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Cigarette Smoking And Thyroid Cancer Risk: A Population-Based Case-Control Study

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CIGARETTE SMOKING AND THYROID CANCER RISK: A POPULATION-BASED CASE-CONTROL STUDY

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Abstract

Objective: Thyroid cancer incidence has increased substantially in the United States. Previous studies of the relationship between cigarette smoking and thyroid cancer have yielded conflicting results.

Methods: In order further clarify the association between cigarette smoking and risk of thyroid cancer, we analyzed data from a population-based case-control study in Connecticut in 2010-2011 including 462 histologically confirmed incident thyroid cancer cases and 498 population-based controls. Multivariate unconditional logistic regression models were used to estimate the associations between cigarette smoking and risk of thyroid cancer adjusting for potential confounders.

Results: Our data showed a decreased risk of well-differentiated thyroid carcinoma among microcarcinomas (tumor size less than or equal to 1cm) by current smoker (OR=0.30, 95%CI 0.13, 0.70), lowest intensity category (OR=0.33, 95%CI 0.15- 0.74) as well as longest duration category (OR=0.18, 95%CI 0.07-0.47). No significant associations were found between these smoking predictors and macrocarcinomas (tumor size larger than 1cm).

Conclusions: Our study findings are consistent with a number of several previous epidemiologic studies indicating that cigarette smoking is associated with a decreased risk of thyroid cancer. The research highlights the significance of distinguishing between microcarcinomas and macrocarcinomas in future research on etiology of thyroid cancer.

Key Words: thyroid cancer, cigarette smoking, case-control study, tumor size

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1. Introduction

Over the last few decades, the age-adjusted incidence rate of thyroid cancer has been rapidly increasing worldwide[1]. Compared to all other cancers, the incidence rate increased fastest from 8.74/100,000 in women and 3.38/100,000 in men in 1994 to 21.82/100,000 in women and 7.37/100,000 in men in 2011[2]. It is now the fifth most common cancer among women in the US[2].While the improvement in diagnostic technology such as fine needle aspiration with ultrasound guidance may be associated with increased detection of microcarcinomas (diameter<1 cm), the incidence for both smaller size tumors and larger size tumors were increasing[1].Besides, studies have shown that approximately fifty percent of the variability in thyroid cancer incidence rates in the US, cannot be explained by the "over-diagnosis"[3, 4]. Therefore, environmental factors may also play a role in the thyroid cancer development. There are some well-established risk factors for thyroid cancer, including radiation exposure[5-7], prior benign thyroid disease[7], and obesity[8]. Other risk factors for thyroid cancer are still unclear.

Cigarette smoking is at least related to 12 cancers according to The International Agency for Research on Cancer (IARC) and US Surgeon General (US-SG)[9, 10]. Previous studies showed controversial results about the effect of cigarette smoking on thyroid cancer risk[6, 7, 11-23]. Several of them found statistically significant negative associations between smoking and thyroid cancer risk[6, 11, 13, 15, 16, 18, 20, 21], while others found no association[12, 14, 19, 22-24] or positive association[17].

In light of the increasing trends of thyroid cancer incidence, especially microcarcinomas, and the inconsistent previous study results, we aimed to further clarify the association between cigarette smoking and thyroid cancer risk by histological type and tumor size and to get a better understanding of the role of cigarette smoking in the risk of thyroid cancer.

2. Literature review

The effects of smoking on the risk of thyroid cancer were controversial in previous literatures, although smoking is a well-established risk factor for many cancers.

There were totally fifteen previous studies investigated the association between smoking exposure and risk of thyroid cancer[6, 7, 11-23]. Six of them found no association between smoking exposure and thyroid cancer risk[12, 14, 19, 22-24] while eight of them found statistically significant negative associations between smoking and thyroid cancer risk[6, 11, 13, 15, 16, 18, 20, 21]. Only one of them found significant positive association[17].

All the smoking exposure measurement in previous studies was self-reported. Majority of the studies examined the association among female populations[6, 7, 12, 13, 15, 16, 18, 21]. Only one study focused on the association among males only[11]. The remaining of the studies assessed the association between smoking and thyroid caner risk among all participants, regardless of

gender[14, 17, 19, 20, 22, 23].

There were 4 cohort studies evaluated the association between smoking and thyroid cancer risk[20-23]. Among them, one of the used retrospective cohort[23] while the other three used prospective cohort[20-22]. Among the remaining 11 out of 15 studies, case-control design was adopted[6, 7, 11-19].

With regard to the exposure assessment, all of the studies assessed smoking status, i.e. never or ever smoking, former or current smoking. Two of them examined smoking status, age at initiation, duration, intensity, pack-years and years since quitting[15, 16]. Other studies did not assess all of these smoking predictors. Among them, five out fifteen only measured smoking status without other smoking predictor measurement[17-19, 23].

3. Materials and Methods

3.1 Study population

The study population has been described elsewhere[25]. In brief, cases were histologically confirmed, incident thyroid cancer patients (ICD-O-3: 8021, 8050, 8052, 8130, 8260, 8290, 8330-8332, 8335, 8340-8346, 8450, 8452, 8510) in Connecticut diagnosed between 2010 and 2011. Eligible subjects were aged 21 to 84 years at diagnosis, having no previous diagnosis

of cancer, with the exception of non-melanoma skin cancer, and were alive at the time of interview. Cases were identified through the Yale Cancer Center's Rapid Case Ascertainment Shared Resource (RCA). RCA acts as an agent of the Connecticut Tumor Registry. The Connecticut Public Health Code requires reporting of cancers from licensed hospitals and clinical laboratories to the Connecticut Tumor Registry. In order to identify newly diagnosed cases, RCA field staffs are assigned geographically to survey all of the state's non-pediatric hospitals. Information on cases identified in the field is sent regularly to the RCA data entry staff where the case's demographic data are entered, verified and screened against the Connecticut Tumor Registry database. The Connecticut Tumor Registry has reciprocal reporting agreements with cancer registries in all adjacent states (and Florida) to identify Connecticut residents with cancer diagnosed and/or treated in these states. A total of 701 eligible incident thyroid cancer cases were identified during the study period with 462 (65.9%) completing in-person interviews. Population-based controls with Connecticut addresses were recruited using a random digit dialing method. A total of 498 subjects participated in the study, with a participation rate of 61.5%. Controls were frequency matched to cases by age (□5 years). Distributions of age, gender and race were similar between the participants and non-participants for both cases and controls.

