

## A pooled analysis of case–control studies of thyroid cancer: cigarette smoking and consumption of alcohol, coffee, and tea

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### Abstract

**Objective:** To analyze the role of smoking, alcohol, coffee and tea in relation to thyroid cancer, we conducted a pooled analysis of 14 case–control studies conducted in the United States, Europe, and Asia.

**Methods:** The sample consisted of 2725 thyroid cancer cases (2247 females, 478 males) and 4776 controls (3699 females, 1077 males). Conditional logistic regression with stratification on study, age at diagnosis, and gender was used to compute odds ratios and 95% confidence intervals.

**Results:** Thyroid cancer risk was reduced in persons who had ever smoked. The relationship was more pronounced in current smokers (OR = 0.6, 95% CI = 0.6–0.7) than former smokers (OR = 0.9, 95% CI = 0.8–1.1). There were significant trends of reduced risk with greater duration and frequency of smoking. For consumption of wine and beer, there was a significant trend of decreasing thyroid cancer risk ( $p = 0.02$ ) that was not maintained after adjustment for current smoking ( $p = 0.12$ ). Thyroid cancer risk was not associated with consumption of coffee or tea. These findings were consistent in both gender-specific and histology-specific (papillary and follicular) analyses.

**Conclusions:** Pooled analyses of these geographically diverse case–control data indicate a reduced thyroid cancer risk associated with current smoking. A reduced risk associated with alcohol was eliminated after adjustment for smoking, and caffeinated beverages did not alter thyroid cancer risk.

### Introduction

Although thyroid cancer is not considered a smoking-related neoplasm, several epidemiological studies have

reported a small inverse association with cigarette consumption [1]. To date, most studies have examined simple cigarette smoking variables, such as ever smoked, or current smokers *versus* former smokers. Only a few of the more recent studies have examined the relationship between smoking and thyroid cancer risk in relation to age at smoking initiation, dose and duration of smoking, and age at diagnosis [2–4]. Because several of these

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studies had either no or only limited numbers of male cases, the relationship between smoking and thyroid cancer risk has been studied even less among men. This relationship has not been examined at all in relation to tumor histology.

Based on correlational data, alcohol consumption was reported to be a risk factor for thyroid cancer [5]. However, most analytic studies have failed to confirm such an association [6–9]. Indeed, sparse available data suggest that if there is a relationship, it lies in the direction of an inverse association.

Case-control studies conducted in Greece [10] and Japan [8], as well as a pooled analysis of four European case-control studies [11], all reported a decreased thyroid cancer risk with coffee consumption. This finding was not observed in a study from Northern Europe [9].

We undertook a pooled analysis of 14 case-control studies of thyroid cancer conducted internationally. The objectives of this paper were to use this rich, uniquely large database to assess more fully the relationships between thyroid cancer risk and cigarette smoking, alcohol and caffeine consumption, lifestyle factors that are strongly correlated at the population level. Variation in risk associations by gender, histology (papillary *versus* follicular), age, and geographic region also were examined. We also evaluated whether these relationships were confounded or modified by other thyroid cancer risk factors, namely a history of radiation treatment to the head or neck, a history of benign thyroid conditions [12], elevated body mass [13], or parity.

### Materials and methods

Detailed methods for this pooled analysis are reported elsewhere [14]. Fourteen case-control studies of thyroid cancer were identified from the United States (four studies, one each in Washington State [15], Los Angeles [16], Connecticut [6], and Hawaii [17]), Asia (one in Hiroshima and Nagasaki, Japan and the other in Shanghai, China [18]), and Europe (three in Sweden [9, 19, 20], two in Norway [9, 21], and one each in Northern Italy [22], Switzerland [23], and Greece [10]). These 14 studies represented case-control studies published between 1980 and 1997, or otherwise identified through personal knowledge of the authors.

Because of variation in the exposure data collected in each of the studies, the number of studies included and the sample sizes differ depending on the exposure evaluated. Table 1 provides the included studies, and the number of cases and controls for the four exposures reported in this paper (smoking, alcohol, coffee, and tea). All 14 studies provided smoking data, yielding a

total sample with smoking data of 2716 cases (474 males, 2242 females) and 4758 controls (1076 males, 3682 females). Detailed smoking data on duration of smoking, number of cigarettes smoked, and age at initiation of smoking were not available in all studies. In addition, two studies that did have data on duration, amount and age at initiation of smoking did not provide information on whether the subject was a current or former smoker. Therefore, numbers of subjects contributing to smoking analyses vary. Data on intake of selected alcoholic beverages were obtained in 10 studies, for a total sample of 1732 cases (379 males, 1353 females) and 3134 controls (756 males, 2378 females). Eight of these 10 studies provided data on wine and beer consumption, while data from two studies were limited to beer. Data on intake of other alcoholic beverages were so sparse that we restricted our analyses to wine and beer. Nine studies provided data on coffee consumption, yielding 1653 cases (343 males, 1310 females) and 2967 controls (696 males, 2271 females). The same nine studies provided data on intake of tea, for a total sample of 1589 cases (334 males, 1255 females) and 2666 controls (639 males, 2027 females). The methods of data collection for each study (in-person, telephone-, or self-administered questionnaire) are detailed elsewhere [14].

The following variables were restructured to provide a common format for the pooled analysis: smoking status, number of cigarettes smoked per day, years of smoking, age at starting smoking, number of glasses of wine per week, number of glasses of beer per week, number of cups of coffee per month and number of cups of tea per month. Restructured ancillary variables were a history of radiation treatment to the head or neck, a history of benign thyroid conditions (including hypothyroid, hyperthyroid, goiter, and benign nodules), height, weight, body mass index ( $\text{kg}/\text{m}^2$ ), parity and education. For the majority of studies, body weight and height at the time of diagnosis were reported. In the Swedish and Norwegian studies, these data were reported at the time of interview. Because we modified variable definitions to fit a common format, the data reported here may vary somewhat from that presented in the original reports of individual studies.

