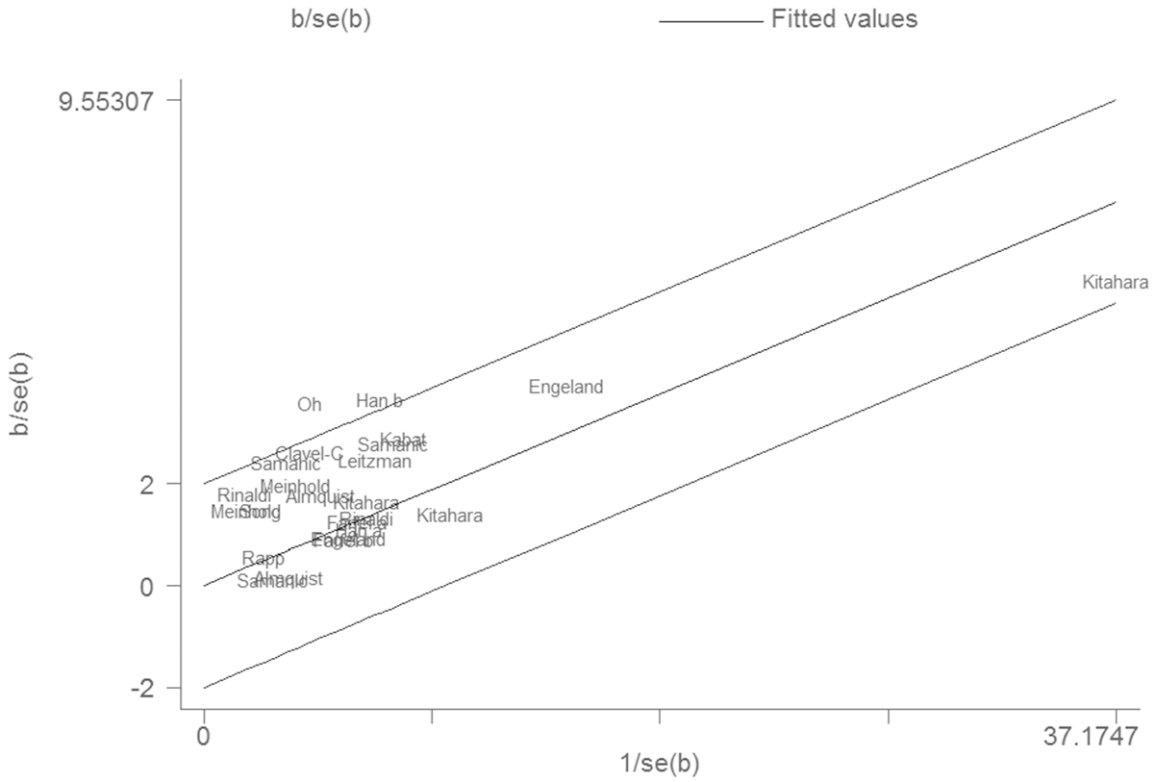

Figure 2. Galbraith plot of the association between obesity and thyroid cancer risk.

by the z test. Publication bias was investigated with the funnel plot, in which the Standard Error (SE) of log OR of each study was plotted against its OR. Funnel-plot asymmetry was further assessed by the method of Egger's linear regression test. All the *P* values were two sided. *P* value less than 0.05 was considered statistically significant.

Results

Eligible studies

In this current study, a total of 16 eligible studies met the inclusion criteria [7-22]. Eight articles reported two cohorts, and each cohort was considered as a study. There were 11 studies performed using male, 12 studies using female, and 1 studies using mixed populations. A total of 12616154 subjects were included in this meta-analysis. The characteristics of each study included in this meta-analysis are presented in **Table 1**.

Quantitative synthesis

The main results of this meta-analysis and the heterogeneity test were shown in **Table 2**. A significantly elevated thyroid cancer risk was found in overall analysis (RR = 1.29, 95% CI 1.20-1.37, *P* < 0.00001, **Figure 1**). In the gender subgroup analyses, a statistically significant association was found in male patients (RR = 1.35, 95% CI 1.16-1.58, *P* = 0.0001) and in female patients (RR = 1.29, 95% CI 1.19-1.40, *P* < 0.00001). When we limited the meta-analysis to studies that controlled for age (RR = 1.34, 95% CI 1.24-1.44, *P* < 0.00001), smoke (RR = 1.36, 95% CI 1.22-1.52, *P* < 0.00001), alcohol use (RR = 1.40, 95% CI 1.15-1.71, *P* = 0.0009), and history of benign thyroid disease (RR = 1.51, 95% CI 1.24-1.83, *P* < 0.0001), a significant association between obesity and thyroid cancer risk remained.

The Galbraith plot was used to find the source of the heterogeneity. As shown in **Figure 2**, two studies were the outliers. After excluding these studies, the between-study heterogeneity effectively decreased and there was no obvious heterogeneity among the remaining studies (I^2 = 0%). Besides, the result was still statistically significant (RR = 1.21, 95% CI 1.16-1.26, *P* < 0.00001).

