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Risk factors for thyroid cancer: A prospective cohort study

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Given the higher incidence rate of thyroid cancer among women compared to men and evidence that smoking and alcohol consumption may be inversely related to thyroid cancer risk, we examined thyroid cancer risk in association with menstrual, reproductive and hormonal factors, and cigarette and alcohol consumption, in a prospective cohort study of 89,835 Canadian women aged 40–59 at recruitment who were enrolled in the National Breast Screening Study (NBSS). Linkages to national cancer and mortality databases yielded data on cancer incidence and deaths from all causes, respectively, with follow-up ending between 1998 and 2000. Cox proportional hazards models (using age as the time scale) were used to estimate hazard ratios and 95% confidence intervals for the association between each of the potential risk factors and risk of thyroid cancer overall and by the main histologic subtypes. During a mean of 15.9 years of follow-up, we observed 169 incident thyroid cancer cases. There was no evidence of altered overall thyroid cancer risk with any of the menstrual, reproductive, or hormonal factors. There was evidence of a decreased risk of papillary thyroid cancer among women with 5 or more live births (*vs.* nulliparous). Age at which smoking commenced, duration of smoking, number of cigarettes smoked per day, pack-years of smoking and alcohol consumption were not associated with altered thyroid cancer risk. The present study provides little support for associations with hormonal factors, smoking, or alcohol consumption, but there is a need for additional prospective data.

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Key words: thyroid neoplasms; prospective cohort; reproductive and hormonal risk factors; smoking history; alcohol consumption

Thyroid carcinomas are generally rare, with an annual incidence rate of approximately 5.7 per 100,000 in the United States.¹ Other than ionizing radiation, the only definitively established risk factor for this disease,² little is known about the etiology of thyroid cancer. However, given that the incidence of thyroid cancer is consistently higher in women than in men^{3,4} and the finding that estrogen receptors are present in papillary and follicular thyroid carcinomas (the 2 major histologic subtypes of thyroid cancer),⁴ it has been hypothesized that hormonal factors may be involved in the etiology of thyroid cancer. Furthermore, there is experimental evidence that elevated thyroid-stimulating hormone (TSH) levels may play a role in the development of thyroid carcinomas^{5–9} and epidemiologic evidence that smoking^{10–13} and alcohol consumption¹⁴ may be inversely associated with TSH production, which suggests that they might be inversely associated with thyroid cancer risk.

The epidemiologic literature regarding the risk of thyroid cancer in association with menstrual and reproductive factors and use of exogenous hormones is based primarily on the results of case-control studies, and findings, with respect to the roles of parity, age at first birth, age at menarche, oral contraceptive use, use of hormone replacement therapy and menopausal status, have been inconsistent.^{15,16} Similarly, the epidemiologic literature regarding smoking and alcohol and thyroid cancer risk is also based primarily on case-control studies and the results have largely indicated inverse associations with ever smoking and any consumption of beer or wine.¹⁷

To date, it appears that there have been only 3 prospective cohort studies of the associations between reproductive and/or hormonal factors and thyroid cancer risk,^{18–20} 1 of which²⁰ also examined the association with cigarette smoking and alcohol con-

sumption. These studies have suggested no association with age at menarche, duration of oral contraceptive use, postmenopausal status, ever use of hormone replacement therapy, age at first birth,^{18–20} smoking, or alcohol consumption,²⁰ and only 1 out of 3 reported a positive association with parity.¹⁹ Two of these prospective studies examined thyroid cancer risk overall and by the main histologic subtypes of thyroid cancer.^{18,19} However, one¹⁹ focused only on the association between parity and thyroid cancer risk, and the other¹⁸ focused on a limited range of reproductive and menstrual factors.

Given the current lack of data from prospective studies regarding the etiology of thyroid cancer, we examined the association between menstrual, reproductive and hormonal factors, smoking history, alcohol consumption and thyroid cancer risk, overall and by histologic subtype, in a cohort of Canadian women.

