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Cigarette smoking, alcohol intake, and thyroid cancer risk: a pooled analysis of five prospective studies in the United States

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Abstract

Objective—We examined the associations between cigarette smoking, alcohol intake, and thyroid cancer risk in a pooled analysis of five prospective studies.

Methods—Data from five prospective U.S. studies were standardized and then combined into one aggregate dataset (384,433 men and 361,664 women). Pooled hazard ratios (HR) and 95% confidence intervals (CI) for thyroid cancer were estimated from mutually-adjusted models of cigarette smoking and alcohol intake, which were additionally adjusted for age, sex, education, race, marital status, body mass index, and cohort.

Results—Over follow-up, 1,003 incident thyroid cancer cases (335 men and 668 women) were identified. Compared to never smokers, current smoking was associated with reduced risk of thyroid cancer (HR=0.68, 95% CI:0.55-0.85); this association was slightly stronger among non-drinkers (HR=0.46, 95% CI:0.29-0.74). No reduction in risk was observed for former, compared to never, smokers. Greater smoking intensity, duration, and pack-years were associated with further reductions in risk among former and current smokers. Alcohol intake was also inversely associated with thyroid cancer risk (7 drinks/week versus 0, HR=0.72, 95% CI:0.58-0.90, *P-trend*=0.002). Inverse associations with smoking and alcohol were more pronounced for papillary versus follicular tumors.

Conclusion—The results of this pooled analysis suggest that both cigarette smoking and alcohol consumption are associated with reduced risks of papillary thyroid cancer and, possibly, follicular thyroid cancer.

Keywords

thyroid neoplasms; cigarette smoking; alcohol intake; prospective study; epidemiology

Introduction

In the U.S., incidence rates for thyroid cancer have increased since the early 1980s and most dramatically in the past decade, with an average increase of 6.0% per year in men and 6.9%

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per year in women since 1997 [1]. Enhanced detection of small, clinically insignificant thyroid tumors through increasingly widespread use of sensitive screening and diagnostic procedures appears to only partly account for these observed patterns [2]. There are few known or suspected risk factors for thyroid cancer, apart from ionizing radiation exposure [3], medical history of benign thyroid conditions (e.g., goiter and thyroid nodules) [4], and obesity [5], and the impact that secular trends in the prevalence of these and other, yet unknown, risk factors have had on thyroid cancer incidence trends remains unclear.

There is some evidence that cigarette smoking and alcohol consumption, two highly-modifiable behaviors, may be associated with thyroid cancer risk. Several case-control [6-11] and prospective cohort [12, 13] studies, but not all [14-18], have shown inverse associations for current, versus never, cigarette smoking and thyroid cancer risk. Of those finding an inverse relationship with current smoking, the results for smoking duration and intensity have been somewhat mixed [7-9, 11, 13]. Results from studies examining the association between alcohol intake and thyroid cancer risk have also been inconsistent though generally supportive of an inverse relationship [9-11, 13-15, 17-20], with the two largest prospective studies on this topic having shown significant inverse dose-response associations with alcohol consumption [19, 20]. However, there is little evidence regarding the independence of the associations for these two (often related) behaviors on thyroid cancer risk [9, 11, 19].

To further clarify the associations between cigarette smoking, alcohol consumption, and thyroid cancer risk, we pooled data from five large, prospective U.S.-based cohort studies. This is the first pooled analysis of prospective studies on the association between cigarette smoking and alcohol consumption, and with over 1,000 incident thyroid cancer cases, one of the largest studies on this topic to date. This large sample size enabled examination of the association for smoking and alcohol intake among non-drinkers and never smokers, respectively, which was necessary to eliminate residual confounding as an explanation for our results.