Publication bias was examined by the funnel plot. The shape of the funnel plot was symmet-

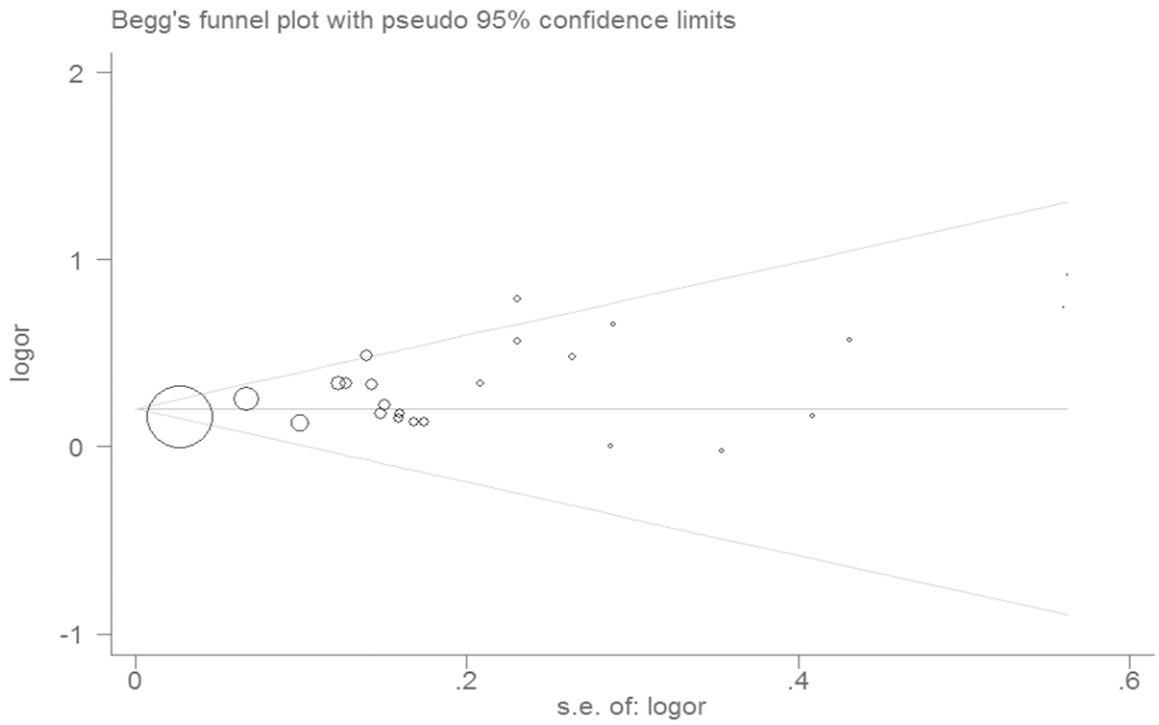

Figure 3. Funnel plot for the association between obesity and thyroid cancer risk.

rical (**Figure 3**). Egger's test indicated no significant publication bias ($P = 0.427$).

Discussion

Although many studies analyzing the research results about obesity and the risk of thyroid cancer, definite conclusions cannot be drawn. Therefore, we did this meta-analysis to estimate the relationship between obesity and susceptibility to thyroid cancer. We found that obesity individuals showed an increased risk of thyroid cancer. The subgroup analysis based on sex found that obesity showed increased thyroid cancer risk in female patients and in male patients.

Obesity is a serious problem which heightens the risk of several chronic illnesses including cancer development. Potential mechanisms linking obesity and thyroid cancer risk include elevated TSH levels, insulin resistance, and adipokines effect [23]. TSH and insulin influence the growth and differentiation of follicular cells [24]. Adipokines such as adiponectin, leptin, and hepatocyte growth factor may regulate cancer cell proliferation and may be related to cancer progression [23]. Increased expression of leptin and its receptor in thyroid cancer were reported [25]. Its association with tumor aggressiveness and biological behavior was also demonstrated [25].

We had to mention the importance of heterogeneity and publication bias, which might influence the results of meta-analysis. In our study, significant heterogeneity was observed. We used Galbraith plot to explore the sources of heterogeneity. We found that I^2 value was decreased after excluding the outliers. The results suggested that the two outlying studies might be the major source of the heterogeneity. However, heterogeneity did not seem to influence the results, because the significance of the result was not altered after excluding the outliers. Additionally, funnel plots and Egger's tests were used to find potential publication bias. The results indicated that there was no significant publication bias.

This meta-analysis has limitations that must be acknowledged. First, the numbers of published studies were not sufficient for a comprehensive analysis, particularly for smoker. Second, lacking of the original data of the eligible studies limited the evaluation of the effects of the gene-obesity interactions in thyroid cancer.

In summary, this meta-analysis suggested that obesity was associated with the risk of thyroid

cancer. However, large and well-designed studies are warranted to validate our findings.

Disclosure of conflict of interest

None.

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