Material and methods

Study population

The design of our study has been described in detail elsewhere.²¹ Briefly, 89,835 women aged 40–59 years were recruited into the Canadian National Breast Screening Study (NBSS) between 1980 and 1985 from the general Canadian population.²²

Questionnaires

At recruitment into the cohort, participants completed self-administered questionnaires that sought information on demographic characteristics, lifestyle factors, menstrual and reproductive history and use of oral contraceptives and replacement estrogens. Specifically, participants were asked questions about their use of hormone replacement therapy (HRT), use of oral contraceptives, age at menarche, number of pregnancies lasting greater than 4 months (parity), age at first live birth and menopausal status. Information on smoking history was also obtained from participants by asking them whether or not they had ever smoked; those who reported ever smoking were then asked to provide information on how many cigarettes they smoked per day, how many years they had smoked and, for former smokers, the year that they had ceased smoking.

Starting in 1982, a self-administered food frequency questionnaire (FFQ)²³ was distributed to all new attendees at all screening centers and to women returning to the screening centers for rescreening. The FFQ sought information on usual portion size and frequency of consumption of 86 food items, including the frequency of consumption of beer, wine and spirits. A comparison between the self-administered questionnaire and a full interviewer-administered questionnaire, which has been subjected to both validity and reliability testing²³ and used in a number of epidemiologic studies,²⁴ revealed that the 2 methods gave estimates of intake of the major macronutrients that were moderately to strongly correlated

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with each other.²⁵ A total of 49,613 dietary questionnaires were returned and available for analysis.

Ascertainment of incident thyroid cancer cases and deaths

Incident cases of thyroid cancer and deaths from all causes were ascertained respectively by means of computerized record linkages to the Canadian Cancer Database and to the National Mortality Database, both of which are maintained by Statistics Canada. The linkages to the databases yielded data on cancer incidence and mortality to 31 December 2000 for women in Ontario, 31 December 1998 for women in Quebec and 31 December 1999 for women in other provinces. Given the small number of follicular carcinoma cases in our study population and given that both papillary and follicular carcinomas arise from follicular cells,⁴ we examined the role of each of the risk factors of interest among papillary carcinoma cases alone and combined papillary and follicular carcinoma cases in addition to their association with overall thyroid cancer risk.

Statistical analysis

Of the 89,835 women for whom data were available, we excluded women with prevalent thyroid cancer at baseline ($n = 38$), leaving 89,797 women available for analyses of hormonal and reproductive variables, among whom there were 169 incident cases of thyroid cancer (87 papillary thyroid cancer, 144 combined papillary and follicular thyroid cancer). In addition, we excluded women who did not report any information on smoking history ($n = 1,072$), leaving 88,725 women available for analyses of smoking variables, among whom there were 163 incident cases of thyroid cancer. Among the 49,613 women who completed an FFQ, there were 103 incident cases of thyroid cancer (51 papillary thyroid cancer, 89 combined papillary and follicular thyroid cancer). An indicator variable for those missing information on alcohol intake was created and included in multivariate analyses of smoking history and thyroid cancer risk.

Cases contributed person-time to the study from their date of enrollment until the date of diagnosis of their thyroid cancer, and noncases contributed person-time from their date of enrollment until the termination of follow-up or death, whichever was earlier. Cox proportional hazards models (using age as the time scale) were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between each of the potential risk factors and overall thyroid cancer risk as well as for papillary thyroid cancer and combined papillary and follicular thyroid cancer. All models included age (as the time to event variable) as well as terms for study center and randomization group (intervention or control). For analyses of risk in association with cigarette consumption, age at which smoking began was calculated for each smoker by subtracting the total years of smoking from age at recruitment. Pack-years of smoking was calculated by multiplying the total years of smoking by the number of cigarettes smoked per day divided by 20 (given 20 cigarettes per pack). Multivariate models for the smoking history analyses included body mass index [defined as weight (kg)/height (m²); weight and height were measured at baseline²⁶], highest level of education attained (less than high school or high school graduate or more) and alcohol consumption (none, 1–3, 3–10, ≥ 10 , or missing). Multivariate models for alcohol consumption likewise included body mass index (BMI), highest level of education obtained and pack-years of smoking (none, 1–10, 10–19, ≥ 20). Multivariate models for hormone and reproductive risk factors included the variables listed in the footnote of Table II. Menopausal status was determined as follows: women who reported having regular menstrual periods within the past 12 months or who had had a hysterectomy without bilateral oophorectomy and were less than 45 years of age were classified as premenopausal, while women whose menstrual periods ceased prior to 12 months before baseline, those who had had a bilateral oophorectomy and those who had had a hysterectomy and were over 55 years of age were considered to be postmeno-