Methods

Study population

Study participants were enrolled in one of five U.S.-based prospective cohorts from the National Cancer Institute: NIH-AARP Diet and Health Study (NIH-AARP), Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO), Breast Cancer Detection and Demonstration Project (BCDDP), Agricultural Health Study (AHS), and US Radiologic Technologists Study (USRT). The institutional review boards from the National Cancer Institute and all participating institutions approved the use of these data. Details of this pooled study, including methods for data standardization, outcome ascertainment, and statistical analysis, were published previously [5]. However, for this analysis, we redefined the BCDDP study baseline as the date at which participants responded to the second questionnaire, when participants were first asked to provide information on cigarette smoking and alcohol consumption. We also restricted the PLCO study population to participants in the intervention arm who responded to the Dietary Questionnaire (DQX). In total, there were 746,097 subjects (384,433 men and 361,664 women) who responded to a baseline questionnaire, accrued follow-up time, did not have a history of cancer other than non-melanoma skin cancer, and were not missing information on the date of diagnosis of incident cancer, cigarette smoking status, or alcohol consumption.

Exposure assessment and data standardization

Each study utilized self-administered questionnaires which elicited information on general demographics, personal medical history, height and weight, and certain health behaviors and lifestyle characteristics, including cigarette smoking and alcohol consumption. At baseline, all cohorts collected information on smoking status (never, former, current), smoking intensity (number of cigarettes smoked per day), smoking duration (number of years smoked; not available in NIH-AARP), and, for former smokers, number of years since quitting (not available in AHS). To calculate total number of years smoked at baseline, we either used self-reported smoking duration (USRT, BCDDP, AHS) or subtracted the age started smoking from the age stopped smoking (or, for current smokers, age at enrollment; PLCO). To calculate pack-years, we multiplied the number of years smoked by number of packs smoked per day. To calculate years since quitting smoking, we either used self-reported years since smoking (NIH-AARP) or we subtracted as the difference between baseline age and the age when the subject reported having quit smoking (NIH-AARP, USRT, PLCO, BCDDP). Questionnaire items regarding alcohol intake typically referred to intake during the previous 12 months. Within each of the cohorts, we converted alcohol servings into grams of ethanol consumed per day: beer (12 fluid ounces=13.9 grams ethanol [regular] or 11 grams ethanol [light]), wine (5 fluid ounces=15 grams ethanol), and liquor (1.5 fluid ounces=14 grams ethanol). If a questionnaire did not distinguish among different alcohol types, we considered one alcohol serving to equal 14 grams of ethanol. All subjects were assigned an average number of drinks consumed per day by dividing usual gram intake of ethanol by 14. Subjects who reported consuming, on average, less than one alcoholic drink per month were combined with non-drinkers in the analysis. For assessment of continuous exposures ascertained in categories, we defined the subject's exposure level as the mid-point of the range.

The level of detail collected on potential confounding factors (e.g., body mass index [BMI], education, race, and marital status) differed slightly across the five cohorts. These variables were recoded using standardized definitions and categories prior to inclusion in statistical models.

Outcome assessment

Subjects were followed from the date of completion of the baseline questionnaire to the date of any cancer diagnosis other than non-melanoma skin cancer, date of death, last date of follow-up, or study-specific administrative end date, whichever came first. Thyroid cancer cases were defined as participants who were diagnosed with a malignant first primary thyroid neoplasm during follow-up. Cancer information was obtained through different sources: self-report followed by validation by medical record review (USRT, PLCO, BCDDP), cancer registry linkage (NIH-AARP, AHS, BCDDP), death certificates (USRT, PLCO, BCDDP), and/or the National Death Index (NIH-AARP, USRT, BCDDP). Using information from medical and pathology records and cancer registry linkage, we further classified cases by histology according to the International Classification of Diseases for Oncology, 3rd edition codes [21]: papillary (8050, 8052, 8130, 8260, 8340-8344, 8450, and 8452) and follicular (8290, 8330-8332, 8335), medullary (8345, 8346, 8510), and anaplastic (8021).

Statistical analysis

We used Cox proportional hazards models to calculate study-specific hazard ratios (HRs) and 95% confidence intervals (CIs) for thyroid cancer using attained age as the underlying time metric. All multivariable models were adjusted for sex, education (up to high school degree, post-high school up to college degree, post-college, missing), race (white, black, American Indian/Alaskan Native, Asian/Pacific Islander, other, missing), marital status

(married/living together, divorced/separated, widowed, single/never married, missing), body mass index (<18.5, 18.5-24.9, 25.0-29.9, 30.0 kg/m², missing), cigarette smoking (never, former, current), and usual alcohol intake during the previous 12 months (none, <1 drink/week, 1-6 drinks/week, 7 drinks/week). Heterogeneity in the HRs between studies was assessed using the I² index and the Mantel-Haenszel test for heterogeneity [22, 23].