Conditional logistic regression was used to compute odds ratios as estimators of relative risk and associated 95% confidence intervals. For studies that were individually matched by design with age and gender as a matching variable [14], the original matching was maintained. The Hawaiian study also used ethnicity to define matching strata. In the remaining studies, age strata were defined by 5-year age intervals. Analyses were conducted within each study utilizing the original matching or defined age- and gender-strata. The com-

Table 1. Case-control studies included in pooled analyses

Study	Cases (female/male)	Controls (female/male)	Contributed to analysis of								
			Smoking	Alcohol		Coffee		Tea			
Connecticut	109/50	208/76	Yes	Wine		No		No			
Los Angeles	292/0	292/0	Yes	Beer		Yes		Yes			
Western Washington	185/0	393/0	Yes	Wine		No		No			
Hawaii	140/51	328/113	Yes	Beer		Yes		Yes			
Japan	307/58	307/58	Yes	Wine		Yes		Yes			
Shanghai	207/0	207/0	Yes	Beer		No		No			
Uppsala	133/37	203/54	Yes	Wine		Yes		Yes			
Norway	71/21	355/105	Yes	Beer		Yes		Yes			
Tromso	58/24	138/58	Yes	Wine		Yes		Yes			
North Sweden	123/48	240/85	Yes	Beer		No		No			
Southeast Sweden	149/26	187/200	Yes	Wine		No		No			
Switzerland	100/23	318/94	Yes	Beer		Yes		Yes			
Italy	291/108	427/190	Yes	Wine		Yes		Yes			
Greece	82/32	96/44	Yes	Beer		Yes		Yes			
				Cases <sup>a</sup>	Controls <sup>a</sup>	Cases	Controls	Cases	Controls	Cases	Controls
Total <sup>b</sup>	2247/478	3699/1077		2242/474	3682/1076	1353/379	2378/756	1310/343	2271/696	1255/334	2027/639

<sup>a</sup> Number of females/number of males.

<sup>b</sup> Number of subjects in smoking, alcohol, and coffee and tea analyses represent subjects with data available for those analyses and therefore do not sum to the total number of subjects across the 14 studies.

bined data from all studies were pooled and analyzed as one dataset using conditional logistic regression with the stratification variables defined above and the added stratification by study. Additional analyses to explore potential confounding adjusted for body mass index as a continuous variable, which may be a confounder of the relationship between thyroid cancer and smoking, alcohol, and caffeinated beverages [13] and education as a measure of social class. Smoking analyses were further adjusted for alcohol consumption and *vice versa*. In analyses conducted among females only, we also controlled for parity. We present the unadjusted results since in general adjustments did not alter our findings and also maximize the number of studies available for analysis. Pooled analyses were conducted overall and by gender, major histologic types (papillary and follicular), geographic region (United States, Asia, Northern Europe and Southern Europe) and age ( $\leq 35$ , 36–55,  $\geq 56$  years). Heterogeneity of the OR by study, gender, region, and age was tested by a likelihood ratio test, comparing the model with a common OR to a model estimating a separate OR for each stratum (*e.g.*,

heterogeneity by study was evaluated by statistically comparing a model estimating a separate OR for each study to a model estimating a single OR assumed to be common over studies). The resulting likelihood ratio test was a  $\chi^2$  statistic with degrees of freedom equal to the number of strata minus one. Study-specific results for simple dichotomized exposure variables are presented graphically, in which the center projection of a square represents the estimated OR and the size of the square is inversely proportional to the variance of the log OR. Additional analyses investigated effect modification by prior radiation treatment, hyperplastic thyroid disease, body mass index, body weight, and parity (women only).

## Results

Smoking, alcohol and caffeine consumption were strongly related among controls in this combined sample. Controls who smoked were more likely to use alcohol (72% of smokers *versus* 54% of non-smokers)