TABLE I – BASELINE CHARACTERISTICS OF THE STUDY POPULATION BY OUTCOME

Factor	Cases ($n = 169$)	Noncases ($n = 89,547$)
Mean age (years)	48.0 (5.3)	48.5 (5.6)
Mean BMI (kg/m ²)	25.2 (4.3)	25.1 (4.8)
Smoking history (% ever) ¹	49.7	48.9
Mean age started smoking	22.7 (7.0)	22.7 (7.5)
Mean number of years smoked	17.6 (10.6)	19.0 (10.4)
Mean number of cigarettes smoked per day	17.8 (11.2)	16.7 (11.2)
Mean number of pack-years	17.9 (15.1)	18.3 (16.7)
Alcohol consumption (% any) ²	72.7	76.9
Mean alcohol consumption (g/day)	10.2 (13.2)	11.1 (14.2)
Mean age at menarche (years)	12.9 (1.5)	12.8 (2.2)
Mean age at first live birth (years) ³	24.5 (4.7)	24.2 (4.8)
Parity		
Nulliparous	12.4	14.4
1–2	32.0	35.4
3–4	44.4	38.4
5+	11.2	11.7
Postmenopausal %	41.3	43.2
HRT use ⁴ (% ever)	47.4	47.0
Oral contraceptive use (% ever)	61.5	58.5

¹Results for smoking duration, intensity, pack-years and age started smoking are among ever smokers only. ²Results for mean alcohol consumption are among drinkers only. ³Among parous women only. ⁴Among postmenopausal women only.

pausal. Women who were between 45 and 55 years of age whose menstrual periods did not cease 12 months before baseline, and who had not undergone surgical menopause, were classified as perimenopausal (not included in these analyses due to small number of thyroid cancer cases in this category; $n = 31$). To test for trends in risk with increasing levels of the exposures of interest, we either assigned the categorical variables their ordinal number (parity) or the category median (age at first live birth, duration of oral contraceptive use, smoking history and alcohol consumption) and then fitted the assigned value of each risk factor as a continuous variable in the risk models and evaluated the statistical significance of the corresponding coefficient using the Wald test.²⁷ Use of the life test procedure in SAS showed that the proportional hazards assumption was met in this data set (SAS Institute Cary, NC). All analyses were performed using SAS version 9.

Results

The average duration of follow-up for cohort members was 15.9 years (1,429,037 person-years for the cohort as a whole), during which 169 incident cases of thyroid cancer were diagnosed, of which 87 were papillary cancers, 20 were follicular cancers and 37 showed both papillary and follicular histology. Table I shows the demographic characteristics of the study population by case status at the end of follow-up. Briefly, cases and controls were largely similar with respect to age, body mass index, smoking history, alcohol consumption and each of the hormonal/reproductive factors (Table I).

Table II shows multivariate adjusted estimates of the risk of thyroid cancer in association with the menstrual, reproductive and hormonal variables of interest. Although the adjusted hazard ratios for each level of parity (compared to nulliparous women) were below unity with respect to both overall thyroid cancer risk and risk of the histologic subtypes of interest, most of the point estimates and the associated trends in risk were not statistically significant. There was likewise no association between parity and thyroid cancer among parous women (1–2 live births as referent group). There was no association between age at first live birth, age at menarche, menopausal status, use of oral contraceptives, or use of hormone replacement therapy and risk of thyroid cancer overall or by histologic subtype.

