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A pooled analysis of case–control studies of thyroid cancer. VII. Cruciferous and other vegetables (International)

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Abstract

Objective: To investigate the association between cruciferous and other vegetables and thyroid cancer risk we systematically reanalyzed the original data from 11 case–control studies conducted in the US, Asia, and Europe.

Methods: A total of 2241 cases (1784 women, 457 men) and 3716 controls (2744 women, 972 men) were included. Odds ratios (OR) and the corresponding 95% confidence intervals (CI) were estimated for each study by logistic regression models, conditioned on age and sex, and adjusted for history of goiter, thyroid nodules or adenomas, and radiation. Summary ORs for all studies combined were computed as the weighted average of the estimates from each study.

Results: A decreased risk for the highest level of cruciferous vegetable intake, as compared to the lowest, was observed in Los Angeles, Hawaii, Connecticut, southeastern Sweden, Tromsø, and Switzerland; the OR were above unity in Japan and Uppsala, whereas no material association was found in northern Sweden, Italy, or Greece. The OR values for all studies combined were 0.87 (95% CI 0.75–1.01) for moderate and 0.94 (95% CI 0.80–1.10) for high cruciferous vegetables intake. The results were similar in studies from iodine-rich areas and endemic goiter areas, and were consistent when the analysis was restricted to papillary carcinomas and women. The summary OR values for vegetables other than cruciferous were 1.04 (0.88–1.22) for moderate and 0.82 (0.69–0.98) for high consumption.

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Conclusions: This combined analysis indicates that cruciferous vegetables are not positively related to thyroid cancer risk. Their effect does not seem to be substantially different from that of other vegetables, which appear to be protective on this cancer.

Introduction

A history of goiter increases the risk of thyroid cancer [1], and rates of thyroid cancer are high in some mountainous areas characterized by endemic goiter, such as the Alps, Himalayas, and Andes [2, 3]. Iodine deficiency appears to cause goiter, and has been associated with enhanced risk of follicular and possibly anaplastic thyroid cancer, while excess iodine intake has been related to an increase in papillary thyroid cancer [4, 5].

Besides iodine itself, some other aspects of diet have been related to thyroid cancer risk, including fish [6] and cruciferous vegetables. These vegetables, in particular, contain thioglucosides, which may be degraded to form goitrogens and induce thyroid tumors in laboratory animals [7, 8]. This has led to the hypothesis that cruciferous vegetables may increase the risk of thyroid cancer in humans.

However, epidemiologic studies give only limited support to this hypothesis. A population-based case–control study of thyroid cancer conducted in Connecticut on 159 cases and 285 controls found an odds ratio (OR) of 0.77 for consumption of cruciferous vegetables a few times per week or daily, compared to a few times per year or never [9]. In a case–control study on 191 cases of thyroid cancer and 441 controls from five ethnic groups in Hawaii, the OR for the highest quartile of consumption of cruciferous vegetables was 1.0 in males and 0.6 in females [10]. In a pooled analysis of four studies conducted in Italy and Switzerland on 385 cases of thyroid cancer and 798 hospital controls the OR was 0.8 for the highest tertile of cabbage and other cruciferae consumption [11]. A case–control study conducted in southeastern Sweden on 104 cases of papillary thyroid cancer and 387 population controls found a significantly increased risk (OR = 4.3) of papillary thyroid cancer for those who ate cruciferous vegetables seldom or never, compared to those who ate them several times a week [12]. In a study from northern Sweden, based on 180 thyroid cancer cases and 360 controls, the OR was around 1.0 for consumption of cabbages several times per week, as compared to less than once per week [13]. The OR of thyroid cancer associated with a consumption of more than six portions of cruciferous vegetables per month, compared to less than three, was 0.9 in a population-based case–control study conducted in two areas of Sweden and Norway on 246 cases of thyroid cancer and 440 controls [14].

Since thyroid cancer is a rare disease, single studies were based on a relatively small number of cases, and were consequently subject to considerable random variation, and inadequate to look at specific subgroups. We therefore decided to investigate the association between cruciferous or other vegetables and thyroid cancer risk using data from a pooled analysis of case–control studies on thyroid carcinogenesis [15].