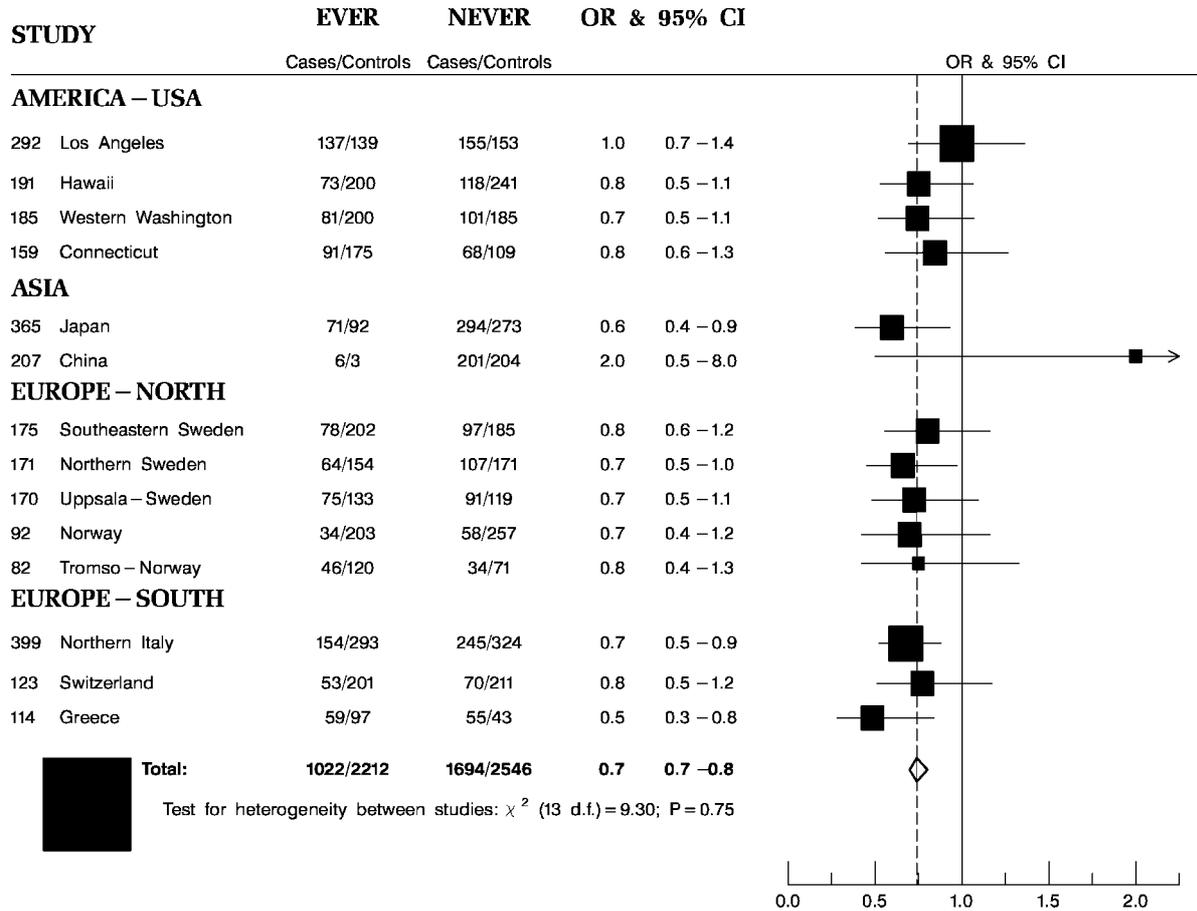


Fig. 1. Study-specific and total pooled association of thyroid cancer risk with ever smoking. Analyses conducted with conditional logistic regression, with stratification on study, age, gender, and ethnicity (in Hawaii). Numbers to the far left represent the total number of cases included in each study (see Table 1); studies in each geographic region are sorted by the number of cases.

and drink coffee (89% of smokers *versus* 82% of non-smokers), and were less likely to drink tea (50% of smokers *versus* 60% of non-smokers).

*Smoking*

Figure 1 shows the study-specific and overall odds ratios for ever smoking in women and men in the 14 studies. Twelve of fourteen studies found an inverse association with thyroid cancer, and only one study (based on only nine female smokers in Shanghai, China) showed a non-significant positive association. The confidence intervals for 11 of the 14 studies included the null value of 1.0, and there was no significant heterogeneity across studies ( $p=0.75$ ). Excluding the two studies (Uppsala and Tromso) that did not collect data on whether subjects were current or former smokers, we found that current smokers, but not former smokers, had a significantly decreased risk of thyroid

cancer (Table 2). In men and women combined, the risk for current smokers was significantly lower than for former smokers (likelihood ratio  $p=0.0001$ , comparing a model with ‘ever/never smoking’ to a model with never, former, and current smoking). This result also was evident for men and women separately (Table 3). Adjusting for study, age, and gender, there were highly significant trends of reduced thyroid cancer risk with greater pack-years, numbers of daily cigarettes, and total years smoked (all  $p < 0.0001$ ). These trends were attenuated with further adjustment for current smoking. Compared to persons who had never smoked, the reduction in risk was equivalent among subjects who began smoking before *versus* after age 18 (Table 2). Smoking associations were similar in both papillary and follicular thyroid cancers (Table 4; smoking variables other than smoking status adjusted for current smoking), and associations with smoking did not significantly vary by age or region (data not shown). Adjustments

Table 2. Pooled analysis of thyroid cancer case-control studies

	Ca/Co <sup>a</sup>	OR (95% CI)	<i>p</i> -Trend	OR (95% CI): adjusted for current smoking	<i>p</i> -Trend
<b>Smoking status<sup>b</sup></b>					
Never smoked	1694/2546	1.0			
Ever smoked	1022/2212	0.7 (0.7–0.8)			
Current smoker	524/1277	0.6 (0.6–0.7)			
Former smoker	377/681	0.9 (0.8–1.1)			
<b>Pack-years of smoking</b>					
Never smoked	1694/2546	1.0		1.0	
<20	705/1456	0.8 (0.7–0.9)		1.0 (0.9–1.2)	
20–40	168/414	0.6 (0.5–0.7)		0.8 (0.6–1.0)	
>40	79/171	0.6 (0.5–0.8)		0.9 (0.6–1.2)	
			<0.0001		0.003
<b>Number of cigarettes smoked</b>					
Never smoked	1694/2546	1.0		1.0	
≤10 per day	451/826	0.9 (0.8–1.0)		1.1 (0.9–1.4)	
>10 per day	526/1255	0.6 (0.6–0.7)		0.8 (0.6–0.9)	
			<0.0001		0.01
<b>Smoking duration</b>					
Never smoked	1694/2546	1.0		1.0	
≤15 years	473/990	0.8 (0.7–1.0)		1.0 (0.8–1.2)	
>15 years	487/1082	0.7 (0.6–0.8)		0.8 (0.7–1.0)	
			<0.0001		0.04
<b>Age started smoking</b>					
Never smoked	1694/2546	1.0		1.0	
≤18	421/945	0.7 (0.6–0.9)		0.9 (0.7–1.1)	
>18	497/1039	0.7 (0.6–0.8)		0.9 (0.7–1.1)	
			<0.0001		0.63
<b>Weekly drinks of wine<sup>c</sup></b>					
None	680/1192	1.0		1.0	
≤2	186/346	0.9 (0.7–1.2)		1.0 (0.8–1.3)	
>2–11	196/396	0.8 (0.7–1.1)		0.9 (0.7–1.2)	
>11	213/375	0.9 (0.7–1.1)		1.0 (0.8–1.3)	
			0.06		0.20
<b>Weekly drinks of beer</b>					
None	1186/1900	1.0		1.0	
≤1	185/345	0.9 (0.8–1.2)		0.9 (0.7–1.1)	
>1–3	135/244	0.8 (0.6–1.0)		0.9 (0.7–1.2)	
>3	160/319	0.8 (0.6–1.0)		0.8 (0.6–1.0)	
			0.08		0.20
<b>Weekly drinks of wine and beer</b>					
None	787/1146	1.0		1.0	
≤2	263/555	0.8 (0.7–1.0)		0.8 (0.6–1.0)	
>2–7	321/558	0.8 (0.7–1.0)		0.8 (0.7–1.0)	
>7–14	146/250	0.9 (0.7–1.2)		1.0 (0.8–1.3)	
>14	149/299	0.8 (0.6–1.0)		0.9 (0.7–1.1)	
			0.02		0.12
<b>Monthly cups of coffee<sup>d</sup></b>					
None	315/461	1.0		1.0	
≤30	571/1152	0.9 (0.7–1.1)		0.9 (0.7–1.2)	
>30	402/989	0.8 (0.6–1.0)		0.9 (0.6–1.2)	
			0.16		0.63
<b>Monthly cups of tea</b>					
None	716/1256	1.0		1.0	
≤8	261/540	1.0 (0.8–1.2)		1.0 (0.8–1.2)	
>8	247/505	1.0 (0.8–1.3)		1.1 (0.8–1.4)	
			0.87		0.85