TABLE II – MULTIVARIATE-ADJUSTED HAZARD RATIOS AND 95% CONFIDENCE INTERVALS FOR THE ASSOCIATION BETWEEN REPRODUCTIVE, MENSTRUAL AND HORMONAL FACTORS AND RISK OF INCIDENT THYROID CANCER

Factor	Thyroid (n = 169)	Papillary (n = 87)	Papillary and/or follicular (n = 144)
Parity¹			
Nulliparous	1.00 (reference)	1.00 (reference)	1.00 (reference)
Parous	0.75 (0.42–1.33)	0.53 (0.22–1.25)	0.66 (0.35–1.24)
1–2	0.65 (0.35–1.23)	0.45 (0.18–1.16)	0.56 (0.28–1.14)
3–4	0.85 (0.47–1.54)	0.71 (0.30–1.71)	0.76 (0.39–1.46)
5+	0.65 (0.32–1.33)	0.23 (0.07–0.80)	0.56 (0.25–1.24)
<i>p</i> _{trend} ²	0.63	0.76	0.58
Age (years) at first live birth³			
Nulliparous	1.00 (reference)	1.00 (reference)	1.00 (reference)
< 23	0.79 (0.44–1.41)	0.77 (0.34–1.75)	0.79 (0.42–1.50)
23–25	1.13 (0.65–1.97)	1.22 (0.56–2.65)	1.19 (0.65–2.19)
> 25	0.94 (0.55–1.60)	0.97 (0.46–2.06)	0.98 (0.54–1.76)
<i>p</i> _{trend}	0.41	0.23	0.14
Age (years) at menarche³			
< 12	1.00 (reference)	1.00 (reference)	1.00 (reference)
≥ 12	1.03 (0.76–1.41)	0.99 (0.64–1.52)	1.08 (0.77–1.52)
Menopausal status⁴			
Pre	1.00 (reference)	1.00 (reference)	1.00 (reference)
Post	0.80 (0.51–1.26)	0.59 (0.30–1.15)	0.68 (0.41–1.13)
Oral contraceptives³			
Never	1.00 (reference)	1.00 (reference)	1.00 (reference)
Ever	1.11 (0.80–1.54)	1.00 (0.64–1.57)	1.09 (0.77–1.55)
1–11 months	1.28 (0.79–2.07)	1.36 (0.73–2.56)	1.40 (0.85–2.32)
12–35 months	1.39 (0.88–2.19)	1.23 (0.66–2.32)	1.41 (0.87–2.29)
> 35 months	0.94 (0.64–1.38)	0.79 (0.46–1.35)	0.85 (0.56–1.30)
<i>p</i> _{trend}	0.85	0.96	0.60
Hormone replacement therapy³⁵			
Never	1.00 (reference)	1.00 (reference)	1.00 (reference)
Ever	1.16 (0.68–1.98)	1.29 (0.56–2.95)	1.45 (0.78–2.69)

¹Multivariate adjusted for age (time to event variable), age at first live birth, study center and randomization group (intervention vs. control).²Test for trend among parous women only.³Multivariate adjusted for age (time to event variable), parity, study center and randomization group (intervention vs. control).⁴Multivariate adjusted for age (time to event variable), HRT use (ever/never), study center and randomization group (intervention vs. control).⁵Postmenopausal women only.

Table III shows that in multivariate-adjusted models, there was no association between thyroid cancer risk overall and smoking history (ever vs. never) or status (never/former/current). In addition, the number of cigarettes smoked, smoking duration, pack-years and age at which the study participant began smoking were not associated with altered thyroid cancer risk. Although there was a 25% decreased risk of papillary thyroid carcinoma among current smokers compared to never smokers, this association was not statistically significant (95% CI = 0.41–1.37).

Consumption of at least 10 grams of alcohol per day was associated with a 14–20% reduction in thyroid cancer risk after adjustment for education, BMI and smoking history (pack-years). However, the reductions in risk were not statistically significant (Table IV).

Discussion

In the prospective study reported here, we found that overall thyroid cancer risk was not associated with menopausal status, parity, age at first live birth, age at menarche, oral contraceptive use, or use of hormone replacement therapy. There was some evidence, however, that relatively high parity may be associated with decreased risk of papillary thyroid carcinoma.