Methods

The pooled analysis included 14 studies on thyroid cancer identified through Medline searches, and published between 1980 and 1997, or found through personal knowledge of the authors. A detailed description of the studies has been given in a separate paper [15]. Briefly, four studies were conducted in the US, including one in Los Angeles [16], one in Western Washington [17], one in Hawaii [10], and one in Connecticut [9]. Two were conducted in Asia, one in Hiroshima and Nagasaki, Japan (Mabuchi, personal communication), and the other in Shanghai, China [18]. Five of the eight European studies were conducted in Scandinavian countries, three in Sweden [12–14, 19] and two in Norway [14, 19, 20], and the remaining three in northern Italy [21], the Swiss canton of Vaud [22], and Athens, Greece [23]. The studies from Western Washington [17], China [18] and one of those from Norway [20] were not considered in the present analysis, since they had no information on vegetable consumption.

Eleven studies thus contributed to this analysis, including a total of 2241 cases (1784 women, 457 men) and 3716 controls (2744 women, 972 men). About 79.7% of the cancers were papillary, whereas the others were follicular (13.3%), medullary (2.6%), anaplastic (0.7%), and a few of undefined histology (3.7%).

The original data were collected and recoded according to a uniform format, and analyzed in a standardized way. In this combined analysis cruciferous vegetables (including cabbages, broccoli, Brussels sprouts, cauliflowers, etc.) and other vegetables were considered and analyzed separately. Different information on vegetable intake was provided by each study. For cruciferous vegetables there was one item for turnip and rutabaga only in Los Angeles; one summary item for total intake in southeastern Sweden, northern Sweden, Italy and Switzerland; whereas a few separate items for various cruciferous vegetables were collected in Connecticut (three), Japan (four), Uppsala (three), Tromsø (three), and Greece (two). For Hawaii the dietary questionnaire was much more extensive than those used in the other studies, and information on different cruciferous vegetables was collected. These were analyzed into four broad categories, *i.e*. broccoli, cabbages, Chinese cabbages, and one group for all other cruciferous vegetables less frequently consumed (including cauliflowers, Brussels sprouts, turnips, rutabagas, mustard cabbages, and Swiss chards). For vegetables other than cruciferous there was one summary item for total intake in southeastern and northern Sweden, and a number of separate items for various vegetables in Hawaii (23), Japan (11), Uppsala (three), Tromsø (three), Italy (five), Switzerland (six), and Greece (14). Los Angeles and Connecticut did not provide any information on vegetables other than cruciferous.

Summary items for total cruciferous and other vegetable intake were obtained summing up the frequency of consumption of each separate item in the two groups of vegetables. Since we were mainly interested in cruciferous vegetables, for vegetables other than cruciferous we presented only the summary results.

The original frequency of intake of each item was expressed in times per week or per month in Hawaii, Italy, Switzerland, and Greece, whereas in the other studies it was expressed into a few precoded categories. In our analysis vegetable consumption was categorized into three levels, corresponding as far as possible to study-specific marginal tertiles. Since intakes within each study tended to be given in a limited number of discrete categories, no definition of a continuous term was possible.

Odds ratios (OR) and the corresponding 95% confidence intervals (CI) were estimated for each study by conditional logistic regression models [24], using the original matching sets for matched studies, and stratifying by sex and quinquennia of age for unmatched ones. For Hawaii the model was conditioned also on ethnic group. In all studies the ORs were adjusted for history of goiter, thyroid nodules, and adenomas; and history of radiation. The result of the present analysis may differ somewhat from those already published because of different variable definitions and statistical models used to maintain uniformity across studies.

Summary OR were computed as the weighted average of the estimates from each study, using weights proportional to the inverse of the variance of the estimate [25]. The degree of heterogeneity between studies was quantified, using a chi-square test with degree of freedom equal to the number of studies minus one [25]. Heterogeneity was also evaluated in relation to the residence in endemic goiter areas, and the level of detail of the questionnaires, in order to investigate whether these variables explained, at least in part, the difference between studies. Graphs are presented displaying for each study the OR and the corresponding 95% CI for the highest level of intake of total cruciferous and other vegetables, as compared to the lowest one. The OR are represented as black squares, whose size is inversely related to the variance of each estimate. A diamond is used to plot the summary OR, whose center represents the OR and the extremes show the 95% CI.