Data from all five cohorts were subsequently combined into one aggregate dataset to calculate the pooled HR for thyroid cancer, overall and by histological type, according to cigarette smoking behaviors and alcohol intake. Models were adjusted for all of the variables above and for cohort. As all of these studies collected detailed information on baseline smoking habits, we additionally examined the association for smoking intensity (number of cigarettes per day) and smoking duration (number of years smoked) among current smokers and, among former smokers, years since quitting. Effect modification by other thyroid cancer risk factors, including baseline age, sex, education, BMI, alcohol intake (when smoking was the main exposure variable), and smoking status (when alcohol was the main exposure variable), as well as follow-up time (<5 years, 5-9 years, and 10 years), was assessed by comparing the magnitude of the HRs within strata of these factors and by evaluating the statistical significance of the likelihood ratio test comparing models with cross-product terms to models without. Differences according to thyroid cancer histology were evaluated using the Mantel-Haenszel test for heterogeneity. Tests for trends were conducted by modeling categorical variables as continuous and evaluating the statistical significance of the Wald test.

We examined consistency between race- and sex-specific trends in current smoking and alcohol drinking with thyroid cancer incidence between 1965 and 2009 in the U.S. Trends were plotted so that a slope of 10 degrees represented a change of 1% per year (i.e., 40 years on the horizontal axis is the same length as one logarithmic cycle on the vertical axis) [24-27]. Incidence rates were age-adjusted to the 2000 U.S. standard using SEER*Stat [28] from the SEER 9 registries, representing approximately 10% of the population.

All analyses were conducted using Stata software (version 9.2, College Station, TX). All statistical tests were two-sided and were considered statistically significant if $P < 0.05$.

Results

The mean age of the subjects across the five cohorts was 58 years at baseline, with 52% being male, 14% being current smokers, and 66% having consumed alcohol over the previous 12 months (Table 1). Compared to women, men were more likely to be former smokers (53% versus 34%) and less likely to be never smokers (34% versus 51%). Among current smokers, men and women reported similar duration (median=40 years for men versus 38 for women) and intensity of smoking (median=15 cigarettes per day for men and women). Men reported consuming more alcohol than women, with 26% of men drinking 7 drinks per week versus 10% of women. Over follow-up (median=10.5 years), 1,003 participants (335 men and 668 women) were diagnosed with a first primary thyroid cancer. There were 96 thyroid cancer cases with missing information on histology. Of the 907 thyroid cancer cases with complete information on histology, 714 were papillary (79%), 145 were follicular (16%), 33 were medullary (4%), and 15 were anaplastic (2%).

Baseline smoking status was positively associated with alcohol intake in the pooled dataset, with a 58% prevalence of drinking among never smokers as opposed to 73% among ever smokers. Among never smokers, 34% consumed one or more drinks per week while 52% of ever smokers consumed one or more drinks per week.

Compared to having never smoked, current smoking at baseline was associated with a significantly reduced risk of thyroid cancer (HR=0.68, 95% CI: 0.55-0.85, Figure 1). The HR comparing former to never smoking was 0.98 (95% CI: 0.85-1.12). The association with current smoking was significant in the USRT cohort only (HR=0.63, 95% CI: 0.44-0.88), but the HRs were below unity in the other four cohorts, ranging between 0.18 and 0.90, and there was no evidence of a significant heterogeneity by cohort ($I^2=0.0\%$, P -heterogeneity=0.50). The HRs changed little after excluding individual cohorts, with the HR for current smoking ranging from 0.62 (after excluding NIH-AARP) to 0.74 (after excluding AHS). There were no significant interactions by age, sex, education, BMI, or by histology; however, the HRs were significant only for subjects under age 60 at baseline, women, those with post-high school education, and for papillary histology. HRs for current versus never smoking were 0.40 (95% CI: 0.09-1.75) for medullary thyroid cancer and 1.77 (95% CI: 0.18-17.36) for anaplastic thyroid cancer, but these results were based on a small number of cases. The association did not differ significantly by follow-up period (P -interaction=0.46); the HRs for current smoking for <5 years, 5-9 years, and 10 years of follow-up were 0.66 (0.46-0.96), 0.58 (0.41-0.80), and 0.65 (0.43-1.00), respectively. However, there was a significant interaction by alcohol intake (P -interaction=0.004). The inverse association for current smoking was strongest for subjects reporting no alcohol intake (HR=0.46, 95% CI: 0.29-0.74), while the HR for current smoking among subjects who reported one or more drinks per day was 0.86 (95% CI: 0.59-1.26). When we restricted the results by cohort, age, sex, education, BMI, and alcohol intake to papillary thyroid cancer cases, the inverse associations slightly strengthened in magnitude across most of the subgroups, and the interaction by sex was found to be statistically significant (Supplementary Table 1).