While we found no association between thyroid cancer risk and menopausal status in our study population, Negri *et al.*¹⁵ reported a borderline increased risk among women reporting natural menopause compared to premenopausal women in a pooled analysis of data from 11 case-control studies. In contrast to the findings reported by Negri *et al.*,¹⁵ Iribarren *et al.*²⁰ analyzed data from a prospective cohort of men and women in the San Francisco Bay

Area (123 incident cases) and reported a 40% reduction in risk among postmenopausal (nonsurgical menopause) vs. premenopausal women (95% CI = 0.35–1.02).

A number of case-control studies have examined the relationship between parity and thyroid cancer risk.^{28–39} Although 8 studies reported odds ratios above unity (comparing parous vs. nulliparous),^{28–30,32,34,36–38} only one of these findings was statistically significant.³⁸ However, a pooled analysis of 12 case-control studies (including unpublished data from a case-control study conducted in Nagasaki, Japan) found a borderline increased risk when comparing parous vs. nulliparous women (OR = 1.2; 95% CI = 1.0–1.6).¹⁵ In contrast, we found no evidence of an association between overall thyroid cancer risk and parity. Our findings also differ from the results of an analysis of complete Norwegian birth cohorts, which included 1.1 million Norwegian women ascertained through the Central Population Register of Norway (976 incident cases of thyroid cancer), wherein Kravdal *et al.*¹⁹ observed a positive association between parity (defined as the number of live births) and overall thyroid cancer risk (*p*_{trend} = 0.03; unadjusted analysis). However, our findings for overall thyroid cancer risk are similar to those of Akslen *et al.*,¹⁸ who analyzed prospective data for 63,090 Norwegian women (124 incident cases), and to those of Iribarren *et al.*,²⁰ both of whom reported no association between parity and thyroid cancer risk. Unlike the pooled analysis of case-control data¹⁵ and the results reported by Akslen *et al.*¹⁸ and Kravdal *et al.*,¹⁹ which reported no association between parity and papillary thyroid cancer, we observed an inverse association among women with 5 or more live births compared to nulliparous women.

TABLE III – MULTIVARIATE-ADJUSTED HAZARD RATIOS AND 95% CONFIDENCE INTERVALS FOR THE ASSOCIATION BETWEEN CIGARETTE SMOKING AND RISK OF INCIDENT THYROID CANCER

Factor	Thyroid (n = 163)	Papillary (n = 85)	Papillary and/or follicular (n = 140)
Never smoked	1.00 (reference)	1.00 (reference)	1.00 (reference)
Ever smoked	1.04 (0.76–1.43)	0.85 (0.55–1.32)	1.07 (0.76–1.51)
Former smoker	1.07 (0.74–1.54)	0.93 (0.56–1.53)	1.14 (0.77–1.69)
Current smoker	1.01 (0.67–1.53)	0.75 (0.41–1.37)	0.97 (0.62–1.54)
Age started smoking (years)			
< 20	1.07 (0.70–1.62)	0.86 (0.47–1.55)	1.10 (0.70–1.72)
20–29	0.91 (0.59–1.40)	0.80 (0.45–1.44)	0.96 (0.61–1.51)
≥ 30	1.25 (0.72–2.17)	0.83 (0.35–1.95)	1.20 (0.65–2.23)
<i>p</i> _{trend}	0.90	0.26	0.24
Number of years smoked			
< 10	1.18 (0.70–2.00)	1.04 (0.51–2.14)	1.20 (0.68–2.11)
10–19	0.98 (0.58–1.64)	0.92 (0.46–1.82)	1.01 (0.58–1.75)
≥ 20	1.02 (0.70–1.49)	0.75 (0.43–1.30)	1.05 (0.70–1.58)
<i>p</i> _{trend}	0.77	0.32	0.30
Number of cigarettes/day			
< 10	1.04 (0.63–1.72)	0.66 (0.30–1.46)	1.22 (0.73–2.04)
10–19	0.69 (0.39–1.23)	0.59 (0.26–1.30)	0.58 (0.30–1.13)
≥ 20	1.24 (0.86–1.81)	1.11 (0.67–1.84)	1.27 (0.85–1.91)
<i>p</i> _{trend}	0.91	0.67	0.65
Pack-years			
< 10	1.06 (0.70–1.62)	0.90 (0.50–1.61)	1.16 (0.74–1.80)
10–19	0.79 (0.44–1.42)	0.41 (0.15–1.14)	0.71 (0.36–1.38)
≥ 20	1.17 (0.78–1.75)	1.06 (0.61–1.84)	1.19 (0.77–1.85)
<i>p</i> _{trend}	0.89	0.43	0.41

Multivariate adjusted for age (time to event variable), education (<high school, ≥high school), body mass index (<25, 25–29, ≥30) and alcohol consumption (0 plus 3 levels of intake).