All procedures were performed in accordance with a protocol approved by the Human Investigations Committee at Yale and the Connecticut Department of Public Health. After

approval by the hospitals and by each subject's physician (cancer cases), or following selection through random digit dialing sampling (control population), potential participants were approached by letter and then by phone. Those who agreed were interviewed by trained study interviewers, either at the subject's home or at a convenient location. After obtaining written consent, a standardized, structured questionnaire was used to obtain information on sociodemographic characteristics, gynecological and reproductive history, medical history, family history, habitual diet, clinical information as well as smoking history.

3.2 Exposure assessment

Ever smokers were defined as those who smoked at least 100 cigarettes prior to 1 year before the disease diagnosis for cases or the interview for controls. Never smokers were those who reported smoking less than a total of 100 cigarettes in their lifetime. Ever smokers were further questioned as to the age when first started smoking cigarettes, whether or not they were smoking at diagnosis (yes/no), age at quitting (former smokers), number of years quitting between first and last smoked, and number of cigarettes smoked per day.

3.3 Statistical analysis

Unconditional logistic regression models were used to estimate the odds ratio (ORs) and 95% confidence intervals (95%CI). By using never smokers as the reference group, ORs and 95% CI

were estimated for ever smokers, current smokers, former smokers, age at initiation of smoking (<20 and ≥20 years old), intensity of smoking (<10, 10- 20, and ≥20 cigarettes per day), duration of smoking (<10, 10- 29, and ≥29 years), pack-years (pack-years= number of packs smoked per day times number of years smoked) of exposure (<5, 5 - 24 and ≥24 pack-years), and years since quitting smoking (<13, 13- 28 and ≥28 years).All cut points were based on the distribution among control subjects. We also restricted our analyses to papillary and well-differentiated (papillary and follicular combined due to the small sample size of follicular carcinoma) thyroid cancer subtypes. In order to exam the effect of smoking status on tumor size, analyses were also conducted by dividing the cases into two groups according to the tumor size (≤ 1cm, >1 cm) among papillary and well-differentiated carcinoma, respectively. We also analyzed thyroid cancer among women because the number of men was too small for a meaningful analysis.

462 cases and 498 controls were included in the final analysis with known smoking status. Age, gender, race, family history of any cancer, education, BMI, previous benign thyroid diseases, history of radiation exposure and previous alcohol consumption were considered as potential confounding variables and were controlled in the model. Decisions on which covariates to include in the final model were based on a greater than 10% change in the estimates. Tests for linear trends were calculated by using smoking predictor variables as continuous variables in the multivariate unconditional logistic regression models.

Statistical analyses for this study were performed by using the SAS system version 9.3 (SAS Institute Inc., Cary, NC, USA). Results were considered statistical significance when 2-sided p-values were <0.05.

4. Results

4.1 Description of study population

The majority of 462 cases were diagnosed with papillary thyroid cancer (392, 84.8%) followed by follicular (56, 12.1%), medullary (12, 2.6%), anaplastic (1, 0.2%), and others (1, 0.2%). A total of 217 (47.0%) cases were microcarcinomas, and among them, 190 were papillary and 24 were follicular.

As illustrated in Table 1, the selected demographic characteristics of cases and controls were compared. Interviewed cases and controls were similar with respect to race and family history of any cancer, as well as previous radiation exposure. Compared to controls, cases tended to be less highly educated and have a higher BMI ($p<0.01$). Cases were more likely to have prior benign thyroid disease ($p<0.01$). Besides, 40.7% of cases had ever used alcohol compared to 53.6% of alcohol usage among controls ($p<0.01$). Cases were also more likely to be female compared to controls ($p=0.0003$).

4.2 Primary analysis

Table 2 showed the risk of thyroid cancer associated with smoking for all thyroid cancer subtypes combined. When compared to those who have never smoked, the risk of thyroid cancer did not seem to be changed significantly by ever, current, former smoking status, or pack-years. And the results did not show a trend of increasing risk associated with increasing years since stopping smoking or the age started smoking. Reduced risk was seen in the low intensity category with less than 10 cigarettes per day (OR=0.52, 95%CI 0.30-0.90) and longest duration category (OR=0.42, 95%CI 0.23-0.81). And there is a statistical significant negative trend of duration (P for trend linear=0.01).

4.3 Stratified analysis

When we restricted the analysis to different histological subtypes, there was a reduction in the risk of well-differentiated thyroid cancer with regard to current smoker (OR=0.51, 95%CI 0.28-0.94) and lowest intensity category (OR=0.53, 95%CI 0.31-0.93)(Table 3). Moreover, smokers who smoked 29 years or more experience a 60% reduced risk (OR=0.40, 95%CI 0.21- 0.76) of developing well-differentiated carcinoma compared with never smokers, illustrating a dose-response relationship between smoking duration and well-differentiated carcinoma (P for linear trend=0.01). There was a negative association between papillary carcinoma and smoking

duration more than 29 years (OR=0.38, 95%CI 0.19-0.77) as well as a significant linear trend (p for linear trend=0.01). No significant associations were observed for ever or former smokers, age at initiation, pack-years, or years since quitting with the risk of well-differentiated and papillary thyroid carcinoma.

The risk of thyroid cancer associated with cigarette smoking by tumor size was presented in Table 4. A reduction in the risk of well-differentiated thyroid microcarcinomas were observed for current smokers (OR=0.30, 95%CI 0.13- 0.70), lowest intensity category (OR=0.33, 95%CI 0.15- 0.74), as well as the longest duration category (OR=0.18, 95%CI 0.07-0.47). A dose-response relationship between duration of smoking and well-differentiated thyroid microcarcinomas (P for linear trend<0.01) was also observed. Similar patterns were also seen in papillary thyroid microcarcinomas. No significant associations with smoking were shown for either well-differentiated or papillary thyroid carcinoma with tumor size larger than 1cm.

We also analyzed the risk of thyroid cancer by smoking among women (Table 6). Similar associations were found among women which suggests that gender was not an effect modifier. Table 7 showed the association between thyroid cancer risk and cigarette smoking among men where no significant results were observed.

Risk of thyroid cancer associated with cigarette smoking by tumor size among all cancer types is showed in Table 8. No significant result was observed among macrocarcinomas.

4.4 Sensitivity analysis

Sensitivity analyses showed that the association between smoking predictors and risk of well-differentiated microcarcinomas (Table 6) and papillary microcarcinomas (Table 7) did not materially changed, implying the robust association between smoking and thyroid cancer.

