

A pooled analysis of thyroid cancer studies. V. Anthropometric factors

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Summary

Objective: To assess the relation between anthropometric factors and thyroid cancer risk in a pooled analysis of individual data from 12 case-control studies conducted in the US, Japan, China and Europe.

Methods: 2056 female and 417 male cases, 3358 female and 965 male controls were considered. Odds ratios (OR) were derived from logistic regression, conditioning on age, A-bomb exposure (Japan) and study, and adjusting for radiotherapy.

Results: Compared to the lowest tertile of height, the pooled OR was 1.2 for females for the highest one, and 1.5 for males, and trends in risk were significant. With reference to weight at diagnosis, the OR for females was 1.2 for the highest tertile, and the trend in risk was significant, whereas no association was observed in males. Body mass index (BMI) at diagnosis was directly related to thyroid cancer risk in females (OR = 1.2 for the highest tertile), but not in males. No consistent pattern of risk emerged with BMI during the late teens. Most of the associations were observed both for papillary and follicular cancers, and in all age groups. However, significant heterogeneity was observed across studies.

Conclusions: Height and weight at diagnosis are moderately related to thyroid cancer risk.

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Introduction

Thyroid hormones are relevant to the growth and development of several body tissues, and anthropometric factors are affected by thyroid disorders, such as hypothyroidism and thyrotoxicosis. Although dietary

and nutritional correlates of thyroid cancer are still poorly defined, there are suggestions that a diet poor in vegetables, but rich in meat and starches, is associated with an increased risk [1, 2].

An increased risk of thyroid cancer among women with higher body mass index (BMI) and who reported weight gain has also been suggested. Ron *et al.*, in a study from Connecticut [1], reported a relative risk (RR) of 1.5 for women (but not men) in the highest BMI quartile at age 18 and in adult life. Goodman *et al.*, in a study of 51 men and 140 women from Hawaii [3], reported an RR of about 4.0 for men and 2.0 for women in the highest quartile of weight or BMI, and a significant direct association with weight in women. In that study, height also was directly related to thyroid cancer risk in men. In a case-control study of 207 women in Shanghai, China [4], the RR was 2.3 for the highest weight level, and 2.0 for the highest level of weight gain; both estimates were significant.

Because the number of cases in each study was small, and results were not always consistent, we decided to conduct a pooled analysis of original data from 12 case-control studies of thyroid cancer, to systematically consider the relation between anthropometric factors and thyroid cancer risk.

Methods

Fourteen studies were identified through MEDLINE searches or personal knowledge of the authors. A detailed description of the studies included in this pooled analysis is provided in a separate paper [5].

Four studies were conducted in the United States, including one in Los Angeles [6], one in western Washington [7], one in Hawaii [8], and one in Connecticut [1]. Two were conducted in Asia, one in Hiroshima and Nagasaki, Japan (Mabuchi, personal communication), and the other in Shanghai, China [4]. Of the eight European studies, five were conducted in Scandinavian countries (three in Sweden [9–12] and two in Norway [9, 10, 13]). The remaining three were from Northern Italy [14], the Swiss canton of Vaud [15], and Athens, Greece [16]. The studies from Uppsala, Sweden and Tromsø, Norway [9, 10] did not collect information on anthropometric factors and, therefore, are not included in the present analysis. The distribution of cases and controls of the remaining 12 studies by sex is given in Table 1.

Cases were 2056 women and 417 men with cancer of the thyroid; most (78%) had papillary carcinomas (1630

women and 304 men). Other histologic types included follicular (14%), medullary (2%), anaplastic carcinomas (0.6%), and cancers with undefined histology (4%). Controls were 3358 females and 965 males (Table 1). The median ages for cases and controls were 42 and 43 years, respectively, among females, and 48 and 45 years among males, but the age ranges varied across studies (Table 1).

The original datasets were restructured according to a predefined format. The variables considered in the present analysis were: reported height, weight, and BMI (kg/m^2) at diagnosis (or pseudodiagnosis for controls) and during the late teens, *i.e.* between ages 17 and 20 years. Information on anthropometric factors at interview was collected in studies from Sweden and Norway. Information for ages 17–20 was not available for western Washington, Norway and the three southern European studies. Data included in the present analysis may differ somewhat from published ones because definitions of variables or selection of matching criteria were modified to maintain uniformity across studies. Since there were large differences in the distribution of the variables considered among the study populations, we computed study-specific tertiles.

