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Baseline and lifetime alcohol consumption and risk of differentiated thyroid carcinoma in the EPIC study

Abhijit Sen[1,2], Konstantinos K Tsilidis*[,1,3,4], Naomi E Allen[5], Sabina Rinaldi[6], Paul N Appleby[3], Martin Almquist[7,8], Julie A Schmidt[3], Christina C Dahm[9], Kim Overvad[9], Anne Tjønneland[10], Agnetha L Rostgaard-Hansen[10], Françoise Clavel-Chapelon[11,12,13], Laura Baglietto[14,15], Marie-Christine Boutron-Ruault[11,12,13], Tilman Kühn[16], Verena A Katze[16], Heiner Boeing[17], Antonia Trichopoulou[18,19,20], Christos Tsironis[18], Pagona Lagiou[19,20,21], Domenico Palli[22], Valeria Pala[23], Salvatore Panico[24], Rosario Tumino[25], Paolo Vineis[4,26], HB(as) Bueno-de-Mesquita[4,27,28,29], Petra H Peeters[30], Anette Hjartåker[31], Eiliv Lund[32], Elisabete Weiderpass[32,33,34,35], J Ramón Quirós[36], Antonio Agudo[37], María- José Sánchez[38,39], Larraitz Arriola[39,40], Diana Gavrila[39,41], Aurelio Barricarte Gurrea[39,42], Ada Tosovic[43], Joakim Hennings[44], Maria Sandström[45], Isabelle Romieu[6], Pietro Ferrari[6], Raul Zamora-Ros[6], Kay-Tee Khaw[46], Nicholas J Wareham[47], Elio Riboli[4], Marc Gunter[4] and Silvia Franceschi[6]

Background: Results from several cohort and case–control studies suggest a protective association between current alcohol intake and risk of thyroid carcinoma, but the epidemiological evidence is not completely consistent and several questions remain unanswered.

Methods: The association between alcohol consumption at recruitment and over the lifetime and risk of differentiated thyroid carcinoma was examined in the European Prospective Investigation into Cancer and Nutrition. Among 477 263 eligible participants (70% women), 556 (90% women) were diagnosed with differentiated thyroid carcinoma over a mean follow-up of 11 years. Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated using multivariable Cox proportional hazards models.

Results: Compared with participants consuming 0.1–4.9 g of alcohol per day at recruitment, participants consuming 15 or more grams (approximately 1–1.5 drinks) had a 23% lower risk of differentiated thyroid carcinoma (HR = 0.77; 95% CI = 0.60–0.98). These findings did not differ greatly when analyses were conducted for lifetime alcohol consumption, although the risk estimates were attenuated and not statistically significant anymore. Similar results were observed by type of alcoholic beverage, by differentiated thyroid carcinoma histology or according to age, sex, smoking status, body mass index and diabetes.

Conclusions: Our study provides some support to the hypothesis that moderate alcohol consumption may be associated with a lower risk of papillary and follicular thyroid carcinomas.

Thyroid carcinoma incidence rates have been rapidly increasing in high-income countries, and the disease is more common among women (Davies and Welch, 2006; Kilfoy *et al*, 2009). Differentiated thyroid carcinoma, including papillary and follicular carcinoma, represents 98% of thyroid cancer (Kilfoy *et al*, 2009; Dal Maso *et al*, 2011). The only well-defined risk factors for thyroid carcinoma are exposure to ionizing radiation especially in childhood (Reynolds *et al*, 2005), thyroid adenoma and history of goiter (Franceschi *et al*, 1999; Balasubramaniam *et al*, 2012). Alcohol consumption is an important correlate to other dietary and lifestyle factors, and

*Correspondence: Dr KK Tsilidis; E-mail: ktsilidi@cc.uoi.gr

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results from several prospective (Galanti *et al*, 1997; Navarro Silvera *et al*, 2005; Allen *et al*, 2009; Meinhold *et al*, 2009; Kabat *et al*, 2012; Kitahara *et al*, 2012) and case–control studies (Rossing *et al*, 2000; Mack *et al*, 2003) have suggested a protective association between current moderate alcohol intake and thyroid carcinoma risk. However, the extent of the lower risk has been varying, and only two prospective studies of women from the United Kingdom and the United States (Allen *et al*, 2009; Meinhold *et al*, 2009) and a pooled-analysis of five prospective studies on both sexes from the United States (Kitahara *et al*, 2012) have shown statistically significant inverse associations. A few smaller studies have observed null results (Iribarren *et al*, 2001; Mack *et al*, 2002; Guignard *et al*, 2007). Data about alcohol intake and thyroid carcinoma in men are limited, and no study has previously reported on the association between lifetime alcohol consumption and thyroid carcinoma risk. In the present large study within the European Prospective Investigation into Cancer and Nutrition (EPIC), we investigated the association between both baseline and lifetime alcohol consumption with risk of differentiated thyroid carcinoma, and also performed analyses by cancer stage, type of alcoholic beverage and according to potential modifying variables.

MATERIALS AND METHODS

Study design and recruitment. EPIC is a multicentre prospective cohort study designed to investigate the relation between diet, other lifestyle factors, environmental factors and cancer risk. The cohort consists of approximately half a million participants, 70% of which are women, mostly aged 35–70 years and recruited between 1992 and 2000 in 23 centres in 10 European countries, that is, Denmark, France, Greece, Germany, Italy, the Netherlands, Norway, Spain, Sweden and United Kingdom. The rationale, design and data collection methods of EPIC have been previously described in detail elsewhere (Riboli *et al*, 2002). This study was approved by the Internal Review Boards of the International Agency for Research on Cancer and of the participating centres.