5. Discussion

In this population-based case-control study, ever smokers did not seem to change the risk of thyroid cancer overall. Being a current smoker, smoking less than 10 cigarettes per day, and increasing duration of smoking appeared to be associated with a reduced risk of thyroid cancer overall. Besides, smoking duration showed a significant inverse linear dose-response in risk of thyroid cancer. Restriction to females alone demonstrated similar results pattern with regard to thyroid cancer risk by current smokers, lowest smoking intensity category as well as longest smoking duration category. Similar results, except for significant negative linear trends in duration, were only shown in well-differentiated carcinoma, although it is not surprising due to the smaller sample size of papillary carcinoma subtypes if the association is weak. When further stratified by tumor size among well-differentiated and papillary carcinomas, similar patterns only

appeared in microcarcinomas.

Among previous studies examining the association between thyroid cancer risk and smoking, Four[15, 18, 20, 21]showed an inverse association for current versus never smokers and thyroid cancer risk. Consistent with these studies[15, 18, 20, 21], our results also show an inverse association of being a current smoker.

It remains unclear why the relation between smoking status and thyroid cancer risk only exists for current smokers regardless of thyroid cancer subtypes, tumor size and gender. Previous studies have demonstrates some potential underlying mechanisms[26]. In comparison with never or former smokers, the level of thyroid stimulating hormone (TSH), serum thyroid autoantibodies are lower in current smokers[26]. High TSH and serum thyroid autoantibody level have been suggested to be related with increased risk of thyroid cancer[16]. Therefore, any agent that could lower TSH and thyroid autoantibodies level may play a protective role. Another potential mechanism is by altering sex steroid hormone levels[27, 28]. Incidence of thyroid cancer is higher in women than men[1], which provides support for the role of estrogens in thyroid carcinogenesis[29]. Thus, by functioning as an anti-estrogen, current smoking status could possibly influence the thyroid cancer risk and similar inverse association has been already observed in endometrial cancer[30].

Another possible biologic support for our finding of association between thyroid cancer risk and smoking predictor variable may be due to gene-environmental interaction. Studies have shown that Cytochrome P4501A1 (CYP1A1) gene variants are associated with thyroid cancer risk[31, 32]. CYP1A1 gene encodes for the enzyme aryl hydro-carbon hydroxylase (AHH), which plays a very critical part in transforming polycyclic aromatic hydrocarbons (PAH) that found in cigarette smoke, into carcinogens[33]. Variable ability in different individual to biotransform potentially toxic substances has been associated with greater or lesser susceptibility to toxicity and subsequent thyroid cancer risk[34]. It is possible that distinct patterns of CYP1A1 genotypes provide a partial explanation for discrepancies in the association between smoking status and susceptibility to thyroid cancer. Further study with regard to the interaction of smoking and CYP1A1 polymorphism and its influence on thyroid carcinomas is needed.

Our study suggests that longer smoking duration was associated with decreased thyroid cancer risk, which is consistent with two previous case-control studies by Krelger et al. [16] and Galanti et al.[6]. Besides, the results also showed an inverse dose-response effect associated with smoking duration, which is also consistent with previous epidemiology studies. In a population-based case control study conducted in Canada by Krelger et al.[16], smoking duration was associated with decreased risk of thyroid cancer, in both women and men, and the inverse dose-response was

highly statistically significant. Women's Health Initiative (WHI) study[20] also showed a marginally significant inverse linear association between papillary carcinoma and smoking duration. There is no reduced risk among smokers who initiated smoking younger than 20 years old or smokers who had quit smoking less than 13 years prior to enrollment in our study. Similar findings were also observed among previous studies with regard to age started smoking [6, 16, 20] and years since stopped smoking[16, 20].

A significant decreased risk only among lowest intensity category (less than 10 cigarettes per day) is demonstrated in our results and there is no inverse trends compared to the results reported in the Canadian study[16]. It may be due to the smaller sample size in our study and potential under reporting of cigarette smoking history among cases. Although lowest intensity category and longest duration are associated with reduced risk of thyroid cancer, there is no significant association in any pack-years category, which is defined as pack per day times years of smoking. Among five studies that examined the effect of pack years[12, 15, 16, 20, 22], the Canadian case-control study[16] and prospective WHI cohort study[20] found negative association between pack-years and thyroid cancer risk, which might still due to its large sample size. The remaining three studies found no association.

When we stratified by tumor size in both well-differentiated carcinoma and papillary carcinoma,

similar results seen in Table 2 are only observed among microcarcinomas, but not in macrocarcinomas. And the point estimate is smaller in microcarcinomas compared to all cases combined. It is still unequivocal why microcarcinomas are more susceptible to smoking exposure. It is very likely that smoking-associated-thyroid microcarcinomas is related to a new disease with a different etiology. An observational study of papillary microcarcinomas from Japan demonstrated that 6.4% and 15.9% of patients whose papillary microcarcinomas showed enlargement by 3 mm or more on 5-year and 10-year follow-up, respectively, and enlargement process was not associated with patient background or clinical features [35].

In this study, trained interviewers used in-person, standardized, and structured interviews to minimize the information bias resulting from exposure misclassification. Subjects were asked standard, detailed questions with respect to their smoking history. Therefore the smoking status, instead of yes or no, was measured in several different aspects including age began smoking, intensity and duration of smoking, lifetime cumulative exposure to smoke and age since quitting smoking. Thus we could investigate which part of cigarette smoking, if any, has an impact on the risk of thyroid cancer. Another strength is that the participation rate in both cases and controls are high. Besides, carefully reviewed pathologic reports allowed the stratified analysis based on the pathological information.

Some limitations should be taken into consideration when interpreting the results. One of our drawbacks is that the smoking predictors were based on self-reporting. Therefore, potential recall bias cannot be ruled out. Bias could result from social desirability, which may affect the accuracy of smoking status[36]. In addition, there is no internal exposure measurement of smoking. Study has showed that the saliva cotinine levels of smokers varies, even though they smoked same number of cigarettes everyday[37]. Other factors such as the depth and duration of inhalation, number of puffs per cigarette and tapering of ventilation holes, etc. could also have an impact on the precise smoking exposure measurement[38]. Finally, due to the sample size limitation, we could not investigate the association between smoking status and rare histologic subtypes such as follicular, medullary and anaplastic thyroid cancer.