Results

Table 1 shows the association between total cruciferous vegetables and thyroid cancer risk, by study. A decreased risk for the highest level of intake, as compared to the lowest one, was observed in Hawaii, Connecticut, southeastern Sweden, Tromsø, and Switzerland (OR between 0.50 and 0.80), whereas the risks were above unity in Japan and Uppsala (OR = 1.56 and 1.65, respectively). The OR were around unity for northern Sweden, Italy, and Greece (sign test, $p = 0.23$). Most of the estimates – and the corresponding tests for linear trend – were, however, not significant, with the exception of the inverse association in Connecticut and the positive one in Japan. The OR for the highest versus the lowest level of total cruciferous consumption in each study (with the exception of Los Angeles, which provided information for turnip/rutabaga only), and the corresponding 95% CI, are also shown in Figure 1.

The results for various cruciferous vegetables are presented in Table 2. The general pattern was similar to that of total cruciferous vegetables, and most of these items did not show strong or significant associations with thyroid cancer risk. A significant inverse relation was observed only for broccoli in Hawaii, and cabbage and broccoli in Connecticut, whereas a direct one was found for cabbage in Japan.

Table 3 gives the OR for all studies combined (again with the exception of Los Angeles) according to total cruciferous vegetable consumption. These were 0.87 (95% CI 0.75–1.01) for moderate and 0.94 (95% CI 0.80–1.10) for high level of intake. A significant heterogeneity between studies ($p = 0.02$) was found for the highest level of consumption, largely due to the estimates from Japan. The summary OR with the exclusion

Table 1. Odds ratios[a] (OR) of thyroid cancer and corresponding 95% confidence intervals (CI) according to the intake of cruciferous vegetables, by study

Study	Level of consumption			χ^2 trend (*p*-value)
	Low	Moderate	High	
America – USA				
Los Angeles[b]				
Upper cutpoint	Never	Sometimes/year		
Ca:Co	243:225	27:42	15:20	
OR (95% CI)	1[c]	0.45 (0.22–0.89)	0.69 (0.31–1.51)	3.25 (0.07)
Hawaii[d]				
Upper cutpoint	1.7/week	4.0/week		
Ca:Co	75:135	65:147	51:159	
OR (95% CI)	1[c]	0.91 (0.58–1.43)	0.67 (0.42–1.07)	2.85 (0.09)
Connecticut				
Upper cutpoint	<1/month	<1/week		
Ca:Co	68:91	44:80	47:113	
OR (95% CI)	1[c]	0.66 (0.38–1.14)	0.49 (0.29–0.84)	6.90 (0.009)
Asia				
Japan				
Upper cutpoint	6/week	8.5/week		
Ca:Co	90:102	118:140	157:123	
OR (95% CI)	1[c]	0.97 (0.64–1.48)	1.56 (1.07–2.31)	5.59 (0.02)
Europe – North				
Southeastern Sweden[e]				
Upper cutpoint	Sometimes/month	Sometimes/week		
Ca:Co	59:111	65:159	47:104	
OR (95% CI)	1[c]	0.66 (0.41–1.06)	0.75 (0.45–1.26)	1.26 (0.26)
Uppsala, Sweden				
Upper cutpoint	<2/month	<6/month		
Ca:Co	35:68	63:93	69:91	
OR (95% CI)	1[c]	1.26 (0.70–2.26)	1.65 (0.95–2.88)	3.32 (0.07)
Northern Sweden[e]				
Upper cutpoint	Sometimes/month	Sometimes/week		
Ca:Co	54:100	70:144	47:80	
OR (95% CI)	1[c]	0.95 (0.61–1.49)	1.14 (0.69–1.88)	0.23 (0.63)
Tromsø, Norway				
Upper cutpoint	<4/month	<8/month		
Ca:Co	25:49	24:69	23:55	
OR (95% CI)	1[c]	0.70 (0.34–1.44)	0.84 (0.40–1.78)	0.20 (0.66)
Europe – South				
Italy[e]				
Upper cutpoint	<1/week	1/week		
Ca:Co	174:262	122:193	103:162	
OR (95% CI)	1[c]	0.94 (0.68–1.28)	0.91 (0.65–1.26)	0.37 (0.54)
Vaud, Switzerland[e]				
Upper cutpoint	<1/week	1/week		
Ca:Co	33:71	60:238	30:103	
OR (95% CI)	1[c]	0.59 (0.34–1.05)	0.68 (0.35–1.30)	1.19 (0.28)
Athens, Greece				
Upper cutpoint	1/month	3/month		
Ca:Co	41:58	37:45	29:37	
OR (95% CI)	1[c]	1.14 (0.58–2.22)	0.94 (0.47–1.89)	0.02 (0.89)

[a] Estimates from conditional logistic regression models, conditioned on age and sex, and adjusted for history of goiter, thyroid nodules and adenomas, and history of radiation.
[b] Information on turnip and rutabaga only.
[c] Reference category.
[d] Conditioned also on ethnicity.
[e] Information based on a single summary item.