Table 2. (Continued)

<sup>a</sup> Ca/Co = #exposed cases/# exposed controls; OR = odds ratio; 95% CI = 95% confidence interval on the odds ratio. Analyses conducted with conditional logistic regression, with stratification on study, age, gender, and ethnicity (in Hawaii).

<sup>b</sup> Smoking analyses: 14 studies included; two studies deleted with adjustment for current smoking.

<sup>c</sup> Alcohol analyses: 10 studies analyzing beer, eight studies analyzing wine and combined wine plus beer; two studies deleted with adjustment for current smoking.

<sup>d</sup> Coffee and tea analyses: nine studies included; two studies deleted with adjustment for current smoking.

for body mass index, education, alcohol consumption, and parity did not substantially alter the estimates. These results were also not significantly modified by a history of benign hyperplastic thyroid disease, body mass index or body weight. For example, the OR (95% CI) for ever smoking was 0.7 (0.7–0.8) for persons at or below their gender-specific median and 0.7 (0.6–0.9) for persons above their gender-specific median body mass index. Although there was some suggestion that the smoking association might vary by parity (OR for ever smoking = 0.7 (0.5–0.9) for nulliparous women, 0.8 (0.6–0.9) for women with 1–3 pregnancies, and 0.5 (0.4–0.8) for women with more than three pregnancies), the test of effect modification was not significant ( $p = 0.28$ ).

#### Alcohol

Figure 2 displays odds ratios for the 10 studies that collected data on wine or beer consumption. Six studies showed an inverse association (four of these were statistically significant) and four studies showed a non-significant positive association with thyroid cancer. The association of thyroid cancer risk with any alcohol intake significantly differed among the studies ( $p < 0.001$ , Figure 2), and the average alcohol intake significantly varied across the 10 studies ( $p < 0.0001$ ; data not shown). In general, average alcohol intake was lower in the Scandinavian and Japanese studies, mid-range in the North American studies, and highest in the Southern European (Italy, Switzerland, Greece) studies. However, there was no pattern of association between the average study intakes and the Figure 2 odds ratios. The inter-study heterogeneity in the alcohol association remained when we analyzed the data by a quantified (ordinal categorical) alcohol variable ( $p = 0.004$  for study heterogeneity) and also after adjustment for smoking ( $p = 0.001$  for study heterogeneity). Significant study heterogeneity was apparent for beer alone ( $p < 0.01$ ) and for wine alone ( $p < 0.001$ ).

In the combined sample, there was no statistically significant relationship to wine consumption alone (Table 2). The trend in thyroid cancer risk with increasing wine consumption was of borderline significance with stratification on study, age, and gender (Table 2,  $p = 0.06$ ), and was not apparent with further adjustment

for current smoking ( $p = 0.20$ ). The frequency of consumption of beer also was not related to thyroid cancer risk in the combined sample. For total units of wine and beer consumed, there was a significant trend of decreasing thyroid cancer risk ( $p = 0.02$  with stratification on study, age, and gender). The trend was not apparent after adjustment for current smoking (adjusted  $p$  for trend = 0.12). With adjustment for current smoking, associations of thyroid cancer risk with total wine and beer consumption did not significantly vary by gender (Table 3), histology (Table 4), geographical region or age at diagnosis.

#### Caffeinated beverages – coffee and tea

Figure 3 displays odds ratios for the nine studies with data on coffee consumption. Six studies found an inverse association with any consumption of coffee, but only one (Greece) was statistically significant. There was no significant heterogeneity among studies. In Figure 4, the same nine studies showed more heterogeneity evaluating associations with tea drinking ( $p = 0.08$  for heterogeneity). Only one study showed a significant association (in a positive direction) with tea. In the combined sample, there were no clear trends in thyroid cancer risk by level of consumption of coffee or tea. In southern Europe, drinking more than 30 cups of coffee a month was associated with a reduced risk of thyroid cancer (OR = 0.6, 95% CI = 0.4–1.0), but the test for trend was not significant ( $p = 0.31$ ) and there was no significant regional heterogeneity ( $p = 0.78$ , data not shown). There was also a suggestion of increased risk associated with high consumption of tea in studies conducted in southern Europe, and reduced risk in US studies, yielding a test for regional heterogeneity of marginal significance ( $p = 0.07$ , data not shown). No associations were apparent in analyses conducted by gender, histology, or age.