6. Conclusion

In summary, this population-based case-control study supported that hypothesis that cigarette smoking is associated with a reduced risk of thyroid cancer, and the risk may varied by histologic subtype. The novel finding that a reduced risk was only associated with thyroid microcarcinomas warrant further investigation.

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Appendix

A.1 List of abbreviations

- AHH: aryl hydro-carbon hydroxylase
- BMI: Body mass index
- CI: Confidence interval
- CYP1A1: Cytochrome P450 1A1
- IARC: The International Agency for Research on Cancer
- ICD: International Classification of Diseases
- OR: Odds ratio
- PAH: Polycyclic aromatic hydrocarbon
- RCA: Rapid Case Ascertainment Shared Resource
- SD: Standard deviation
- TSH: thyroid stimulating hormone
- US-SG: US Surgeon General
- WHI: Women's Health Initiative

A.2 List of previous studies on smoking and thyroid cancer

Author (by year)	Setting	Design	Sample Size/Cases	Exposure assessment	Exposure measurement	Result OR (95% CI)	Conclusion
Zivaljevic (2013)[11]	Belgrade, Serbia 2005-2010	Case-control study	408/204 All males	Self-report	Smoking status, duration, intensity	Smoking status: Ever smoker, among males 0.36 (0.19-0.69)	Significantly negative association
Kabat (2010)[20]	WHI study, USA 1991-2010	Prospective cohort study	159,340 (331 cases)	Self-report	Smoking status, age at initiation, duration, intensity, pack-years,	All cancer combined: Current: 0.54 (0.29-1.00) Intensity: 0-4: 1.13 (0.79-1.60) 5-14: 1.22 (0.91-1.65) Age at initiation: <20: 1.13 (0.88-1.45) >=20: 1.00 (0.75-1.33) Duration: >=30: 0.79 (0.55-1.22) P for linear trend: 0.12 Among papillary carcinoma Current: 0.34 (0.15-0.78) Intensity: 0-4: 1.20 (0.82-1.74) 5-14: 1.26 (0.91-1.75) Duration: >=30: 0.68 (0.44-1.04) P for linear trend: 0.06 Pack-years >=40: 0.44 (0.21-0.89) P for linear trend: 0.08	Negative association between papillary carcinoma risk and current smoking status and pack-years greater or equal to 40.

A.2 List of previous studies on smoking and thyroid cancer (continued)

Author (by year)	Setting	Design	Sample Size/cases	Exposure assessment	Exposure measurement	Result OR (95% CI)	Conclusion
Melnhold (2010)[21]	US 1983-2006	Prospective cohort study	90,713 (282 cases)	Self-report	Smoking status, intensity	Among females: (HR) Current smoker: 0.54 (0.35-0.82) Intensity: Current>=20: 0.38 (0.18-0.82)	Significantly negative association among current smoker and intensity greater or equal to 20 cigarettes per day.
Gulgnard (2007) [12]	New Caledonia, France 1993-1999	Case-control study	744/232	Self-report	Smoking status, pack-years	Smoking status: Among females: Current smoker 0.96 (0.63-1.45) Pack years: 0-10: 1.24 (0.79-1.95) 10-20: 0.48 (0.21-1.07) 20-30: 1.09 (0.53- 2.77) >30: 0.87 (0.37-2.02) P for trend: 0.39	No association
Navarro Silvers (2005)[22]	Canada 1982-2000	Prospective cohort study	89,716 (169 cases)	Self-report	Smoking status, age at initiation, duration, intensity, pack-years	Among all cancer types combined: (HR) Current smoker: 1.01 (0.67-1.53) Duration: >=20: 1.02 (0.70-1.49) P for linear trend: 0.77 Intensity: <10: 1.04 (0.63-1.72) P for linear trend: 0.91	No association
Zivaljevic (2004)[13]	Belgrade, Serbia 1996-2000	Case-control study	408/204	Self-report	Age at initiation	Initiation age<20, among females 0.66 (0.50-0.90)	Significantly negative association

A.2 List of previous studies on smoking and thyroid cancer (continued) (continued)

Author (by year)	Setting	Design	Sample Size/cases	Exposure assessment	Exposure measurement	Result OR (95% CI)	Conclusion
Mack (2003)[24]	Los Angeles, USA 1980-1983	Case-control study	598/302	Self-report	Smoking status, age at initiation, intensity, duration	Among females: Current smoker: 1.1 (0.7-1.7) Former smoker: 0.9 (0.6-1.4)	No association
Memon (2002)[14]	Kuwait 1998-1999	Case-control study	626/313	Self-report	Smoking status	Ever smoker: 1.6 (1.0-1.8)	No association
Iribarren (2001)[23]	California, USA 1964-1997	Retrospective cohort study	204,964 (196 cases)	Self-report	Smoking status	Current smokers: RR:1.01 (0.71-1.42)	No association
Rossing (2000)[15]	Washington, USA 1988-1994	Case-control study	1,042/468	Self-report	Smoking status, age at initiation, duration, intensity pack-years, years since quitting	Among female papillary carcinoma Current smoker: 0.5 (0.4-0.7) Age at initiation: 8-14: 0.5 (0.3-0.9) 15-17:0.6 (0.3-1.0) 18-19: 0.5 (0.3-1.0) 20-36: 0.5 (0.2-1.0) Intensity: <10: 0.5 (0.3-1.2) >10: 0.5 (0.3-0.9) Pack-years: <5: 0.5 (0.3-1.0) 5-10: 0.6 (0.3-1.1) 10-20: 0.5 (0.2-0.9) >20: 0.6 (0.3-1.0)	Significantly negative association in current smoker, age at initiation 8-14, intensity greater than 10 cigarettes per day and 10-20 pack-years.