Cruciferous vegetables

Study	Low Ca/Co	High Ca/Co	OR[a]	95% CI
Hawaii	75/135	51/159	0.67	0.42-1.07
Connecticut	68/91	47/113	0.49	0.29-0.84
Japan	90/102	157/123	1.56	1.05-2.31
Southeastern Sweden	59/111	47/104	0.75	0.45-1.26
Uppsala, Sweden	35/68	69/91	1.65	0.95-2.88
Northern Sweden	54/100	47/80	1.14	0.69-1.88
Tromsø, Norway	25/49	23/55	0.84	0.40-1.78
Italy	174/262	103/162	0.91	0.65-1.26
Switzerland	33/71	30/103	0.68	0.35-1.30
Greece	41/58	29/37	0.94	0.46-1.89
All studies[b]	654/1047	603/1027	0.94	0.80-1.10

Heterogeneity between studies: χ^2 (9df)=20.33; p=0.016

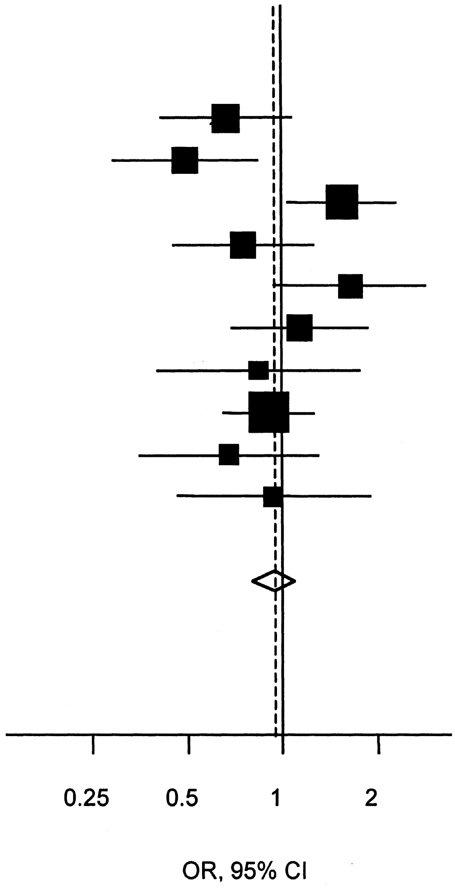

Fig. 1. Odds ratios (OR) of thyroid cancer and corresponding 95% confidence intervals (CI) for high *versus* low intake of cruciferous vegetables, by study and overall.

[a] Estimates from conditional logistic regression models, conditioned on age and sex, and adjusted for history of goiter, thyroid nodules, and adenomas, and history of radiation.

[b] Weighted mean of the OR from each study.

of Japan was 0.85 (95% CI 0.73–1.00) and 0.85 (95% CI 0.72–1.01), respectively for low and high intake, and no more heterogeneity between studies was found ($p = 0.55$ and 0.12, respectively).

The results were similar in studies conducted in iodine-rich areas (OR = 0.84 for moderate and OR = 0.90 for high intake) and in endemic goiter ones (OR = 0.88 and OR = 0.97). The pattern of risk was also consistent when the analysis was restricted to papillary carcinoma and to women: the combined OR of papillary thyroid cancer were 0.84 (95% CI 0.71–0.99) for moderate and 0.94 (95% CI 0.79–1.11) for high cruciferous consumption; the corresponding OR of thyroid cancer for women were 0.84 (95% CI 0.70–1.00) and 0.90 (95% CI 0.75–1.08).

Table 4 shows the association between vegetables other than goitrogenous and thyroid cancer risk, in each study. An inverse relation for other vegetable intake was observed in most of the studies; only in Japan and Uppsala was a positive association found (sign test, $p = 0.18$). The inverse associations and the linear trends for increasing consumption of vegetables were statistically significant in Hawaii and Italy only. The OR for all studies combined were 1.03 (95% CI 0.88–1.22) for moderate and 0.82 (95% CI 0.69–0.98) for high consumption (p for heterogeneity = 0.68 and 0.015, respectively for low and high consumption). The summary OR with the exclusion of Japan was 0.98 (95% CI 0.81–1.17) and 0.71 (95% CI 0.58–0.86), respectively for low and high intake (p for heterogeneity = 0.81 and 0.43, respectively).