We also examined the associations of smoking duration, intensity, pack-years, and number of years since quitting among the cohorts that had collected the relevant data (Table 2). As in the main results, compared to never smoking, greater reductions in risk were observed for current versus former smoking. Within categories of former and current smokers, small reductions in thyroid cancer risk were observed with greater smoking intensity, smoking duration, and pack-years of smoking. We also observed a weak reduction in risk with greater number of years since quitting among former smokers.

Overall, we observed a significant inverse association between alcohol intake and thyroid cancer risk (<7 drinks per week versus 0, HR=0.72, 95% CI: 0.58-0.90, P -trend=0.002 [Table 3]; per drink per day, HR=0.88, 95% CI: 0.82-0.95 [Figure 2]). The test for heterogeneity by cohort was borderline-significant ($I^2=57.2\%$, P -heterogeneity=0.05); however, there was no evidence of inconsistency after the exclusion of BCDDP, the cohort with the smallest number of cases ($I^2=0.0\%$, P -heterogeneity=0.99). The HR per drink per day varied somewhat with the exclusion of individual cohorts, ranging from 0.87 (after excluding BCDDP) to 0.91 (after excluding NIH-AARP). The associations did not differ significantly by follow-up time (P -interaction=0.42). The inverse association between alcohol and thyroid cancer risk was stronger for papillary (HR=0.82, 95% CI: 0.74-0.92) versus follicular (HR=0.95, 95% CI: 0.93-1.18) thyroid cancers (P -interaction=0.08). The HR per drink/day was 0.94 (95% CI: 0.72-4.68) for medullary thyroid cancer and 0.86 (95% CI: 0.51-1.46) for anaplastic thyroid cancer, but these results were based on a small number of cases. When we restricted the results by cohort, age, sex, education, BMI, and smoking status to papillary thyroid cancer cases, the inverse associations slightly strengthened in magnitude across most of the subgroups (Supplementary Table 2).

We also examined the joint association of smoking and drinking on thyroid cancer risk. Compared to never smoking and non-drinking, current smoking and drinking 1 drink per week was associated with a 36% reduced risk (joint HR=0.64, 95% CI: 0.47-0.86). The joint HR was slightly weaker than the HR observed for current smoking among non-drinkers

(HR=0.46, 95% CI: 0.29-0.73) and similar to that observed for 1 drink per week among never smokers (HR=0.70, 95% CI: 0.56-0.87). Thus the relationship for the joint association of smoking and alcohol appeared to be sub-multiplicative (P -interaction=0.004). The exclusion of individual cohorts from the analysis had little influence on the joint HR, which ranged from 0.62 with the exclusion of USRT or PLCO to 0.65 with the exclusion of NIH-AARP.

U.S. trends in the prevalence of current smoking and alcohol drinking and the incidence of thyroid cancer by sex and race, as well as per capita alcohol consumption, are presented in Figure 3. The prevalence of current cigarette smoking declined for all sex and race categories since the 1960s. Thyroid cancer incidence increased since the early 1980s, which is consistent with an approximate 10- to 20-year time lag after the reduction in current smoking, and at a similar rate across sex and race categories. Data on alcohol consumption show a less clear trend during this time period. However, a decline in alcohol consumption between 1982 and 1998 is not inconsistent with the rise in thyroid cancer incidence which occurred during, and subsequent to, this time period.