A.2 List of previous studies on smoking and thyroid cancer (continued))

Author (by year)	Setting	Design	Sample size	Exposure assessment	Exposure measurement	Result OR (95% CI)	Conclusion
Krelger (2000)[16]	Canada 1986-1988	Case-control study	3883/1224 for smoking status; 1316/264 for other smoking predictors	Self-report	Smoking status, age at initiation, intensity, duration, pack-years, Years since quitting	Among females: Ever smoker: 0.71 (0.60-0.83) Age at initiation: <15: 0.75 (0.51-1.08) 15-19: 0.69 (0.57-0.84) 20-24: 0.63 (0.46-0.85) >24: 0.83 (0.56-01.21) P for linear trend: ns Duration: <10: 1.05 (0.82-1.34) 11-20: 0.68 (0.52-0.89) 21-30: 0.48 (0.35-0.66) >30: 0.55 (0.40-0.76) P for linear trend:0.0003 Intensity: <10: 0.91 (0.72-1.14) 11-19: 0.86 (0.65-1.14) 20-25: 0.54 (0.42-0.69) >25 0.46 (0.30-0.70) P for linear trend:0.0002 Pack-years: <=4: 1.02 (0.79-1.31) 4.1-10: 0.79 (0.60-1.05) 10.1-25: 0.58 (0.45-0.75)	Significantly negative associations

						>25: 0.46 (0.33-0.64) P for linear trend:0.0001 Years since quitting: <3: 0.67 (0.55-0.81) 3-8: 0.97 (0.70-1.35) 9-15: 0.59 (0.41-0.85) >15: 0.73 (0.51-1.06) P for linear trend: ns	
Galanti (1996)[6]	Norway and Sweden 1993-1994	Case-control study	532/191	Self-report	Intensity, duration, age at initiation	Among females: Intensity: 1-7: 0.69 (0.47-1.01) 8-10: 0.94 (0.54-1.62) 11-15: 0.64 (0.38-1.06) >=16: 0.71 (0.33-1.51) Duration: 1-10: 0.85 (0.50-1.46) 11-20: 0.55 (0.31-0.97) >=21: 0.71 (0.41-1.23) Age at initiation: <15: 0.38 (0.18-0.80) 15-19: 0.74 (0.47-1.16)	Significantly negative association among 11-20 years of duration, and age at initiation less than 15 years.
Sokic (1994)[17]	Belgrad, Serbia	Case-control study	200/100	Self-report	Smoking status	Ever smoker: 7.12 (1.53-32.99)	No association
Hallquist (1993)[18]	Sweden	Case-control study	540/180	Self-report	Smoking status	Among females: Former smoker: 0.5 (0.2-0.96) Current smoker: 0.6 (0.3-0.96)	Significantly negative association among former and current smokers
Ron (1987)[19]	Connecticut, USA	Case-control study	444/159	Self-report	Smoking status	No OR and 95% CI was provided	No association

Table 1. Selected characteristics of thyroid cancer among cases and controls

	Cases (n=462)		Controls (n=498)		p-value
	#	%	#	%	
Age (years)					<0.01
Mean (SD)	51.2 (12.3)		54.2 (13.1)		
<40	64	12.9	86	18.6	
40-	123	24.7	115	24.9	
50-	139	27.9	149	32.3	
60-	100	20.1	81	17.5	
≥ 70	72	14.5	31	6.7	
Gender					0.0003
Femal	375	81.2	344	69.1	
Male	87	18.8	154	30.9	
Race					0.33
White	415	89.8	450	90.5	
Black	18	3.9	25	5.0	
Other	29	6.3	23	4.5	
BMI (kg m-2)					<0.01
<25	145	31.4	203	40.8	
25-29.99	146	31.6	168	33.7	
≥30	166	35.9	118	23.7	
Education					<0.01
High school or less	129	27.9	88	17.7	
Some college	31	6.7	25	5.0	
College graduate or more	285	61.7	366	73.5	
Others	13	2.8	13	2.6	
Family history of any cancer					0.75
None	143	31.0	159	31.9	
Any cancer	319	69.0	339	68.1	
Prior benign thyroid disease§					<0.01
Yes	259	56.0	20	4.0	
No	203	44.0	478	96.0	
Previous radiation exposure‡					0.68
Yes	456	98.7	488	98.0	
No	1	0.2	2	0.4	
Alcohol consumption†					<0.01
Never	270	58.4	226	45.4	
Ever	188	40.7	267	53.6	

§ Benign thyroid diseases included hyperthyroidism, hypothyroidism, goiter, thyroid nodules, and thyroid adenoma.

‡ Previous radiation exposure included previous diagnosis and therapeutic radiation exposure
†Ever alcohol consumption was defined as ever had more than 12 drinks of alcoholic beverages such as beer, wine, or liquor. 1drink beer=1 can or bottle; 1 drink wine =14 oz glass; 1 drink liquor= 1 shot.

Table 2. Risk of thyroid cancer associated with cigarette smoking for all thyroid cancer cases combined

	Cases (n=458) § #	Controls (n=493) § #	OR*	95% CI
Smoking				
Never	317	321	1.00	-
Ever	141	172	0.82	(0.57, 1.17)
Current	42	52	0.56	(0.31, 1.01)
Former	98	118	0.97	(0.65, 1.46)
Age at initiation (years)				
< 20	106	130	0.74	(0.50, 1.10)
≥ 20	35	42	1.17	(0.62, 2.21)
P for linear trend			0.40	
Intensity (# cig/day)				
<10	39	75	0.52	(0.30, 0.90)
10 -< 20	60	63	0.87	(0.52, 1.46)
≥ 20	39	33	1.42	(0.76, 2.66)
P for linear trend			0.58	
Duration (years)				
< 10	36	50	1.10	(0.63, 1.92)
10 -< 29	70	62	1.00	(0.61, 1.64)
>- 29	34	58	0.42	(0.23, 0.81)
P for linear trend			0.01	
Pack-years				
<5	36	53	1.02	(0.58, 1.77)
5 -< 24	48	61	0.58	(0.33, 1.01)
≥ 24	53	55	0.93	(0.53, 1.62)
P for linear trend			0.85	
Years since quitting				
<13	31	39	0.79	(0.41, 1.52)
13 -< 28	39	40	0.91	(0.49, 1.70)
≥ 28	28	39	1.29	(0.68, 2.46)
P for linear trend			0.45	

*Adjusted for age, gender, race, family history of any cancer, education, BMI, prior benign thyroid disease, and previous alcohol consumption.

§ Numbers may not sum to total due to missing data.