TABLE IV – MULTIVARIATE-ADJUSTED HAZARD RATIOS AND 95% CONFIDENCE INTERVALS FOR THE ASSOCIATION BETWEEN ALCOHOL CONSUMPTION AND RISK OF INCIDENT THYROID CANCER

Factor	Thyroid (n = 103)	Papillary (n = 51)	Papillary and/or follicular (n = 89)
Alcohol intake (g/day)			
None	1.00 (reference)	1.00 (reference)	1.00 (reference)
Any	1.15 (0.73–1.82)	0.99 (0.51–1.90)	0.99 (0.59–1.64)
1–3	1.17 (0.68–2.01)	1.55 (0.75–3.24)	1.50 (0.84–2.68)
3–10	0.67 (0.36–1.22)	0.71 (0.30–1.69)	0.75 (0.39–1.46)
≥ 10	0.80 (0.45–1.42)	0.80 (0.35–1.84)	0.84 (0.44–1.58)
<i>p</i> _{trend}	0.56	0.49	0.64

Multivariate adjusted for age (time to event variable), education (< high school, ≥ high school), body mass index (<25, 25–29, ≥30) and pack-years of smoking (0 plus 3 levels).

Of the 12 published case-control studies that have examined age at first birth as a risk factor for thyroid cancer,^{28–32,34–40} 10 reported an OR above unity in women with a relatively late age at first birth (age at first birth modeled continuously, based on a unit increase of 5 years).^{28,29,31,32,34–37,39,40} Using pooled data from 12 case-control studies (including unpublished case-control data from Nagasaki, Japan), Negri *et al.*¹⁵ reported a statistically significant increased risk of thyroid cancer for women at or above 30 years of age at first birth compared to women below age 20 at first birth (OR = 1.8; 95% CI = 1.0–1.8). Recently, in a population-based case-control study in the San Francisco Bay area (608 incident cases; not included in pooled analysis), Sakoda and Horn-Ross³⁹ reported a 2.8-fold increased risk of thyroid cancer for women ≥35 years of age vs. those < 20 years of age at first birth among those of reproductive age (20–44 years old at the time of the interview). In contrast, no association was found between age at first birth and risk among women of postreproductive age (45–74 years old at the time of the interview).³⁹ As did Akslen *et al.*,¹⁸ we found no association between overall thyroid cancer or papillary thyroid cancer risk and age at first live birth in our cohort of women who were between 40 and 59 years of age at baseline.

Our study supports the current literature that age at menarche is not associated with thyroid cancer risk.^{15,18,20} Similarly, our find-

ings regarding use of oral contraceptives are consistent with those of previous studies, which have largely reported no association with thyroid cancer risk.^{16,20,39} In contrast to the findings of Sakoda and Horn-Ross,³⁹ who observed an inverse association between HRT use and papillary thyroid cancer, we found no association with HRT use in our study population. Our finding is in keeping with that of the only previous prospective cohort study that has examined this association for overall thyroid cancer risk.²⁰

Of the 13 published case-control studies that have examined the association between cigarette smoking and thyroid cancer risk,^{28–35,37,38,41,42} only that of Preston-Martin *et al.*²⁹ suggested an increase in risk in association with ever smoking (OR = 2.0; 95% CI = 0.5–8.0), although this finding was based on only 6 cases and 3 controls and was not statistically significant. Of the remaining 12 studies, 11 reported odds ratios below unity, of which 3 were statistically significant.^{33,37,38} The pooled analysis of these studies (including the unpublished data from Nagasaki, Japan) yielded an OR of 0.7 (95% CI = 0.6–0.8) when comparing ever vs. never smokers (among women only).¹⁷ There was also a statistically significant inverse trend between smoking duration and thyroid cancer risk (*p* = 0.03) in this pooled analysis.¹⁷ In contrast, we found no association between smoking duration and

thyroid cancer risk in our study population. Our results support those of Iribarren *et al.*,²⁰ who analyzed data from a prospective cohort study of men and women in the San Francisco Bay Area (196 incident cases in all, 123 cases in women) who reported no association between smoking status (never/former/current) and risk of thyroid cancer.