Discussion

Overall, we observed an inverse association between current versus never smoking and risk of thyroid cancer, which was consistent across the five prospective studies and stronger among non-drinkers. Our data also showed greater reductions in risk with greater smoking intensity and duration and, among former smokers, with more recent quitting. An inverse association was observed between alcohol consumption and thyroid cancer risk, which was more pronounced among never smokers. These associations were most evident for papillary thyroid cancer versus other histological sub-types.

In 2003, results from an international pooled analysis of 14 case-control studies were published showing a significant 40% reduction in risk for current, compared to never, smoking and a small reduction in risk for alcohol drinkers compared to non-drinkers [10]. The results for smoking were highly consistent across studies, whereas significant between-study heterogeneity was observed for the alcohol-thyroid cancer association. The pooled case-control analysis also showed evidence that lack of adjustment for smoking status biased the association between alcohol and thyroid cancer risk [10]; however, results for alcohol drinking among never smokers (or smoking among non-drinkers), which may have been useful in assessing the degree of confounding, were not shown.

Our finding of a sub-multiplicative interaction between smoking and alcohol intake suggests that there may be common biological mechanisms underlying these associations. Compared to never or former smokers, current smokers have lower levels of thyroid stimulating hormone (TSH) [29, 30], triiodothyronine (T3) [30], and thyroxine (T4) [30], a lower prevalence of serum thyroid autoantibodies [29], and a higher risk of Graves' hyperthyroidism [29]. TSH, in particular, has long been hypothesized to play a major role in the development of thyroid cancer [31-33]. However, studies examining alcohol drinking in relation to thyroid volume, free T4, and TSH have been inconsistent [34, 35]. Cigarette smoking and alcohol could also potentially influence thyroid cancer risk by altering sex steroid hormone levels [31, 36-38].

Similar to the smoking results, the inverse association for alcohol was more pronounced for papillary versus follicular thyroid cancers. However, in previous studies of smoking, alcohol, and thyroid cancer that had examined differences by histology, including the pooled analysis of case-control studies [10], no significant differences between papillary and follicular sub-types were reported [7, 8, 11, 17]. Although the differences by histology

observed in the current study may have arisen due to chance, as the sample sizes for follicular, medullary, and anaplastic thyroid cancers were relatively small despite the large number of study subjects, these results also indicate a possible difference in the etiology of these tumor sub-types. Alternatively, stronger inverse associations for papillary thyroid cancers versus other histological sub-types may reflect less rigorous screening or diagnostic scrutiny for current smokers and heavier drinkers compared to the rest of the population. This type of bias may partly explain the results from a previous analysis in the NIH-AARP cohort which showed a null association for wine intake but an inverse association for beer [19]. Wine drinking has been associated with indicators of higher socioeconomic status in the U.S. compared to beer and liquor drinking and therefore may be associated with health care access and utilization [39]. Studies with greater ability to distinguish tumors according to the likely means of detection (i.e., screen-detected versus symptomatic) would help to address a potential screening bias.

The rise in thyroid cancer incidence in the U.S. since the early 1980s has remained largely unexplained [2, 3]. A decline in the prevalence of cigarette smoking and alcohol intake during this time period would be consistent with inverse associations between these exposures and thyroid cancer risk observed in this and previous studies. Indeed, national data on trends in smoking and, possibly, alcohol consumption over calendar time appear to be consistent with the upward trend in thyroid cancer incidence.

Our restriction to studies that were prospective in design ensured that the exposures preceded the diagnosis of the disease and greatly reduced the potential for differential selection and recall biases to have influenced the results. The large number of thyroid cancer cases allowed for the estimation of relatively precise relative risk estimates, even within subsets of the population, such as never smokers and non-drinkers. There were some limitations as well. Because information on cigarette smoking behaviors and alcohol consumption was based on self-report, it is possible that non-differential misclassification of actual exposure levels in these prospective studies biased our relative risk estimates toward the null. We also had limited information on smoking and alcohol intake during follow-up. Many participants who currently smoked at baseline likely quit during follow-up, and alcohol intake probably changed over time as well. It is also possible that the non-drinking category included some individuals who had recently quit drinking alcohol due to thyroid cancer-related symptoms and were subsequently diagnosed with thyroid cancer during follow-up. However, we did not find significant attenuation of the HRs after excluding the first 10 years of follow-up, and exclusion of USRT, the cohort with the longest follow-up, did not change the results for either smoking or alcohol materially. Data on ionizing radiation exposure and history of benign thyroid conditions, the two most well-established risk factors for thyroid cancer, were not available in all of the cohorts, so we were unable to assess possible confounding by these factors in the pooled dataset. However, in the USRT cohort, additional adjustment for radiation and benign thyroid conditions had little influence on the smoking and alcohol associations (data not shown).