Table 3. Risk of thyroid cancer associated with cigarette smoking for thyroid cancer histological subtypes

Smoking	Controls (n=498)§	Papillary (n= 392)		Well differentiated (n=448)	
		Cases §	OR*95% CI	Cases §	OR*95% CI
Smoking					
Never	326	273	1.00	313	1.00
Ever	172	119	0.85 (0.58, 1.24)	135	0.80 (0.56, 1.16)
Current	52	35	0.59 (0.32, 1.10)	39	0.51 (0.28, 0.94)
Former	118	83	0.99 (0.65, 1.52)	95	0.97 (0.64, 1.47)
Age at initiation (years)					
< 20	130	89	0.75 (0.49, 1.13)	102	0.74 (0.49, 1.10)
≥ 20	42	30	1.31 (0.67, 2.58)	33	1.10 (0.57, 2.14)
P for linear trend			0.32		0.41
Intensity (# cig/day)					
<10	75	36	0.62 (0.36, 1.08)	38	0.53 (0.31, 0.93)
10 -< 20	63	49	0.85 (0.49, 1.48)	58	0.85 (0.50, 1.44)
≥ 20	33	31	1.33 (0.67, 2.62)	36	1.32 (0.69, 2.51)
P for linear trend			0.80		0.84
Duration (years)					
< 10	50	32	1.24 (0.69, 2.20)	36	1.15 (0.65, 2.01)
10 -< 29	62	60	1.01 (0.60, 1.71)	66	0.96 (0.58, 1.59)
≥ 29	58	26	0.38 (0.19, 0.77)	32	0.40 (0.21, 0.76)
P for linear trend			0.01		0.01
Pack-years					
0 - 5	53	32	1.14 (0.65, 2.02)	35	1.06 (0.61, 1.86)
5 - 24	61	46	0.69 (0.39, 1.20)	48	0.60 (0.34, 1.04)
≥ 24	55	37	0.73 (0.39, 1.37)	48	0.81 (0.45, 1.45)
P for linear trend			0.73		0.89
Years since quitting					
<13	39	28	0.81 (0.41, 1.61)	31	0.82 (0.43, 1.58)
13 -< 28	40	31	0.85 (0.44, 1.67)	38	0.88 (0.47, 1.67)
≥ 28	39	24	1.46 (0.74, 2.87)	26	1.32 (0.68, 2.55)
P for linear trend			0.37		0.46

*Adjusted for age, gender, race, family history of any cancer, education, BMI, history of goiter, history of thyroid nodules, history of radiation exposure and previous alcohol use.
§ Numbers may not sum to total due to missing data.

Table 4. Risk of thyroid cancer associated with cigarette smoking for thyroid cancer by tumor size

Smoking	Controls (n=498)[§]	Well-differentiated carcinoma				Papillary carcinoma			
		⩽ 1cm (n=214)		> 1cm (n=229)		⩽ 1cm (n=190)		> 1cm (n=199)	
		Cases[§]	OR*95% CI	Cases[§]	OR*95% CI	Cases[§]	OR*95% CI	Cases[§]	OR*95% CI
Smoking									
Never	321	150	1.00	160	1.00	133	1.00	138	1.00
Ever	172	64	0.65 (0.41, 1.04)	69	0.79 (0.49, 1.27)	57	0.71 (0.44, 1.16)	61	0.81 (0.50, 1.33)
Current	52	15	0.30 (0.13, 0.70)	24	0.73 (0.35, 1.40)	14	0.36 (0.15, 0.84)	21	0.78 (0.37, 1.66)
Former	118	49	0.90 (0.53, 1.50)	44	0.81 (0.47, 1.40)	43	0.96 (0.56, 1.65)	39	0.81 (0.46, 1.43)
Age at initiation (years)									
< 20	130	50	0.57 (0.34, 0.97)	57	0.72 (0.43, 1.21)	41	0.62 (0.36, 1.07)	50	0.71 (0.42, 1.22)
≥ 20	42	14	1.01 (0.44, 2.31)	12	1.12 (0.48, 2.64)	16	1.15 (0.49, 2.72)	11	1.31 (0.55, 3.11)
P for linear trend			0.43		0.51		0.54		0.32
Intensity (# cig/day)									
<10	75	12	0.33 (0.15, 0.74)	26	0.67 (0.35, 1.30)	12	0.39 (0.17, 0.88)	24	0.75 (0.39, 1.47)
10 -< 20	63	36	0.84 (0.45, 1.57)	21	0.55 (0.26, 1.15)	31	0.91 (0.47, 1.76)	17	0.47 (0.21, 1.04)
≥ 20	33	14	0.92 (0.38, 2.20)	21	1.72 (0.77, 3.77)	12	0.94 (0037, 2.39)	19	1.90 (0.85, 4.22)
P for linear trend			0.86		0.88		0.97		0.80
Duration (years)									
< 10	50	20	1.03 (0.51, 2.08)	15	1.06 (0.50, 2.22)	18	1.17 (0.57, 2.43)	13	1.05 (0.48, 2.28)
10 -< 29	62	32	0.90 (0.48, 1.69)	34	0.86 (0.45, 1.67)	27	0.94 (0.48, 1.82)	33	0.96 (0.50, 1.86)
≥ 29	58	12	0.18 (0.07, 0.47)	19	0.50 (0.23, 1.11)	12	0.22 (0.09, 0.58)	14	0.45 (0.19, 1.07)
P for linear trend			<0.01		0.06		<0.01		0.07

Pack-years									
0 - 5	53	13	0.75 (0.35, 1.60)	21	1.35 (0.68, 2.69)	12	0.84 (0.38, 1.85)	19	1.36 (0.67, 2.75)
5 - 24	61	27	0.56 (0.28, 1.10)	21	0.38 (0.18, 0.83)	26	0.67 (0.34, 1.32)	20	0.43 (0.19, 0.93)
≥ 24	55	22	0.66 (0.31, 1.42)	25	0.89 (0.42, 1.86)	17	0.61 (0.27, 1.39)	20	0.87 (0.40, 1.89)
P for linear trend			0.97		0.96		0.92		0.93
Years since quitting									
<13	39	15	0.64 (0.27, 1.52)	15	0.70 (0.29, 1.70)	14	0.72 (0.30, 1.74)	14	0.66 (0.26, 1.64)
13 -< 28	40	20	0.86 (0.39, 1.91)	18	0.70 (0.31, 1.60)	16	0.78 (0.33, 1.84)	15	0.76 (0.32, 1.78)
≥ 28	39	14	1.32 (0.59, 2.97)	11	1.16 (0.48, 2.82)	13	1.61 (0.71, 3.69)	10	1.16 (0.46, 2.95)
P for linear trend			0.45		0.96		0.25		0.87

*Adjusted for age, gender, race, family history of any cancer, education, BMI, prior benign thyroid disease, and previous alcohol consumption.
§ Numbers may not sum to total due to missing data.