Odds ratios (OR) were computed for each study using conditional logistic regression [17, 18]. For individually matched studies, where age was one of the matching variables, the original matching was used to define strata, while quinquennia of age were used for other studies. In the Japanese study, cases and controls were also matched on A-bomb exposure and radiation dose. For Hawaii, the model was conditioned also on ethnicity. To account for possible imbalances in the age distribution of cases and controls within the 5-year age categories used for matching, three additional continuous terms for age were included in the logistic models. After individual study analyses were completed, the studies were pooled, and conditional logistic regression was used to estimate pooled ORs, conditioning also on study. All models were adjusted for history of radiotherapy.

For females, analyses were also conducted in separate strata of histologic type (papillary and follicular), geographical area (US, Asia, Europe-North, Europe-South), and age (≤ 35 ; 36–55, and ≥ 56 years).

To test for heterogeneity among studies, geographical areas (US, Asia, Scandinavia and southern Europe), and age categories (≤ 35 ; 36–55, ≥ 56 years), we compared the difference between the likelihood of the model estimating a common OR and that estimating a specific OR for each group to the chi-square distribution with

Table 1. Age range and number of thyroid cancer cases and controls by study and gender

Study and location	Age range (years)	Females thyroid cancer cases			Males thyroid cancer cases		
		All	(Papillary)	Controls	All	(Papillary)	Controls
<i>America - USA</i>							
1. Los Angeles [6]	15-55	292	(243)	292	-	-	-
2. Western Washington [7]	18-80	185	(129)	393	-	-	-
3. Hawaii [8]	16-80	140	(115)	328	51	(47)	113
4. Connecticut [1]	20-76	109	(88)	208	50	(35)	76
<i>Asia</i>							
5. Hiroshima and Nagasaki, Japan (Mabuchi, personal communication)	23-74	307	(284)	307	58	(51)	58
6. Shanghai, China [4]	18-54	207	(173)	207	-	-	-
<i>Europe - North</i>							
7. Southeastern Sweden [12]	21-60	149	(117)	187	26	(16)	200
8. Northern Sweden [11]	22-71	123	(93)	240	48	(34)	85
9. Norway, NHHS [13]	11-64	71	(45)	355	21	(17)	105
<i>Europe - South</i>							
10. Northern Italy [14]	16-72	291	(210)	427	108	(64)	190
11. Vaud, Switzerland [15]	12-72	100	(75)	318	23	(19)	94
12. Athens, Greece [16]	14-88	82	(58)	96	32	(21)	44
<i>Total</i>		2056	(1630)	3358	417	(304)	965

degrees of freedom given by the number of groups minus one.

Graphs are presented displaying the ORs for height, weight and BMI at diagnosis/interview. A square, in which the center projection on the underlying scale corresponded to the estimated OR, was plotted for each study. The size of the square was proportional to the inverse of the variance of the estimated logarithm of the OR [19].

Results

Table 2 considers the relation between selected anthropometric factors and thyroid cancer risk in various studies, together with their overall pooled estimates. Among females, the ORs for height were above unity in the highest tertile in all studies except for those conducted in Italy and Switzerland, although the point estimate was significant only in the northern Swedish study. Compared to the lowest tertile of height, the overall pooled ORs for females were 1.1 (95% CI 0.9-1.2) for the intermediate, and 1.2 (95% CI 1.0-1.4) for the highest tertile. Corresponding ORs for males were 1.2 (95% CI 0.9-1.7) and 1.5 (95% CI 1.1-2.1), and the trends in risk were significant in both sexes (Table 2). Figure 1 shows the continuous estimate per 5 cm of height. The pooled estimate (for

females and males combined) was 1.08 (95% CI 1.03-1.13).

With reference to weight at diagnosis, the ORs for the highest tertile in females were above unity in nine out of 12 studies, and the pooled ORs were 1.0 (95% CI 0.9-1.2) for the intermediate and 1.2 (95% CI 1.0-1.4) for the highest tertile, as compared with the lowest one. Corresponding figures were 1.1 (95% CI 0.9-1.3) and 1.3 (95% CI 1.1-1.5) after excluding the three Nordic studies, where information on weight was related to date of interview rather than of diagnosis. The trend in risk was significant in females, whereas no association was observed in males (ORs 0.8 and 1.0 for the intermediate and highest tertiles, Table 2). The continuous estimate for each study per 5 kg of weight is shown in Figure 2. The overall pooled estimate was 1.04 (95% CI 1.02-1.07).