The OR of thyroid cancer according to highest level of other vegetable consumption as compared to the lowest in each study are also shown in Figure 2.

Table 2. Odds ratios[a] (OR) of thyroid cancer and corresponding 95% confidence intervals (CI) according to the intake of various cruciferous vegetables, by study

Study and item	Level of consumption			χ^2 trend (*p*-value)
	Low	Moderate	High	
America – USA				
Hawaii[b]				
Broccoli				
Upper cutpoint	0.26/week	0.99/week		
Ca:Co	84:147	57:120	50:174	
OR (95% CI)	1[c]	0.86 (0.55–1.34)	0.57 (0.37–0.90)	5.83 (0.02)
Cabbages				
Upper cutpoint	0.29/week	0.99/week		
Ca:Co	73:141	45:129	73:171	
OR (95% CI)	1[c]	0.75 (0.46–1.22)	0.91 (0.58–1.42)	0.14 (0.70)
Chinese cabbages				
Upper cutpoint	0.11/week	0.73/week		
Ca:Co	64:149	72:137	55:155	
OR (95% CI)	1[c]	1.23 (0.78–1.94)	0.80 (0.49–1.31)	0.92 (0.34)
Other cruciferae[d]				
Upper cutpoint	0.28/week	0.99/week		
Ca:Co	89:162	46:118	56:161	
OR (95% CI)	1[c]	0.69 (0.43–1.10)	0.76 (0.49–1.19)	1.62 (0.20)
Connecticut				
Cabbages				
Upper cutpoint	Never	Sometimes/year		
Ca:Co	28:29	66:110	65:145	
OR (95% CI)	1[c]	0.63 (0.32–1.25)	0.44 (0.23–0.87)	6.00 (0.01)
Broccoli				
Upper cutpoint	Never	Sometimes/year		
Ca:Co	32:41	67:112	60:130	
OR (95% CI)	1[c]	0.60 (0.32–1.10)	0.44 (0.24–0.82)	6.48 (0.01)
Brussels sprouts				
Upper cutpoint	Never	Sometimes/year		
Ca:Co	69:106	62:111	28:67	
OR (95% CI)	1[c]	0.81 (0.49–1.33)	0.59 (0.32–1.09)	2.86 (0.09)
Asia				
Japan				
Cabbages				
Upper cutpoint	Once/week	2–4/week		
Ca:Co	27:31	222:246	116:88	
OR (95% CI)	1[c]	1.10 (0.62–1.97)	1.73 (0.92–3.25)	5.69 (0.02)
Broccoli				
Upper cutpoint	Once/month	2–3/month		
Ca:Co	123:135	78:77	162:152	
OR (95% CI)	1[c]	1.10 (0.71–1.69)	1.16 (0.81–1.66)	0.61 (0.43)
Radish/turnips				
Upper cutpoint	Once/week	2–4/week		
Ca:Co	57:69	256:251	52:45	
OR (95% CI)	1[c]	1.20 (0.79–1.82)	1.29 (0.74–2.28)	0.91 (0.34)
Mustard greens				
Upper cutpoint	Never			
Ca:Co	176:166	61:54		
OR (95% CI)	1[c]	1.00 (0.61–1.64)		
Europe – North				
Uppsala, Sweden				
Cabbages				
Upper cutpoint	<1/month	1–3/month		
Ca:Co	57:94	67:109	41:47	
OR (95% CI)	1[c]	1.01 (0.62–1.65)	1.69 (0.92–3.11)	2.21 (0.14)

Table 2. (Continued)