#### Discussion

Results from this pooled analysis of 14 case-control studies suggest that cigarette smoking, particularly current cigarette smoking, is associated with a moder-

Table 3. Gender: pooled analysis of thyroid cancer case-control studies adjusted for current smoking

	Male				Female				<i>p</i> -Value for gender interaction <sup>b</sup>
	Ca/Co <sup>a</sup>	OR	95% CI	<i>p</i> -Trend	Ca/Co	OR	95% CI	<i>p</i> -Trend	
Smoking status <sup>c</sup>									
Never smoked	170/361	1.0			1524/2185	1.0			
Ever smoked	304/715	0.8	0.6–1.0		718/1497	0.7	0.6–0.8		0.43
Current smoker	156/402	0.7	0.5–1.0		368/875	0.6	0.6–0.8		0.75
Former smoker	116/245	0.9	0.6–1.3		261/436	0.9	0.8–1.1		
Number of cigarettes smoked									
Never smoked	170/361	1.0			1524/2185	1.0			
≤10 per day	99/186	1.3	0.8–2.0		352/640	1.1	0.9–1.3		
>10 per day	185/465	0.8	0.6–1.2		341/790	0.9	0.7–1.1		
				0.07				0.31	0.63
Smoking duration									
Never smoked	170/361	1.0			1524/2185	1.0			
≤15 years	83/240	0.9	0.6–1.3		390/750	1.1	0.9–1.3		
>15 years	195/421	1.0	0.6–1.5		292/661	0.8	0.6–1.1		
				0.84				0.03	0.08
Age started smoking									
Never smoked	170/361	1.0			1524/2185	1.0			
≤18	119/281	0.9	0.6–1.3		302/664	1.0	0.8–1.2		
>18	151/326	0.9	0.6–1.4		346/713	0.9	0.7–1.1		
				0.58				0.85	0.45
Weekly drinks of wine and beer <sup>d</sup>									
None	89/142	1.0			698/1004	1.0			
≤2	66/126	1.2	0.7–2.0		197/429	0.7	0.6–0.9		
>2–7	82/164	0.8	0.5–1.2		239/394	0.9	0.7–1.1		
>7–14	49/89	1.0	0.6–1.7		97/161	1.0	0.7–1.3		
>14	84/181	0.8	0.5–1.3		65/118	0.9	0.6–1.2		
				0.07				0.93	0.31
Monthly cups of coffee <sup>e</sup>									
None	36/81	1.0			279/380	1.0			
≤30	156/312	1.6	0.9–2.7		415/840	0.7	0.6–1.0		
>30	93/245	1.0	0.5–1.8		309/744	0.9	0.6–1.2		
				0.94				0.46	0.18
Monthly cups of tea									
None	160/347	1.0			556/909	1.0			
≤8	71/122	1.6	1.0–2.6		190/418	0.8	0.6–1.1		
>8	45/112	1.2	0.7–1.9		202/393	0.9	0.7–1.2		
				1.0				0.55	0.06

<sup>a</sup> Ca/Co = #exposed cases/# exposed controls; OR = odds ratio; 95% CI = 95% confidence interval on the odds ratio. Analyses conducted with conditional logistic regression, with stratification on study, age, gender, and ethnicity (in Hawaii). All analyses except smoking status adjusted for current smoking.

<sup>b</sup> Likelihood ratio test for differences in association by gender.

<sup>c</sup> Smoking analyses: 14 studies included for smoking status, 12 studies for all other smoking variables.

<sup>d</sup> Alcohol analyses: six studies analyzing combined wine plus beer.

<sup>e</sup> Coffee and tea analyses: seven studies included.

ately reduced risk of thyroid cancer. This association was evident in both men and women, in the two major histological groups (papillary and follicular cancers), and in all geographic regions. Our data also demonstrate a trend of decreasing risk with both smoking intensity and duration. Since the reduction in weight and body mass index associated with smoking may be an explanation for the smoking-related reduction in

thyroid cancer risk, we adjusted our analyses for body mass index. This adjustment did not alter the smoking associations observed. While 12 of the studies had a point estimate consistent with a decreased risk associated with smoking (Figure 1), the confidence interval for nine of these included the null value of 1.0. This suggests that many of the individual studies did not have sufficient power to evaluate the smoking association

Table 4. Histology: pooled analysis of thyroid cancer case-control studies adjusted for current smoking

	Papillary				Follicular				<i>p</i> -Value for histology interaction <sup>b</sup>
	Ca/Co <sup>a</sup>	OR	95% CI	<i>p</i> -Trend	Ca/Co	OR	95% CI	<i>p</i> -Trend	
Smoking status <sup>c</sup>									
Never smoked	1178/2149	1.0			200/1363	1.0			
Ever smoked	789/2088	0.7	0.6–0.8		141/1405	0.7	0.6–0.9		0.53
Current smoker	396/1213	0.6	0.5–0.7		73/840	0.6	0.5–0.9		0.61
Former smoker	289/653	0.9	0.8–1.1		51/533	0.8	0.6–1.1		
Number of cigarettes smoked									
Never smoked	1178/2149	1.0			200/1363	1.0			
≤10 per day	359/750	1.2	1.0–1.5		49/449	0.8	0.5–1.2		
>10 per day	402/1207	0.8	0.7–1.0		82/840	0.8	0.5–1.2		
				0.06				0.17	0.08
Smoking duration									
Never smoked	1178/2149	1.0			200/1363	1.0			
≤15 years	380/927	1.0	0.9–1.3		57/517	0.9	0.6–1.3		
>15 years	372/1023	0.9	0.7–1.2		70/777	0.6	0.4–1.0		
				0.11				0.04	0.51
Age started smoking									
Never smoked	1178/2149	1.0			200/1363	1.0			
≤18	328/875	1.0	0.8–1.3		52/570	0.7	0.4–1.1		
>18	391/1000	0.9	0.7–1.2		71/649	0.7	0.4–1.1		
				0.96				0.36	0.44
Weekly drinks of wine and beer <sup>d</sup>									
None	648/1084	1.0			92/609	1.0			
≤2	215/504	0.8	0.6–1.0		35/177	1.4	0.8–2.4		
>2–7	266/525	0.9	0.7–1.1		32/304	0.8	0.5–1.3		
>7–14	99/243	1.0	0.8–1.3		24/195	1.0	0.5–1.5		
>14	108/295	0.9	0.7–1.2		23/268	0.8	0.5–1.5		
				0.68				0.13	0.34

<sup>a</sup> Ca/Co = #exposed cases/# exposed controls; OR = odds ratio; 95% CI = 95% confidence interval on the odds ratio. Analyses conducted with conditional logistic regression, with stratification on study, age, gender, and ethnicity (in Hawaii). All analyses except smoking status adjusted for current smoking.