Reported body mass index at diagnosis also was directly related to thyroid cancer risk in most studies for females. The pooled ORs were 1.0 for the intermediate and 1.2 (95% CI 1.0-1.4) for the highest tertile. Corresponding figures were 1.1 (95% CI 0.9-1.3) and 1.3 (95% CI 1.1-1.5) after excluding the three Nordic studies. Similar to our weight finding, no consistent association was observed in males (ORs 0.8 and 1.0 in subsequent tertiles). Figure 3 gives the continuous ORs per 5 units of BMI. The pooled estimate was 1.07 (95% CI 0.99-1.15). Body mass index between the ages 17 and 20 years was not clearly associated with thyroid cancer

Table 2. Odds ratios and corresponding 95% confidence intervals (CI)¹ of thyroid cancer by level of selected anthropometric measures

Study and location	Height		Weight		Body mass index at diagnosis/pseudodiagnosis		Body mass index at age 17-20	
	Intermediate	High	Intermediate	High	Intermediate	High	Intermediate	High
Females								
<i>America - USA</i>								
1. Los Angeles	0.9 (0.6-1.5)	1.1 (0.7-1.7)	1.1 (0.7-1.7)	1.0 (0.6-1.7)	1.3 (0.8-2.0)	1.0 (0.6-1.6)	1.2 (0.8-1.8)	1.0 (0.7-1.6)
2. Western Washington	1.2 (0.7-2.1)	1.4 (0.8-2.3)	1.7 (1.0-2.9)	2.3 (1.4-4.0)	1.1 (0.7-1.9)	2.2 (1.4-3.6)	n.a.	
3. Hawaii	1.0 (0.6-1.8)	1.4 (0.8-2.6)	1.6 (0.9-2.9)	2.2 (1.2-4.1)	1.4 (0.8-2.4)	2.0 (1.1-3.5)	1.0 (0.6-1.7)	1.1 (0.6-1.9)
4. Connecticut	1.5 (0.8-3.0)	1.7 (0.9-3.1)	1.1 (0.6-2.1)	1.5 (0.8-2.8)	0.8 (0.5-1.5)	0.9 (0.5-1.6)	0.7 (0.4-1.3)	1.2 (0.7-2.1)
<i>Asia</i>								
5. Japan	1.3 (0.8-2.0)	1.6 (1.0-2.5)	1.1 (0.7-1.6)	1.2 (0.8-1.7)	1.1 (0.7-1.7)	1.1 (0.7-1.7)	1.7 (1.1-2.6)	1.1 (0.7-1.7)
6. Shanghai, China	0.9 (0.5-1.5)	1.2 (0.7-1.9)	0.6 (0.4-1.1)	1.0 (0.6-1.6)	0.6 (0.4-1.0)	0.8 (0.5-1.3)	0.5 (0.3-0.9)	1.0 (0.6-1.5)
<i>Europe - North</i>								
7. Southeastern Sweden	1.4 (0.7-2.5)	1.6 (0.9-2.9)	0.8 (0.4-1.4)	1.2 (0.7-2.2)	0.6 (0.4-1.1)	1.2 (0.7-2.0)	1.4 (0.8-2.5)	1.1 (0.6-2.0)
8. Northern Sweden	1.5 (0.8-2.8)	1.9 (1.0-3.4)	0.8 (0.4-1.4)	1.0 (0.6-1.8)	0.8 (0.5-1.4)	0.7 (0.4-1.3)	0.9 (0.5-1.6)	0.9 (0.5-1.6)
9. Norway	1.0 (0.5-2.0)	1.4 (0.7-2.7)	1.2 (0.7-2.3)	0.8 (0.4-1.6)	1.1 (0.6-2.0)	0.8 (0.4-1.6)	n.a.	
<i>Europe - South</i>								
10. Northern Italy	0.9 (0.6-1.4)	0.7 (0.5-1.1)	1.0 (0.7-1.4)	0.8 (0.6-1.2)	1.2 (0.8-1.7)	1.0 (0.7-1.6)	n.a.	
11. Vaud, Switzerland	0.7 (0.4-1.2)	0.9 (0.5-1.5)	1.2 (0.7-2.1)	1.1 (0.6-2.1)	1.1 (0.6-1.9)	1.3 (0.7-2.3)	n.a.	
12. Greece	1.4 (0.5-3.6)	1.8 (0.7-4.4)	1.0 (0.4-2.8)	2.0 (0.8-4.8)	1.0 (0.4-2.8)	2.2 (0.9-5.5)	n.a.	
<i>Total</i>	1.1 (0.9-1.2) $\chi^2_{trend} = 6.88$	1.2 (1.0-1.4) $p = 0.01$	1.0 (0.9-1.2) $\chi^2_{trend} = 6.84$	1.2 (1.0-1.4) $p = 0.01$	1.0 (0.9-1.2) $\chi^2_{trend} = 4.44$	1.2 (1.0-1.4) $p = 0.04$	1.1 (0.9-1.8) $\chi^2_{trend} = 0.64$	1.1 (0.9-1.3) $p = 0.42$
Males								
<i>Total</i>	1.2 (0.9-1.7) $\chi^2_{trend} = 5.28$	1.5 (1.1-2.1) $p = 0.02$	0.8 (0.6-1.1) $\chi^2_{trend} = 0.06$	1.0 (0.8-1.4) $p = 0.80$	0.8 (0.6-1.1) $\chi^2_{trend} = 0.13$	1.0 (0.8-1.4) $p = 0.71$	0.9 (0.6-1.5) $\chi^2_{trend} = 1.95$	1.4 (0.9-2.1) $p = 0.16$