Table 5. Risk of thyroid cancer associated with cigarette smoking for thyroid cancer among follicular carcinoma

Smoking	Controls (n=498) §	Follicular (n=56)	
		Cases§	OR*95% CI
Smoking			
Never	326	40	1.00
Ever	172	16	0.38 (0.16, 0.90)
Current	52	4	0.19 (0.05, 0.81)
Former	118	12	0.52 (0.20, 1.34)
Age at initiation (years)			
< 20	135	13	0.39 (0.16, 0.99)
≥ 20	37	3	0.34 (0.07, 1.76)
P for linear trend			0.98
Intensity (# cig/day)			
<10	75	2	0.07 (0.01, 0.47)
10 -< 20	63	9	0.44 (0.15, 1.32)
≥ 20	33	5	1.14 (0.29, 4.43)
P for linear trend			0.69
Duration (years)			
< 10	50	4	0.67 (0.18, 2.50)
10 -< 29	62	6	0.36 (0.10, 1.28)
≥ 29	58	6	0.27 (0.08, 0.97)
P for linear trend			0.03
Pack-years			
0 - 5	53	3	0.64 (0.14, 3.04)
5 - 24	61	2	0.04 (0.01, 0.23)
≥ 24	55	11	1.10 (0.37, 3.29)
P for linear trend			0.52
Years since quitting			
<13	39	3	0.43 (0.09, 2.19)
13 -< 28	40	7	0.60 (0.16, 2.17)
≥ 28	39	2	0.52 (0.09, 2.89)
P for linear trend			0.47

*Adjusted for age, gender, race, family history of any cancer, education, BMI, prior benign thyroid disease, and previous alcohol consumption.
§ Numbers may not sum to total due to missing data.

Table 6. Risk of thyroid cancer associated with cigarette smoking among females

	Controls (n=344) §	Cases (n=375) §	OR*95% CI
Smoking			
Never	227	264	1.00
Ever	117	111	0.76 (0.50, 1.15)
Current	39	37	0.52 (0.27, 1.00)
Former	76	73	0.93 (0.58, 1.49)
Age at initiation (years)			
< 20	91	89	0.67 (0.43, 1.06)
≥ 20	26	22	1.14 (0.55, 2.35)
P for linear trend			0.37
Intensity (# cig/day)			
<10	60	35	0.50 (0.27, 0.91)
10 -< 20	38	50	0.89 (0.49, 1.62)
≥ 20	19	24	1.13 (0.52, 2.45)
P for linear trend			0.92
Duration (years)			
< 10	33	30	1.08 (0.57, 2.03)
10 -< 29	45	52	0.87 (0.49, 1.55)
≥ 29	37	28	0.42 (0.20, 0.86)
P for linear trend			0.01
Pack-years			
0 - 5	37	31	0.96 (0.51, 1.79)
5 -< 24	46	40	0.53 (0.29, 0.99)
≥ 24	30	37	0.87 (0.44, 1.71)
P for linear trend			0.72
Years since quitting			
<13	23	22	0.79 (0.36, 1.73)
13 -< 28	29	29	0.77 (0.37, 1.60)
≥ 28	24	22	1.32 (0.63, 2.78)
P for linear trend			0.44

*Adjusted for age, race, family history of any cancer, education, BMI, prior benign thyroid disease, and previous alcohol consumption.
§ Numbers may not sum to total due to missing data.

Table 7. Risk of thyroid cancer associated with cigarette smoking among males

	Controls (n=154) §	Cases (n=87) §	OR*95% CI
Smoking			
Never	99	57	1.00
Ever	55	30	1.07 (0.48, 2.37)
Current	13	5	0.81 (0.18, 3.60)
Former	42	25	1.14 (0.49, 2.64)
Age at initiation (years)			
< 20	44	24	1.05 (0.43, 2.54)
≥ 20	11	6	1.14 (0.28, 4.62)
P for linear trend			0.43
Intensity (# cig/day)			
<10	15	4	0.47 (0.10. 2.27)
10 -< 20	25	10	0.85 (0.27, 2.71)
≥ 20	14	15	2.39 (0.74, 7.66)
P for linear trend			0.34
Duration (years)			
< 10	17	6	1.50 (0.42, 5.42)
10 -< 29	17	18	1.51 (0.52, 4.39)
≥ 29	21	6	0.44 (0.11, 1.78)
P for linear trend			0.43
Pack-years			
0 - 5	14	5	1.35 (0.36, 5.13)
5 -< 24	15	8	0.98 (0.27, 3.64)
≥ 24	25	16	0.99 (0.34, 2.83)
P for linear trend			0.95
Years since quitting			
<13	16	9	0.89 (0.25, 3.13)
13 -< 28	11	10	1.46 (0.42, 5.05)
≥ 28	15	6	1.15 (0.27, 4.93)
P for linear trend			0.85

*Adjusted for age, race, family history of any cancer, education, BMI, prior benign thyroid disease, and previous alcohol consumption.
§ Numbers may not sum to total due to missing data.

Table 8. Risk of thyroid cancer associated with cigarette smoking for thyroid cancer tumor size among all cancer types

Smoking	Controls (n=498) §	⩽ 1cm (n=217)		> 1cm (n=240)	
		Cases §	OR*95% CI	Cases §	OR*95% CI
Smoking					
Never	326	153	1.00	165	1.00
Ever	172	64	0.64 (0.40, 1.02)	75	0.84 (0.53, 1.32)
Current	52	15	0.30 (0.13, 0.69)	27	0.82 (0.41, 1.66)
Former	118	49	0.88 (0.52, 1.47)	47	0.84 (0.49, 1.42)
Age at initiation (years)					
< 20	135	50	0.56 (0.34, 0.95)	61	0.74 (0.45, 1.22)
≥ 20	37	14	1.00 (0.44, 2.27)	14	1.30 (0.59, 2.89)
P for linear trend			0.43		0.48
Intensity (# cig/day)					
<10	75	12	0.32 (0.14, 0.73)	27	0.65 (0.34, 1.24)
10 -< 20	63	36	0.82 (0.44, 1.54)	23	0.62 (0.31, 1.27)
≥ 20	33	14	0.90 (0.38, 2.16)	24	1.88 (0.90, 3.94)
P for linear trend			0.82		0.48
Duration (years)					
< 10	50	20	1.01 (0.50, 2.03)	15	1.00 (0.48, 2.09)
10 -< 29	62	32	0.89 (0.47, 1.67)	38	0.97 (0.52, 1.81)
>- 29	58	12	0.18 (0.07, 0.46)	21	0.56 (0.26, 1.20)
P for linear trend			<0.01		0.11
Pack-years					
0 - 5	53	13	0.73 (0.34, 1.56)	22	1.27 (0.65, 2.51)
5 - 24	61	27	0.55 (0.28, 1.09)	21	0.37 (0.17, 0.81)
≥ 24	55	22	0.65 (0.30, 1.38)	30	1.13 (0.57, 2.24)
P for linear trend			0.97		0.76
Years since quitting					
<13	39	15	0.62 (0.26, 1.48)	15	0.67 (0.28, 1.60)
13 -< 28	40	20	0.84 (0.38, 1.86)	19	0.76 (0.34, 1.70)
≥ 28	39	14	1.29 (0.58, 2.89)	13	1.19 (0.51, 2.76)
P for linear trend			0.50		0.90