Study and item	Level of consumption			χ^2 trend (*p*-value)
	Low	Moderate	High	
Broccoli/Brussels sprouts				
Upper cutpoint	<1/month	1–3/month		
Ca:Co	97:141	56:79	9:20	
OR (95% CI)	1[c]	1.24 (0.78–1.96)	0.54 (0.21–1.38)	0.09 (0.77)
Cauliflowers				
Upper cutpoint	<1/month	1–3/month		
Ca:Co	73:126	82:101	10:22	
OR (95% CI)	1[c]	1.46 (0.94–2.26)	0.97 (0.42–2.23)	0.95 (0.33)
Tromsø, Norway				
Cabbages				
Upper cutpoint	<1/month	1–3/month		
Ca:Co	12:28	39:78	16:58	
OR (95% CI)	1[c]	1.01 (0.44–2.32)	0.56 (0.21–1.49)	1.81 (0.18)
Broccoli/Brussels sprouts				
Upper cutpoint	<1/month	1–3/month		
Ca:Co	18:67	20:50	5:15	
OR (95% CI)	1[c]	1.59 (0.72–3.51)	1.35 (0.30–6.01)	0.79 (0.37)
Cauliflowers				
Upper cutpoint	<1/month	1–3/month		
Ca:Co	18:44	32:88	15:23	
OR (95% CI)	1[c]	1.03 (0.48–2.21)	1.91 (0.68–5.38)	1.24 (0.27)
Europe – South				
Athens, Greece				
Broccoli				
Upper cutpoint	<1/month	1/month		
Ca:Co	68:96	27:23	11:18	
OR (95% CI)	1[c]	1.72 (0.85–3.48)	0.80 (0.31–2.01)	0.05 (0.82)
Cauliflowers				
Upper cutpoint	<1/month	1/month		
Ca:Co	14:21	45:48	48:71	
OR (95% CI)	1[c]	1.34 (0.57–3.16)	0.79 (0.34–1.86)	1.05 (0.31)

[a] Estimates from conditional logistic regression models, conditioned on age and sex, and adjusted for history of goiter, thyroid nodules and adenomas, and history of radiation.
[b] Conditioned also on ethnicity.
[c] Reference category.
[d] Including cauliflowers, Brussels sprouts, turnips, rutabagas, mustard cabbages, and Swiss chards.

None of the results was materially modified when cruciferous and other vegetables were simultaneously included in the same logistic models.

Discussion

It has been suggested that cruciferous plants increase thyroid cancer risk since they contain thioglucosides that may be degraded to form thiocyanates. These goitrogens can influence thyroid function, inhibiting iodine transport to the thyroid gland at low concentration, and the incorporation of iodine into thyroglobulin at high concentrations, thus increasing thyroid-stimulating hormone secretion [26]. Moreover, cruciferous vegetables induce thyroid carcinomas in animals [7, 8, 27].

High cabbage consumption has been suggested to play a role in the etiology of endemic goiter in central Europe, Finland, and in some Mediterranean islands such as Sicily and Krk [28, 29]. A Hawaiian survey on diet from different ethnic populations has also shown that cabbages and turnips were consumed more frequently by groups at highest risk of thyroid cancer [30].

However, the few epidemiologic studies that considered the association between cruciferous vegetables and thyroid cancer risk did not support the hypothesis of an increased risk [31, 32].

Table 3. Combined odds ratio[a] (OR) of thyroid cancer and corresponding 95% confidence interval (CI) according to the intake of cruciferous vegetables, in all studies and in strata of selected covariates

	Level of consumption		
	Low	Moderate	High
All studies[b]			
OR (95% CI)	1[c]	0.87 (0.75–1.01)	0.94 (0.80–1.10)
χ^2 heterogeneity between studies (9 d.f.)		7.18 ($p = 0.62$)	20.33 ($p = 0.02$)
Studies in iodine-rich areas[d]			
OR (95% CI)	1[c]	0.84 (0.65–1.08)	0.90 (0.70–1.15)
χ^2 heterogeneity between studies (3 d.f.)		1.56 ($p = 0.70$)	13.94 ($p = 0.003$)
Studies in endemic goiter areas[e]			
OR (95% CI)	1[c]	0.88 (0.73–1.07)	0.97 (0.79–1.18)
χ^2 heterogeneity between studies (5 d.f.)		5.53 ($p = 0.35$)	6.17 ($p = 0.29$)
χ^2 heterogeneity between areas (1 d.f.)		0.13 ($p = 0.72$)	0.25 ($p = 0.62$)
Papillary only			
OR (95% CI)	1[c]	0.84 (0.71–0.99)	0.94 (0.79–1.11)
χ^2 heterogeneity between studies (9 d.f.)		4.04 ($p = 0.91$)	15.94 ($p = 0.07$)
Women only			
OR (95% CI)	1[c]	0.84 (0.70–1.00)	0.90 (0.75–1.08)
χ^2 heterogeneity between studies (9 d.f.)		6.80 ($p = 0.66$)	15.90 ($p = 0.07$)

[a] Weighted mean of the OR from each study.
[b] Excluding Los Angeles.
[c] Reference category.
[d] Including Hawaii, Connecticut, Japan, and Tromsø.
[e] Including southeastern Sweden, northern Sweden, Uppsala, Italy, Switzerland, and Greece.