n.a. = Not available.

¹ Estimates from conditional-logistic regression, conditioned on age, and adjusted for age and history of radiation.

risk for either females or males: the ORs for the intermediate and highest tertiles were 1.1 and 1.1, respectively, for females, and 0.9 and 1.4 for males (Table 2).

When height and weight at diagnosis for females in separate strata of histology, geographic area and age were considered, no particular subgroup had a striking finding. However, height was not directly associated with thyroid cancer risk in the southern European

studies or hospital-based case-control studies. With respect to weight, investigations from the United States showed the clearest direct relation.

Likewise, with reference to BMI at diagnosis and between the ages 17 and 20, no appreciable heterogeneity was evident, although most ORs for females were moderately above unity for the highest tertile of BMI at diagnosis, whereas no consistent pattern of risk was observed for BMI between ages 17 and 20 years.

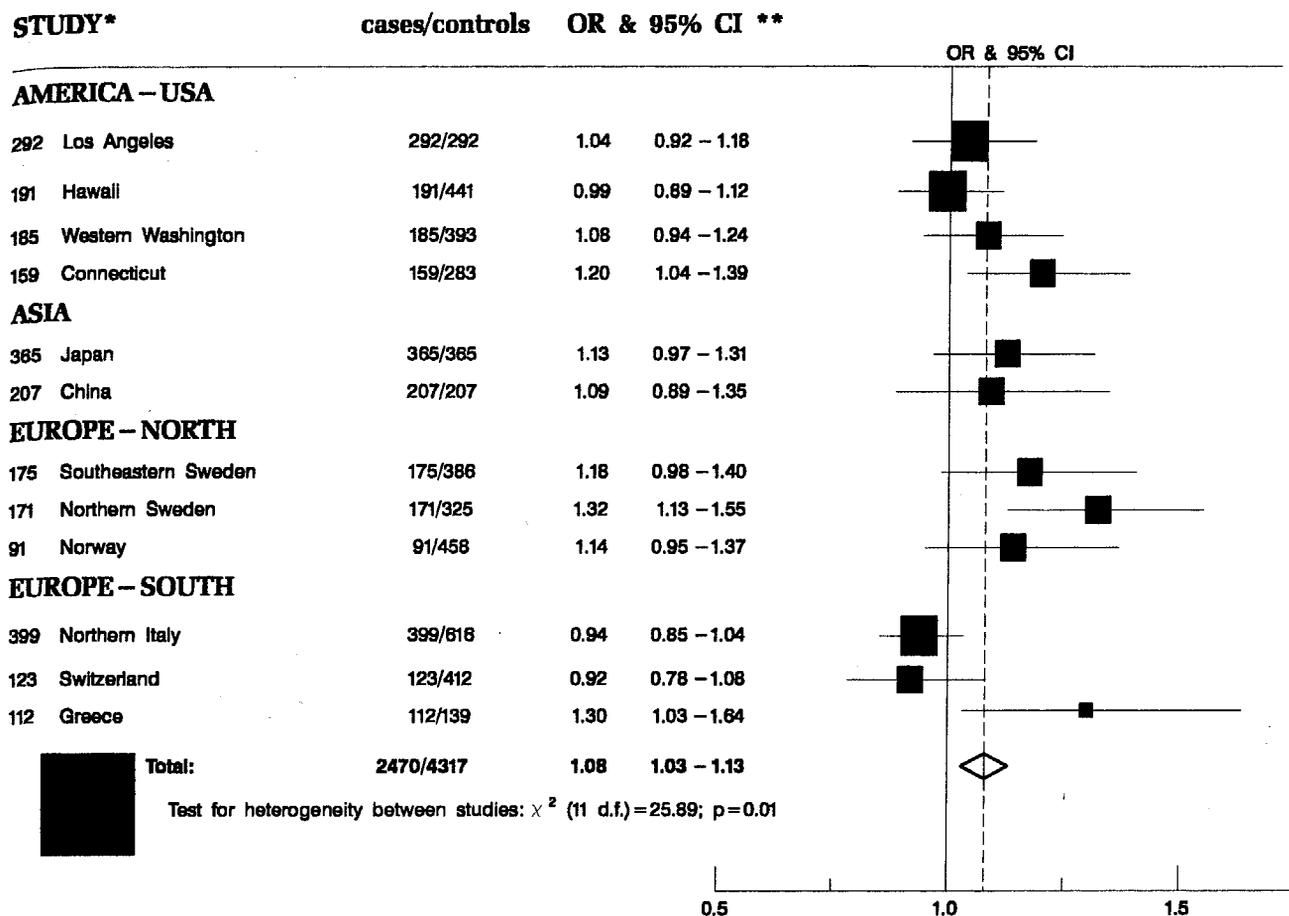


Fig. 1. Odds ratios of thyroid cancer by height. *Studies in each group sorted by number of cases. **Unit for continuous coefficient: 5 centimeters. Conditioned on sex, study, and age and adjusted for age, and history of radiation.

Discussion

This pooled analysis of individual data from 12 case-control studies conducted in eight countries suggests that height is moderately related to thyroid cancer risk in both sexes. Weight, as well as BMI at the time of diagnosis, was associated with a small increased thyroid cancer risk in women only, although the findings were not consistent across studies. These results were based on over 2000 female cases, and were statistically significant. The lack of association with weight and BMI in men may be due to the considerably smaller sample size. Furthermore, the strength of the associations was moderate and, although the ORs were above unity in most studies, significant heterogeneity across studies was observed, which indicates the need for cautious interpretation of these findings. In particular, for weight and BMI in women, the moderate positive association was largely

due to the results from the studies from Hawaii [3] and western Washington [7].

Various measures of body mass have been proposed [20], and there is still debate about the reliability and validity of information on self-reported weight and height [21]. We adopted the standard Quetelet's index, chiefly to facilitate comparison with previous work. A possible source of bias is the misclassification of self-reported information: self-reported measures tend to underestimate weight, particularly in women, and to overestimate height, particularly in men [21-23]. Although such information bias is likely to be similar for cases and controls, this may lead to biased estimates of ORs [24]. Moreover, differential misclassification of weight may occur, (a) if cases' reports of current weight are more accurate, and (b) if cases have lost or gained weight because of their diseases or of selected disorders, including benign thyroid disease. Allowance for benign thyroid diseases, however, did not materially modify the