Due to differences in the data collection instruments, we were limited in our ability to combine data on beer, wine, and liquor intake. Future pooled studies combining similar questionnaire data may be better equipped to address differences in thyroid cancer risk according to alcohol type. We were also unable to examine the relationship between alcohol intake at younger ages or cumulative lifetime alcohol consumption, as most of the baseline questionnaires inquired about alcohol consumed over the previous 12 months. Finally, although the median age of thyroid cancer diagnosis in the U.S. is 50 [40] the mean age at enrollment in the five cohorts was 58. Thus, the associations observed in this pooled analysis may not be applicable to thyroid cancers diagnosed at young ages.

Results of this pooled analysis of prospective studies suggest that cigarette smoking and alcohol consumption are associated with a reduced risk of papillary thyroid cancer and, possibly, follicular thyroid cancer. That the associations were strongest among non-drinkers and never smokers, respectively, suggests that the results for smoking were not influenced by residual confounding by alcohol intake, and vice versa, and that common biological effects on thyroid cancer development may be shared between these two exposures. Additional studies investigating the influence of cigarette smoke and alcohol on the thyroid gland or the role of thyroid and sex steroid hormones in thyroid cancer development could help to improve our understanding of the potential mechanisms underlying the inverse associations with cigarette smoking and alcohol consumption.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between smoking status (former and current, versus never) and thyroid cancer risk (n=746,097). All models used attained age used as the underlying time metric and were adjusted for sex, education, race, marital status, body mass index, alcohol intake, and cohort. *, test for heterogeneity calculated using the Mantel-Haenszel test for heterogeneity, **, test for interaction calculated using the likelihood ratio test comparing a model with a cross-product term to a model without

Figure 2.

Hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between alcohol intake (per drink/day) and thyroid cancer risk (n=746,097). All models used attained age used as the underlying time metric and were adjusted for sex, education, race, marital status, body mass index, smoking status, and cohort. *, test for heterogeneity calculated using the Mantel-Haenszel test for heterogeneity. **, test for interaction calculated using the likelihood ratio test comparing a model with a cross-product term to a model without. ^a One drink of alcohol is equivalent to 14 grams of ethanol.

Figure 3. U.S. trends in the age-adjusted prevalence of current cigarette smoking (*left panel*), 1965-2009 and alcohol drinking (*middle panel*) 1997-2009 among individuals ages 18 and older by race and gender (National Center for Health Statistics [25]), annual per capita alcohol consumption (gallons; *middle panel*) 1965-2007 (National Institute on Alcohol Abuse and Alcoholism [26]), and the age-adjusted incidence of thyroid cancer (*right panel*) by race and gender 1975-2009 (SEER 9 [27]).

Table 1
General characteristics of the cohorts at baseline

Cohort	No. participants	No. cases	Study period	Age at baseline (mean [SD])	Male (%)	Current smokers (%)	Alcohol drinkers (%)
NIH-AARP Diet and Health Study (NIH-AARP)	473,525	549	1995-2006	62.0 (5.4)	60	12	70
US Radiologic Technologists Study (USRT)	89,983	280	1983-2006	40.3 (11.1)	23	23	79
Agricultural Health Study (AHS)	81,101	79	1993-2005	46.0 (12.7)	63	15	45
Prostate, Lung, Colorectal, and Ovarian Screening Study (PLCO)	59,907	64	1993-2009	62.6 (5.3)	51	10	63
Breast Cancer Detection Demonstration Project (BCDDP)	41,581	31	1987-1997	61.9 (8.2)	0	13	39
Total	746,097	1,003	1983-2009	57.7 (11.1)	52	14	66