Besides goitrogenic substances, cruciferous vegetables contain a variety of constituents (such as flavones, phenols, isothyocyanates) known to inhibit carcinogenesis in animal models [33]. In particular they are rich in dithiolthiones and isothiocyanates, which have been shown to increase the activity of enzymes involved in the detoxification of carcinogens and other foreign compounds [34]. Many of these vegetables are also sources of carotenoids, including beta-carotene, and other antioxidant substances, which appear to be protective against certain other forms of cancer [34, 35]. Thus, if any unfavorable effect exists, this may be outweighed by the protective effects of other compounds in this class of vegetables.

The risk estimates for total goitrogenous vegetables were consistent in most studies considered. Only in Japan was a significant increased risk observed. This may, however, be due to the fact that in Japan vegetables are often pickled (highly salted). We had thus provided a pooled estimate excluding this study, which seems to be responsible for the heterogeneity observed. Moreover, no appreciable heterogeneity in the association between goitrogenous vegetables and thyroid cancer risk was observed between iodine-rich areas, such as Hawaii, Connecticut, and Japan, and endemic goiter areas, such as Italy, Switzerland, Sweden, and Greece, or with reference to different histologic types.

Vegetables other than cruciferous appear to have a consistent protective effect on thyroid cancer, in accordance with the results of other studies on thyroid carcinogenesis [11, 12], and the evidence of a beneficial effect of vegetables on several other cancers [34, 36]. Since consumption of cruciferous vegetables tends to be correlated to that of other vegetables, we included the two types of vegetables in the same model, to study the possible confounding effect; the estimates were, however, not materially modified.

This combined analysis had several strengths compared to previous studies. We used, as much as possible, a common coding for the variables of interest and the same multivariate models to estimate the odds ratios, including, besides age and sex, the best-recognized determinants of thyroid cancer, such as history of goiter, thyroid nodules, or adenomas, and history of radiation. This enabled us to evaluate the consistency of the results across studies conducted in various populations and using different methodologies. Moreover, our analysis allowed us to study the potential different effect

Table 4. Odds ratios[a] (OR) of thyroid cancer and corresponding 95% confidence intervals (CI) according to the intake of vegetables other than cruciferous, by study

Study and item	Level of consumption			χ^2 trend (*p*-value)
	Low	Moderate	High	
America – USA				
Hawaii[b]				
Upper cutpoint	12.0/week	21.4/week		
Ca:Co	75:136	65:144	51:161	
OR (95% CI)	1[c]	0.80 (0.52–1.26)	0.55 (0.35–0.88)	6.35 (0.01)
Asia				
Japan				
Upper cutpoint	22.5/week	32/week		
Ca:Co	98:118	134:126	133:121	
OR (95% CI)	1[c]	1.33 (0.90–1.97)	1.57 (1.05–2.35)	4.68 (0.03)
Europe – North				
Southeastern Sweden[d]				
Upper cutpoint	Sometimes/month	Sometimes/week		
Ca:Co	10:16	38:90	125:276	
OR (95% CI)	1[c]	0.58 (0.21–1.57)	0.47 (0.18–1.21)	2.48 (0.12)
Uppsala, Sweden				
Upper cutpoint	<16/month	< 28/month		
Ca:Co	61:91	55:90	52:72	
OR (95% CI)	1[c]	1.09 (0.66–1.80)	1.25 (0.72–2.16)	0.60 (0.44)
Northern Sweden[d]				
Upper cutpoint	Sometimes/month	Sometimes/week		
Ca:Co	14:22	64:103	93:200	
OR (95% CI)	1[c]	1.01 (0.48–2.11)	0.75 (0.36–1.54)	1.83 (0.18)
Tromsø, Norway				
Upper cutpoint	<12/month	<28/month		
Ca:Co	22:57	39:71	20:59	
OR (95% CI)	1[c]	1.45 (0.76–2.77)	0.89 (0.42–1.89)	0.09 (0.77)
Europe – South				
Italy				
Upper cutpoint	10/week	17/week		
Ca:Co	146:208	156:213	97:196	
OR (95% CI)	1[c]	1.03 (0.75–1.41)	0.68 (0.49–0.97)	4.30 (0.04)
Vaud, Switzerland				
Upper cutpoint	12/week	16/week		
Ca:Co	42:142	45:124	36:146	
OR (95% CI)	1[c]	0.98 (0.56–1.70)	0.74 (0.42–1.31)	1.06 (0.30)
Athens, Greece				
Upper cutpoint	4.4/week	7.3/week		
Ca:Co	59:65	29:38	22:37	
OR (95% CI)	1[c]	0.83 (0.43–1.59)	0.52 (0.25–1.09)	2.83 (0.09)