Of the published case-control studies that have examined alcohol consumption as a risk factor for thyroid cancer,^{28,31,32,35,37,38,41,42} 5 have reported inverse associations,^{28,31,35,38,42} of which 2 were statistically significant,^{31,38} and the remaining studies reported odds ratios above unity, although none of them was statistically significant.^{32,35,37,41} A pooled analysis of these studies (including unpublished data from Nagasaki, Japan) reported an OR = 0.8 (95% CI = 0.7–0.9) between beer and wine consumption (any vs. none) and thyroid cancer risk after adjusting for age, gender and ethnicity.¹⁷ However, when the pooled estimate was examined among women only, there was no association between number of drinks of wine and beer per week and thyroid cancer risk.¹⁷ Although we observed a 20% lower risk of thyroid cancer overall among women drinking at least 10 grams of alcohol per day compared to nondrinkers, this finding was not statistically significant and is supported by the similar absence of an association between alcohol consumption (measured as number of drinks per day) and thyroid cancer risk reported in the prospective study of Iribarren *et al.*²⁰

Our study is the first prospective cohort study to investigate the roles of smoking and alcohol consumption and of a wide range of hormonal risk factors with respect to histologic subtypes of thyroid cancer. The main strength of our investigation is its prospective study design, which eliminates the possibility of recall bias. As well, the essentially complete follow-up of the cohort,^{43,44} based on linkage to national cancer incidence and mortality databases, reduces the likelihood that our results reflect bias due to differential follow-up. Our study is limited, however, by the relatively small number of cases of thyroid cancer. In addition, our study is limited in that information on menopausal status was collected only at baseline. Given that the minimum age at baseline was 40 and that, on average, there were 16 years of follow-up, it is likely that most of those who were premenopausal at enrolment would have become postmenopausal during the course of follow-up. Similarly, we did not collect additional information on smoking and alcohol intake during the follow-up period. It is possible that some study participants

altered their smoking and alcohol intake behaviors during follow-up, thus potentially obscuring the true hazard ratios. Our analyses were limited somewhat due to the lack of data on radiation exposure. While radiation exposure is a clearly defined risk factor for thyroid cancer,² there does not appear to be evidence from the epidemiologic literature that radiation is associated with either smoking or alcohol consumption, or with reproductive factors. Additionally, data on family history of thyroid cancer were not collected and therefore could not be controlled for in the analyses. However, approximately only 3% of thyroid cancer cases have a family history of the disease and a family history of thyroid cancer appears to be most strongly associated with medullary carcinomas,⁴ which accounted for less than 2% of the cases in our study. Furthermore, there is no epidemiologic evidence that family history of thyroid cancer is associated with any of the risk factors under study. Therefore, radiation and family history of thyroid cancer are unlikely to have confounded the relationships between smoking history, alcohol consumption, or reproductive factors and thyroid cancer risk. Finally, although we adjusted for a number of potentially confounding variables, we cannot exclude the possibility of residual confounding by other factors.

In conclusion, the results of our study suggest that parity, age at first live birth, age at menarche, menopausal status, use of oral contraceptives, use of hormone replacement therapy, smoking history and alcohol consumption are not associated with risk of thyroid cancer. Despite experimental evidence supporting a detrimental role of hormonal factors in the etiology of thyroid cancer^{45–47} and substantial evidence from case-control studies supporting an inverse association between smoking and alcohol consumption and thyroid cancer risk,¹⁷ the currently available evidence from prospective cohort studies provides limited support for roles for these factors, although the number of cases observed in cohorts has mostly been relatively small. This suggests the need either to pool the results of existing cohort studies or to conduct additional larger prospective studies.

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