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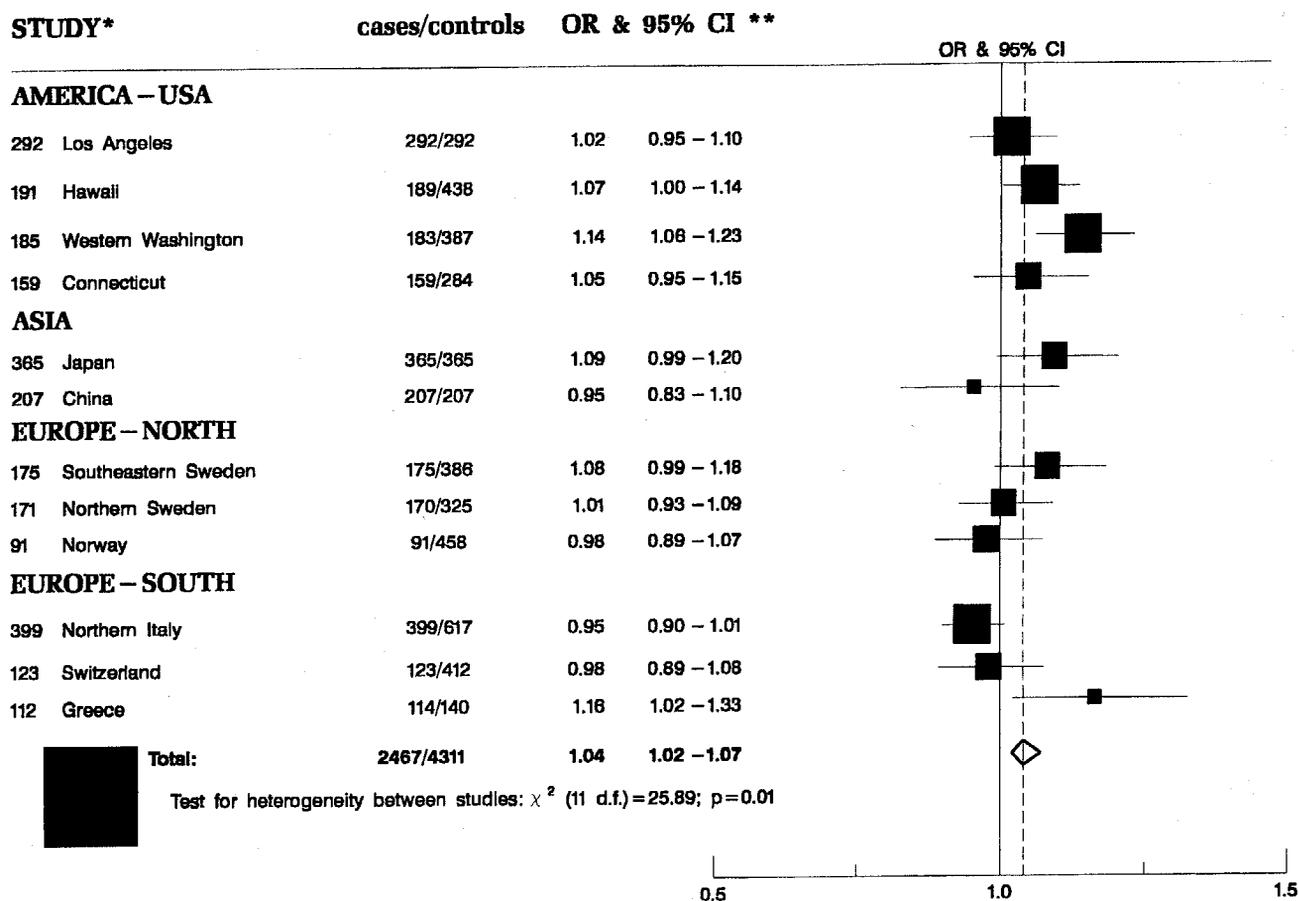


Fig. 2. Odds ratios of thyroid cancer by weight at diagnosis. * Studies in each group sorted by number of cases. ** Unit for continuous coefficient: 5 kilograms. Conditioned on sex, study, and age and adjusted for age, and history of radiation.

association observed. Another potential confounder is physical activity, but information on this variable was unavailable in most studies considered, and any potential relation between physical activity and thyroid cancer risk remains unclear.

Thus, although this pooled analysis includes most data on thyroid cancer worldwide, the issue of the relation between anthropometric factors and thyroid cancer remains unsettled. If such an association exists, it could be related to a potential association between thyroid tumors and steroid hormones or other endocrine factors. In fact, overweight is related to increased estrogen levels in postmenopausal women [25], and exogenous estrogens are weakly related to increased thyroid cancer risk [5, 26].

In our pooled analysis, however, the association with weight or BMI was of similar magnitude in older postmenopausal women and in younger ones. Some association with weight or BMI may be due to more

frequent examination of the thyroid gland in overweight young women, particularly in the United States. In this dataset we did find a diagnosis of hypothyroidism to be more prevalent among women in the United States than in the other study areas.

Height is strongly related to ethnic group. In countries where cancer risk varies from one region to another, the effect of height may thus be confounded by variation in height across regional populations. The association with height in both sexes may indicate a potential influence of some growth hormone or factor [27], but the potential role of growth factors on thyroid carcinogenesis is still undefined. Height and body size are linked to the number of cells, which may be a relevant correlate of cancer risk [28]. Dietary factors in childhood and adolescence may also play a role, and a diet rich in meat and other sources of proteins, which may be a correlate of adult height, has been related to increased thyroid cancer risk in southern Europe [2].