Hazard ratios (HRs)^{a,b} and 95% confidence intervals (CIs) for the associations between smoking duration, intensity, pack-years, and number of years since quitting and thyroid cancer risk (n=746,097)

Table 2

Smoking intensity				
	Never	Former	Current	P-trend*
		20 cigarettes/day	<20 cigarettes/day	20 cigarettes/day
No. cases	498	268	132	69
Pooled HR (95% CI)	1.00 (Ref)	1.02 (0.88-1.19)	0.89 (0.73-1.09)	0.69 (0.53-0.88)
No. cases excluding NIH-AARP	270	103	26	36
Pooled HR (95% CI)	1.00 (Ref)	0.99 (0.79-1.25)	0.68 (0.45-1.03)	0.62 (0.44-0.88)
		0.58 (0.36-0.93)		<0.001
Smoking duration				
	Never	Former	Current	P-trend*
		<20 years	20 years	<20 years
No. cases excluding NIH-AARP	270	94	35	29
Pooled HR (95% CI)	1.00 (Ref)	0.97 (0.76-1.23)	0.79 (0.55-1.14)	0.74 (0.50-1.09)
		0.51 (0.34-0.77)		<0.001
Pack-years				
	Never	Former	Current	P-trend*
		<20	20	<20
No. cases excluding NIH-AARP	270	101	27	34
Pooled HR (95% CI)	1.00 (Ref)	0.98 (0.78-1.24)	0.71 (0.47-1.07)	0.68 (0.48-0.98)
		0.51 (0.32-0.81)		<0.001
Years since quitting				
	Never	Former	Current	P-trend*
		10 years	5-9 years	<5 years
No. cases excluding AHS	448	223	43	33
Pooled HR (95% CI)	1.00 (Ref)	0.98 (0.82-1.16)	0.96 (0.70-1.32)	0.88 (0.61-1.26)
		0.70 (0.56-0.87)		0.001

* test for trend calculated by modeling smoking categories as continuous and evaluating the statistical significance of the Wald test

^a Attained age used as the underlying time metric; adjusted for sex, education, race, marital status, body mass index, alcohol intake, and cohort

^b Results for subjects with missing data not shown

Table 3
Study-specific and pooled hazard ratios (HRs)^a and 95% confidence intervals (CIs) for the association between alcohol intake and thyroid cancer risk (n=746,097)

	Alcohol intake (drinks/week)				<i>P</i> -trend ^a
	0	>0-<1	1-<7	7	
NIH-AARP					
No. cases	201	123	145	80	
HR (95% CI)	1.00 (Ref)	0.82 (0.65-1.02)	0.91 (0.73-1.13)	0.66 (0.50-0.87)	0.01
USRT					
No. cases	62	125	81	12	
HR (95% CI)	1.00 (Ref)	1.04 (0.76-1.42)	0.81 (0.58-1.15)	1.02 (0.54-1.91)	0.29
AHS					
No. cases	54	8	11	6	
HR (95% CI)	1.00 (Ref)	0.60 (0.28-1.26)	0.60 (0.31-1.17)	0.80 (0.33-1.93)	0.16
PLCO					
No. cases	30	13	13	8	
HR (95% CI)	1.00 (Ref)	0.96 (0.50-1.86)	0.80 (0.41-1.55)	0.57 (0.25-1.30)	0.18
BCDDP					
No. cases	14	10	2	5	
HR (95% CI)	1.00 (Ref)	4.04 (1.75-9.31)	0.54 (0.12-2.45)	3.79 (1.27-11.32)	0.13
No. total cases	361	279	252	111	
Pooled HR (95% CI)^b	1.00 (Ref)	0.92 (0.78-1.08)	0.83 (0.70-0.98)	0.72 (0.58-0.90)	0.002

^a Attained age used as the underlying time metric; adjusted for sex, education, race, marital status, body mass index, and smoking status

^a Additionally adjusted for cohort

^{*} test for trend calculated by modeling the categorical variable as continuous and evaluating the statistical significance of the Wald test