<sup>b</sup> Likelihood ratio test for differences in association by histology.

<sup>c</sup> Smoking analyses: 14 studies included for smoking status, 12 studies for all other smoking variables.

<sup>d</sup> Alcohol analyses: six studies analyzing combined wine plus beer.

<sup>e</sup> Coffee and tea analyses: seven studies included.

and highlights the importance of the present pooled analysis to examine the smoking association with greater statistical power.

Recent case-control studies from Canada, conducted in men and women [4] and in the US, conducted among women (papillary cancer only) [3] partially confirm these results. In the US study, a reduced risk of papillary thyroid cancer was evident among currently smoking women, but after stratification by current *versus* former smoking, there was no trend in risk by smoking intensity or duration. In the Canadian study, data were not analyzed by current *versus* former smoking, but significant trends of decreasing risk were found for smoking intensity (females only) and duration (males and females).

While the consistency of results among studies in this pooled sample suggests a causal relationship between

smoking and a reduced risk of thyroid cancer, a convincing biological explanation is lacking. Three possible biologic pathways have been identified. The first potential pathway relates to a smoking-related association with TSH secretion. It has long been hypothesized that elevated levels of TSH may increase the risk of thyroid cancer [24, 25]. Studies comparing thyroid and related hormone levels among smoking groups generally show reduced TSH in current smokers relative to former and never smokers [26–29]. The smoking-related reduction in TSH occurs in both males [26, 29] and females [27]. However, one study found no difference in TSH between heavy smokers and non-smokers [30]. In a longitudinal comparison of 57 male and female regular smokers who had quit smoking, paired serum samples showed an increase in TSH in the smoke-free samples relative to the samples collected

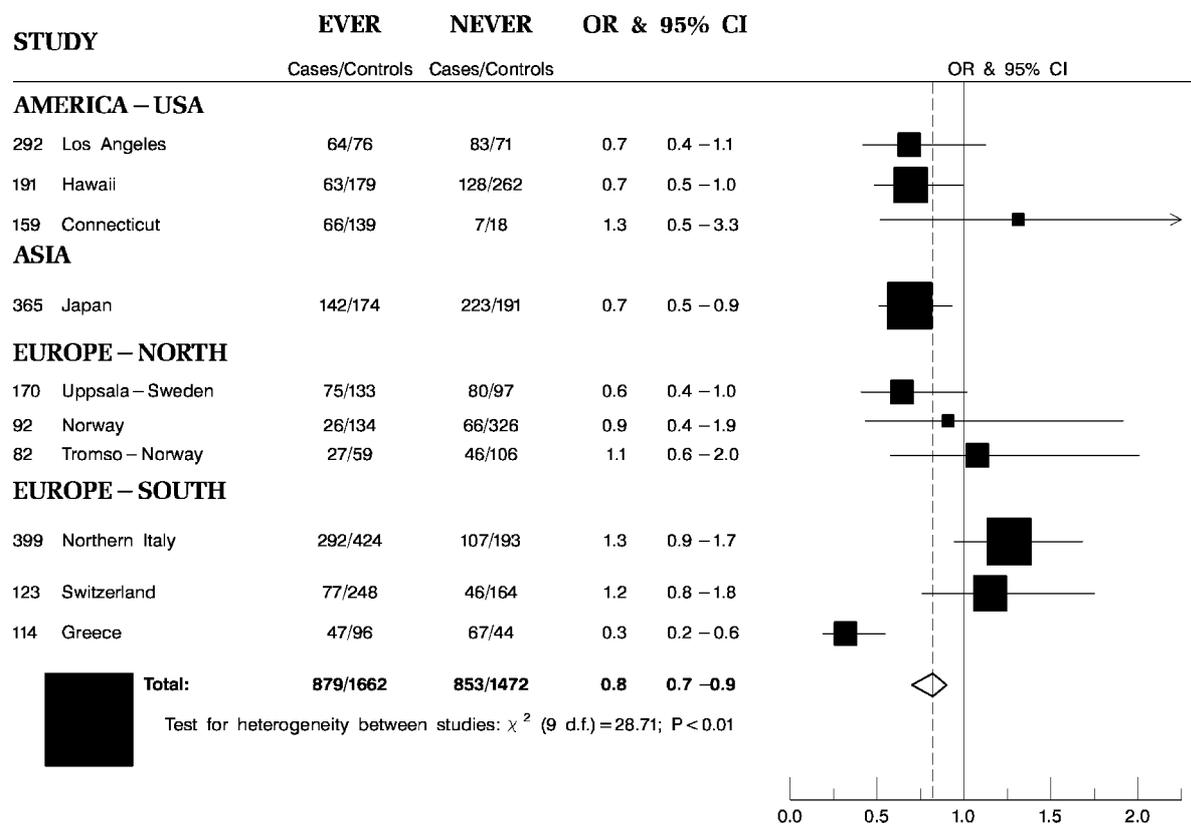


Fig. 2. Study-specific and total pooled association of thyroid cancer risk with any drinking of beer or wine. Analyses conducted with conditional logistic regression, with stratification on study, age, gender, and ethnicity (in Hawaii). Numbers to the far left represent the total number of cases included in each study (see Table 1); studies in each geographic region are sorted by the number of cases.

earlier when the subjects were still smoking [31]. The smoking-related effect on thyroid hormones is inconsistent. Most studies show no effect of smoking on T4 [27, 30]. While some studies show an increase in T3 in smokers relative to non-smokers [27, 30], others show no difference [28, 31]. Our finding of a smoking-related reduction in thyroid cancer risk limited to current smokers is consistent with these data regarding TSH levels and smoking.