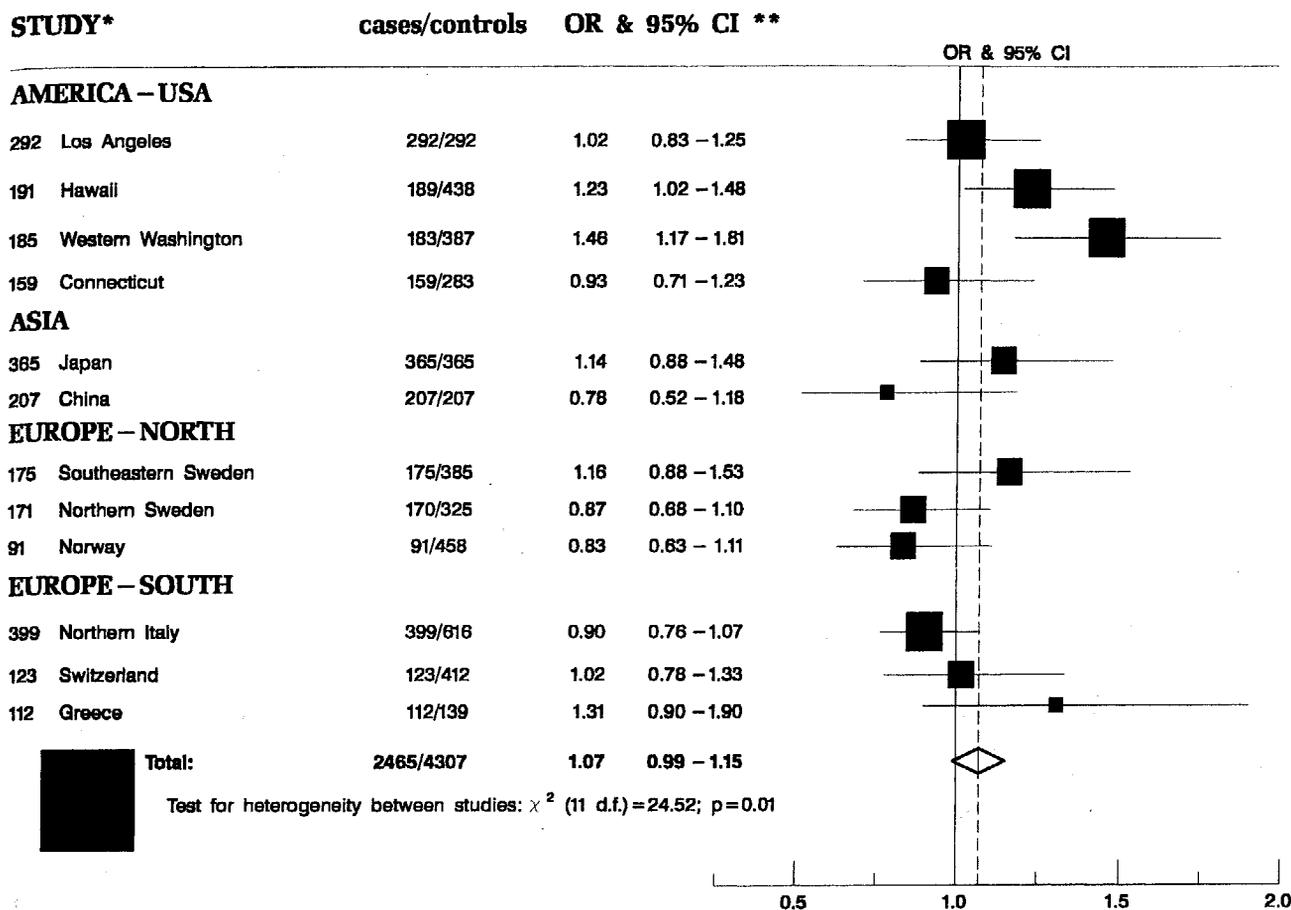


Fig. 3. Odds ratios of thyroid cancer by body mass index at diagnosis. * Studies in each group sorted by number of cases. ** Unit for continuous coefficient: 5 units. Conditioned on sex, study, and age and adjusted for age, and history of radiation.

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