[a] Estimates from conditional logistic regression models, conditioned on age and sex, and adjusted for history of goiter, thyroid nodules, and adenomas, and history of radiation.
[b] Reference category.
[c] Conditioned also on ethnicity.
[d] Information based on a single summary item.

of cruciferous vegetables on papillary thyroid cancer only, and in iodine-rich or endemic goiter areas, which has not been possible in individual studies, given the small number of subjects.

Among the limitations of this combined analysis are the inherent biases of case–control studies, and mostly the differences in study designs. In particular, data on dietary correlates of thyroid cancer are limited and

Studies	Other vegetables Low ca/co	High ca/co	OR[a]	95% CI
Hawaii	75/136	51/161	0.55	0.35-0.88
Japan	98/118	133/121	1.57	1.05-2.35
Southeastern Sweden	10/16	125/276	0.47	0.18-1.21
Uppsala, Sweden	61/91	52/72	1.25	0.72-2.16
Northern Sweden	14/22	93/200	0.75	0.36-1.54
Tromsø, Norway	22/57	20/59	0.89	0.42-1.89
Italy	146/208	97/196	0.68	0.48-0.97
Switzerland	42/142	36/146	0.74	0.42-1.31
Greece	59/65	22/37	0.52	0.25-1.09
All studies[b]	527/855	629/1268	0.82	0.69-0.98

Heterogeneity between studies: χ^2 (8df)=19.92; p=0.015

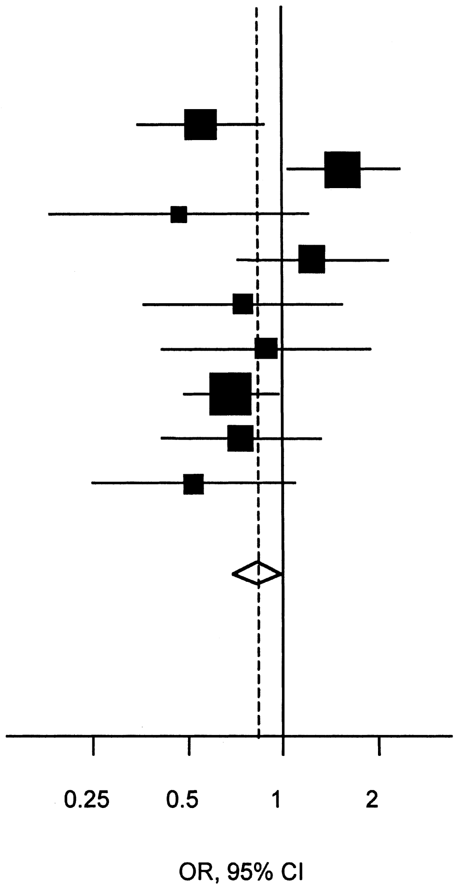

Fig. 2. Odds ratios[a] (OR) of thyroid cancer and corresponding 95% confidence intervals (CI) for high *versus* low intake of vegetables other than cruciferous, by study and overall.

[a] Estimates from conditional logistic regression models, conditioned on age and sex, and adjusted for history of goiter, thyroid nodules, and adenomas, and history of radiation.

[b] Weighted mean of the OR from each study.

dietary information collected in the original studies differed substantially with regard to the frequency of intake of the various vegetables, the level of detail of the questionnaires, the food queries, and the measurement of frequency of intake. These differences prevented us from defining common cut-points for vegetable consumption across all studies. Furthermore, only a few studies used food-frequency questionnaires specifically designed to investigate dietary correlates of thyroid cancer, and tested for validity and reliability, and no allowance for total energy intake was possible.

These limitations and cautions notwithstanding, our combined analysis allowed us to exclude the hypothesis that cruciferous vegetables are positively related to thyroid cancer risk; their effect is not substantially different from that of other vegetables, for which a favorable effect on this cancer is suggested.

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