Cigarette smoking is associated with an increased risk of goiter [27, 28, 32], and goiter has been clearly demonstrated to be a risk (or at least an antecedent) factor for thyroid cancer in these pooled data [12]. Thiocyanate, a by-product of cigarette smoking, is a known goitrogen and inhibits biosynthesis of thyroid hormones [30, 33]. Thus, while evidence suggests that cigarette smoking may directly promote increases in the size of the thyroid gland and goiter, the apparent smoking-related decrease in thyroid cancer risk suggests that smoking has various effects on the thyroid gland and that the smoking association with thyroid cancer is not mediated through alterations in thyroid size.

The lower body weight among smokers compared to non-smokers is a second proposed explanation for the smoking-related reduction in thyroid cancer risk. In this pooled sample, increased height, body weight and body mass index were associated with a slightly increased thyroid cancer risk that was primarily evident in women [13]. A thyroid cancer association with these anthropometric factors might be explained by an association of steroid hormones or certain dietary factors [11] with body weight. When we adjusted our analyses for body mass, the observed smoking associations were not altered. Furthermore, we found no evidence for effect modification by body mass.

A third possible biologic pathway for the reduced thyroid cancer risk lies in the potential anti-estrogenic effect of cigarette smoke [2, 34]. The smoking-related reduction in endometrial cancer risk has been similarly explained as an anti-estrogenic effect [35]. While a role for estrogen in the etiology of thyroid cancer is hypothesized because of the higher incidence of this cancer in females relative to males, the direct influence of smoking on estrogen levels is not clear. The majority

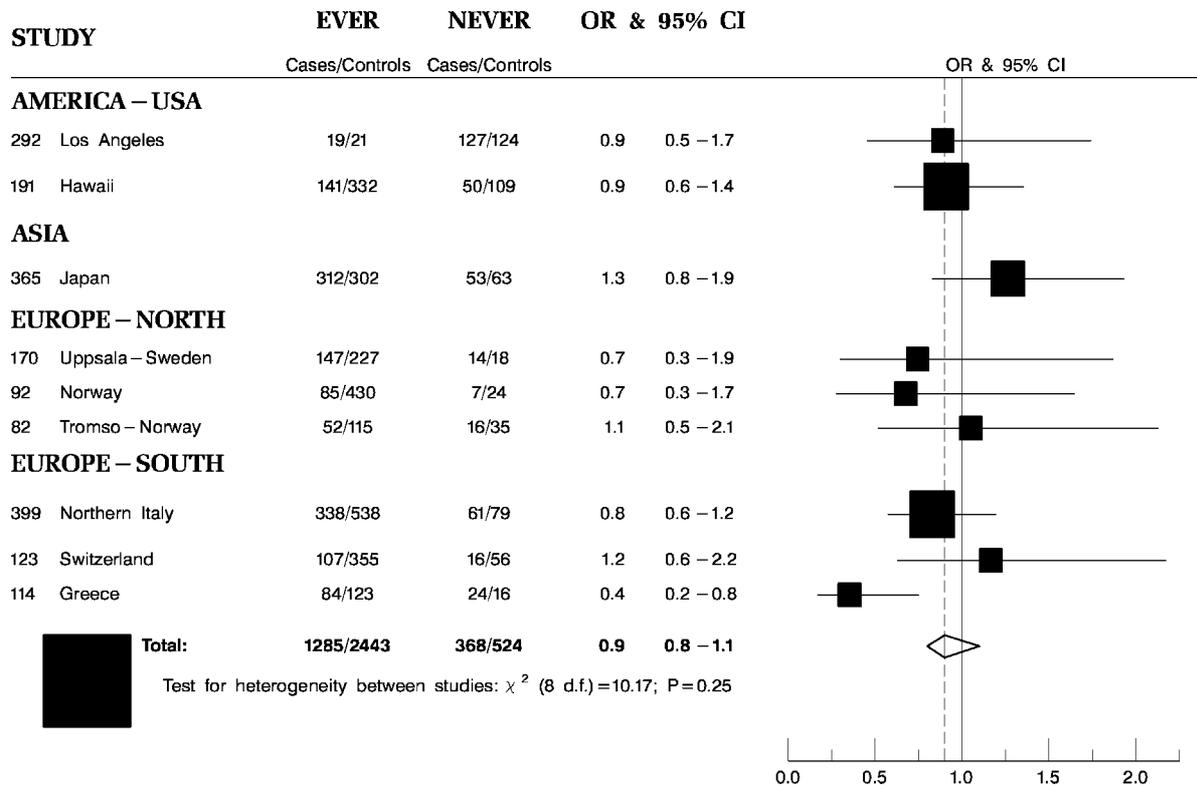


Fig. 3. Study-specific and total pooled association of thyroid cancer risk with any drinking of coffee. Analyses conducted with conditional logistic regression, with stratification on study, age, gender, and ethnicity (in Hawaii). Numbers to the far left represent the total number of cases included in each study (see Table 1); studies in each geographic region are sorted by the number of cases.

of studies show no difference in estrogen levels among smokers and non-smokers in premenopausal females [36–38], postmenopausal females [36, 39, 40], or males [41]. Estriol, but not estradiol or estrone, secretion [36] and unbound estradiol [42] were lower in smoking compared to non-smoking postmenopausal females. Smoking was associated with increased metabolic inactivation of hepatic estrogens in male smokers [43] and in female premenopausal smokers [44] compared to non-smokers. Thus, there is some evidence that smoking may lead to decreased estrogen bioavailability at target tissues. In contrast, both male [41] and female [39, 40, 45] smokers have higher levels of specific androgens. This finding is not consistently found [37]. The idea that androgens may be related to thyroid cancer risk has not been investigated.

A fourth explanation for the inverse association of smoking with thyroid cancer is confounding by social class. Although not a consistent finding, thyroid cancer incidence is higher among the more highly educated and professional occupations in some populations [46], while smoking is inversely associated with these social class variables. While our results did not change with

adjustment for years of formal education, there may have been residual confounding by other unmeasured social class factors.