*Adjusted for age, gender, race, family history of any cancer, education, BMI, prior benign thyroid disease, and previous alcohol consumption.
§ Numbers may not sum to total due to missing data.

Table 9. Sensitivity analysis of among papillary carcinoma

Smoking	Papillary carcinoma					
	≤ 1cm (n=190)			> 1cm (n=199)		
	Controls a	Cases a	OR*95% CI	Controls a	Cases a	OR*95% CI
Smoking						
Never	88	131	1.00	120	136	1.00
Ever	52	57	0.81 (0.44, 1.51)	53	61	1.24 (0.68, 2.27)
Current	15	14	0.38 (0.12, 1.20)	16	21	1.17 (0.46, 2.98)
Former	37	43	1.03 (0.52, 2.02)	37	39	1.23 (0.62, 2.45)
Age at initiation (years)						
< 20	47	45	0.64 (0.33, 1.24)	44	50	1.03 (0.53, 1.99)
≥ 20	5	12	2.53 (0.71, 8.99)	9	11	2.53 (0.81, 7.86)
P for linear trend			0.02			0.03
Intensity (# cig/day)						
<10	26	12	0.35 (0.13, 0.91)	27	24	0.84 (0.38, 1.85)
10 -< 20	15	31	1.46 (0.62, 3.44)	18	17	1.18 (0.46, 3.08)
≥ 20	11	12	0.97 (0.27, 3.42)	8	19	3.33 (1.11, 10.06)
P for linear trend			0.73			0.12
Duration (years)						
< 10	12	18	1.68 (0.66, 4.28)	15	13	1.48 (0.56, 3.91)
10 -< 29	28	27	0.68 (0.31, 1.48)	27	33	1.17 (0.54, 2.50)
≥ 29	12	12	0.23 (0.05, 1.04)	11	14	1.02 (0.34, 3.08)
P for linear trend			0.02			0.82
Pack-years						
0 - 5	14	12	1.08 (0.41, 2.82)	13	19	2.21 (0.89, 5.50)
5 - 24	24	26	0.70 (0.31, 1.56)	26	20	0.67 (0.28, 1.58)
≥ 24	14	17	0.58 (0.17, 2.00)	14	20	1.37 (0.52, 3.65)
P for linear trend			0.70			0.47
Years since quitting						
<13	12	14	1.08 (0.37, 3.15)	10	14	1.83 (0.60, 5.55)
13 -< 28	11	16	1.05 (0.35, 3.16)	13	15	1.02 (0.37, 2.80)
≥ 28	14	13	0.96 (0.34, 2.73)	14	10	1.07 (0.35, 3.23)
P for linear trend			0.63			0.96

*Adjusted for age, race, family history of any cancer, education, BMI, prior benign thyroid disease, and previous alcohol consumption.
§ Numbers may not sum to total due to missing data.

Table 10. Sensitivity analysis among well-differentiated carcinoma

Smoking	Well-differentiated carcinoma					
	≤ 1cm (n=214)			> 1cm (n=229)		
	Controls[§]	Cases[§]	OR*95% CI	Controls[§]	Cases[§]	OR*95% CI
Smoking						
Never	103	148	1.00	125	158	1.00
Ever	53	64	0.80 (0.45, 1.44)	56	69	1.21 (0.68, 2.13)
Current	15	15	0.35 (0.11, 1.11)	16	24	1.09 (0.43, 2.76)
Former	39	49	1.01 (0.53, 1.93)	40	44	1.22 (0.65, 2.32)
Age at initiation (years)						
< 20	49	50	0.63 (0.33, 1.20)	46	57	1.07 (0.58, 1.98)
≥ 20	5	14	2.37 (0.69, 8.19)	10	12	1.92 (0.66, 5.65)
P for linear trend			0.02			0.15
Intensity (# cig/day)						
<10	26	12	0.34 (0.13, 0.86)	31	26	0.72 (0.34, 1.53)
10 -< 20	17	36	1.34 (0.59, 3.03)	18	21	1.40 (0.58, 3.42)
≥ 20	11	14	1.06 (0.32, 3.46)	7	21	3.61 (1.19, 10.93)
P for linear trend			0.72			0.09
Duration (years)						
< 10	16	20	1.29 (0.54, 3.08)	18	15	1.44 (0.58, 3.56)
10 -< 29	27	32	0.75 (0.36, 1.57)	25	34	1.15 (0.55, 2.42)
≥ 29	11	12	0.22 (0.05, 1.09)	13	19	0.99 (0.36, 2.71)
P for linear trend			0.05			0.76
Pack-years						
0 - 5	16	13	0.98 (0.39, 2.46)	17	21	1.98 (0.85, 4.60)
5 - 24	24	27	0.63 (0.29, 1.40)	26	21	0.60 (0.26, 1.39)
≥ 24	14	22	0.80 (0.26, 2.43)	13	25	1056 (0.61, 4.00)
P for linear trend			0.41			0.33
Years since quitting						
<13	12	15	1.06 (0.37, 3.01)	12	15	1.58 (0.57, 4.35)
13 -< 28	12	20	1.26 (0.45, 3.48)	13	18	1.06 (0.40, 2.80)
≥ 28	15	14	0.78 (0.28, 2.17)	15	11	1.12 (0.39, 3.19)
P for linear trend			0.83			0.71

*Adjusted for age, race, family history of any cancer, education, BMI, prior benign thyroid disease, and previous alcohol consumption.
§ Numbers may not sum to total due to missing data.