It has been hypothesized that alcohol consumption might increase the risk of thyroid cancer by increasing TSH levels [5]. The case-control studies included in this analysis and others [3] have failed to support this hypothesis, and our re-analysis of such studies also shows no increased risk with higher levels of alcohol. If anything, there may be a decreased risk with greater consumption of alcoholic beverages. However, our data suggest that the decreased risk associated with alcohol consumption is confounded by smoking, since adjustment for current smoking eliminated any alcohol-related trends in thyroid cancer risk. A case-control study of females with papillary thyroid cancer noted a decreased risk associated with alcohol consumption, which remained after adjustment for smoking [3]. A large population-based study in Denmark showed lower thyroid volumes and a reduced prevalence of thyroid enlargement and nodules for persons drinking at least eight drinks per week, with adjustment for age, gender, and smoking [47]. Our analyses related to alcohol

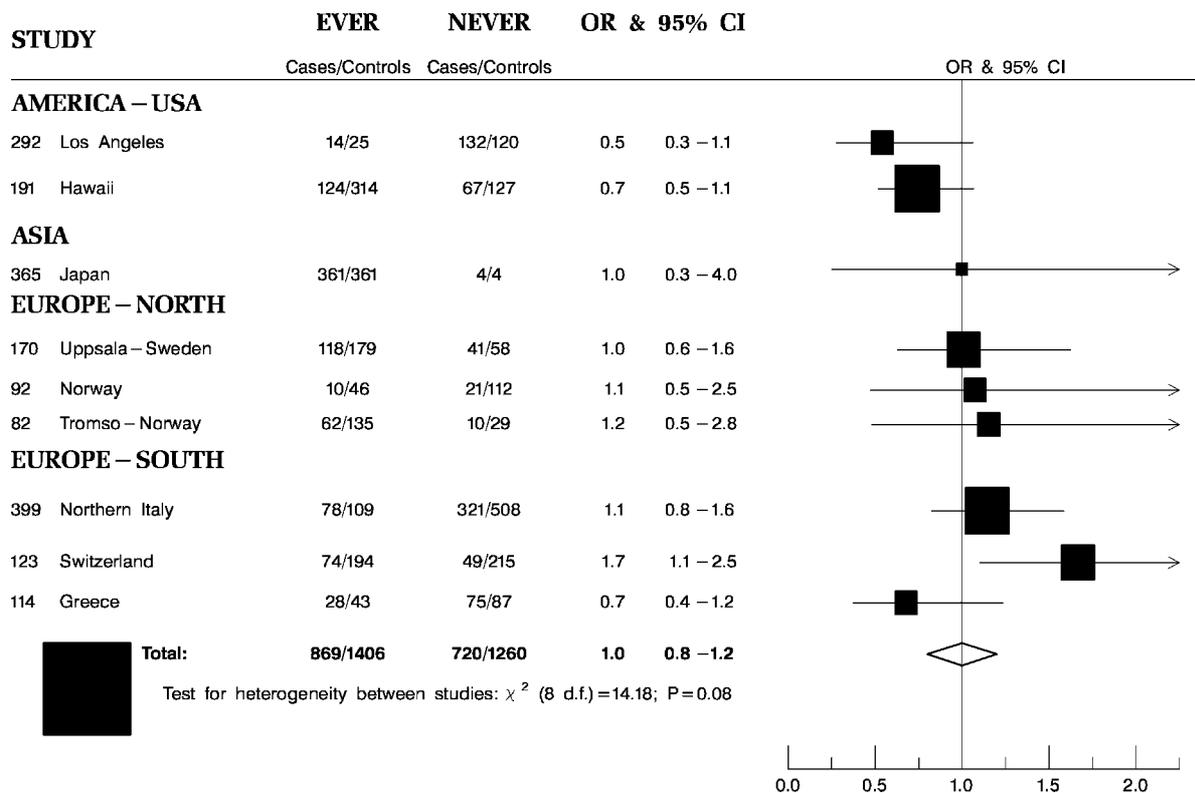


Fig. 4. Study-specific and total pooled association of thyroid cancer risk with any drinking of tea. Analyses conducted with conditional logistic regression, with stratification on study, age, gender, and ethnicity (in Hawaii). Numbers to the far left represent the total number of cases included in each study (see Table 1); studies in each geographic region are sorted by the number of cases.

consumption were limited by crude measures, which did not have standard units or quantifiable alcohol content, and were based only on beer and wine consumption.

Our analysis failed to show any association of thyroid cancer risk with either coffee or tea. The hypothesized mechanism for coffee reducing thyroid cancer risk lies in the observation that caffeine increases intracellular cyclic AMP, which has an inhibitory effect on cell (tumor) growth [10]. Higher consumption of caffeinated beverages reduced thyroid cancer risk in three case-control studies [8, 10, 11]. Two of these studies from southern Europe are represented in the present pooled analysis [10, 11]. More studies, also represented in the pooled analysis, have failed to confirm this association. The study from Greece [10] used a summary variable combining both frequency and duration of coffee consumption. We did not have data on duration of coffee consumption across our studies to evaluate this variable. In light of the reduced thyroid cancer risk with very high consumption of coffee observed in southern European studies in this pooled analysis, we cannot exclude the possibility that regional differences in the association with thyroid cancer risk may exist which we did not have sufficient power to detect. Such regional

differences are not likely to reflect biological differences in the effect of coffee, but would more likely be due to regional variations in methods of preparation and strength of the coffee brew.

In summary, pooled analyses of these geographically diverse case-control data indicate an approximate 40% reduced risk of thyroid cancer associated with current smoking in both males and females. A reduction in risk associated with alcohol was eliminated after adjustment for smoking. No associations were found with consumption of coffee and tea. While a smoking-related reduction in thyroid cancer risk is of biological and etiologic interest, results must also be interpreted in light of the overwhelming public health impact of smoking-related diseases including cancers of the respiratory system and cardiovascular disease.

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