Subjects were excluded if they had prevalent cancer (other than non-melanoma skin cancer) at recruitment, if they were in the top or bottom 1% of the distribution of the ratio of energy intake to estimated energy requirement, and if they had missing information on baseline alcohol consumption. Therefore, this study used data from 477 263 participants, 335 020 (70%) of whom were women.

Assessment of thyroid carcinoma. Data on incident cases of thyroid carcinoma were collected by linkage to regional or national cancer registries from all EPIC centres except those from Greece, France and Germany. Outcome follow-up data from these countries were based on a combination of methods, including the use of health insurance records, contact with cancer and pathology registries, and active follow-up. Closure dates for the present study were defined as the latest update for both cancer incidence and vital status, that is, between 11 December 2006 and 14 June 2010 according to EPIC centre. A total of 556 incident differentiated thyroid carcinoma cases (defined according to the International Classification of Diseases, ICD-10 code C73) were identified after an average follow-up of 11 years, 435 of which had papillary, 76 had follicular and another 45 had unknown or other carcinoma morphology. Thyroid cancer cases with anaplastic ($n=6$), medullary ($n=28$), lymphoma ($n=1$) and other rare morphologies ($n=3$), which are usually considered poorly differentiated tumours with lower cure rates, were excluded. Data on the stage of differentiated thyroid carcinomas at diagnosis were collected from each centre, where possible. A total of 372 cases (67%) had stage information, of which 266 were classified as localised (tumour-node-metastasis staging score of T_0–T_2 and N_0/N_x and M_0, or stage coded in the recruitment centre as localised) and 106 were classified as advanced thyroid carcinoma (T_3–T_4 and/or N_1–N_3 and/or M_1, or stage coded in the recruitment centre as metastatic).

Assessment of alcohol intake and other variables. Dietary assessment was performed by self-administrated country- or centre-specific dietary questionnaires or food records (Riboli *et al*, 2002). The intake of alcoholic beverages at baseline was calculated from these questionnaires that have been previously validated for alcohol consumption (Kaaks *et al*, 1997; Riboli *et al*, 2002; Hjartaker *et al*, 2007). Participants reported the number of standard glasses of beer, wine and distilled spirits consumed per day or week during the 12 months before recruitment. Alcohol intake was calculated by multiplying the mean glass volume with the alcohol content for each type of alcoholic beverage (Slimani *et al*, 2007), using information collected in standardised 24-h dietary recalls from a subset of the cohort (Slimani *et al*, 2000). Information of past alcohol consumption was assessed as glasses of different beverages consumed per week at 20, 30, 40 and 50 years of age in all EPIC centres except for Naples, Bilthoven, Umea, Malmo and Norway (Klipstein-Grobusch *et al*, 2007). Average lifetime alcohol intake was determined as a weighted average of intake at different ages with weights equal to the time of individual exposure to alcohol at different ages.

Information on physical activity, smoking status, level of education, diagnosis of diabetes mellitus, and in women only, age at menarche and menopause, use of oral contraceptives and hormone replacement therapy and number of full-term pregnancies (defined as the sum of live and still births) was self-reported at the baseline questionnaire (Tsilidis *et al*, 2011a, b). Weight and height were measured at recruitment, except for most of the Oxford cohort, the Norwegian cohort, and approximately two-thirds of the French cohort, among whom weight and height were self-reported. Body mass index (BMI) was calculated as weight in kilograms divided by height in metres squared. Menopausal status was defined according to information on menstruation status, hysterectomy, ovariectomy, use of exogenous hormone and age, details of which are provided elsewhere (Tsilidis *et al*, 2011b).

Statistical analysis. Cox proportional hazard models were used to study the association between alcohol intake and differentiated thyroid carcinoma incidence using age as the underlying time scale. Age at entry was defined as the participants' age at recruitment, and exit time was age at diagnosis of thyroid cancer, death, loss to follow-up or censoring at the end of the follow-up period, whichever came first. The proportionality of hazards was verified based on the slope of the Schoenfeld residuals over time, and no evidence of violation was detected. The models were stratified by study centre to control for differences in questionnaires and follow-up procedures, and for sex and age at recruitment in 5-year categories. All multivariate models were adjusted for known or suspected risk factors of thyroid carcinoma, such as smoking status (never, former quitted $\leqslant$10 years ago, former quitted 11–20 years ago, former quitted $>$20 years ago, current with 1–15 cigarettes per day, current with 16–25 cigarettes per day, current with $>$25 cigarettes per day, current with pipe/cigar or occasional cigarette use, missing), education (up to high school, university graduate, missing), BMI (in quintiles, missing), physical activity (inactive, moderate inactive, moderate active, active, missing), diabetes status (no, yes, missing), energy from non-alcohol sources (continuously in kcals) and hormone replacement therapy (never, former, current, missing), use of oral contraceptives (never, former, current, missing), age at menarche ($<$12, 12, 13, 14, $\geqslant$15, missing), number of full-term pregnancies (0, 1, 2, 3, $\geqslant$4, missing) and menopausal status in women (premenopausal, perimenopausal, postmenopausal). Missing values were assigned to separate

categories for smoking status (4%), education (3.6%), BMI (0.8%), physical activity (8.8%), diabetes (3.5%), hormone replacement therapy (10.8%), oral contraceptives (3.2%), age at menarche (2.3%) and full-term pregnancies (5.8%) – and missing indicators were used in the statistical models. Analyses that excluded participants with missing values for any of these covariates, and analyses that included further adjustments for currently having a paid employment, waist circumference, hip circumference, waist to hip ratio, self-reported personal history of thyroid diseases and infertility problems gave very similar results and are not presented here. When we further adjusted the lifetime alcohol consumption models for an indicator variable for participants who quitted alcohol drinking and for time since alcohol quitting to deal with the potential existence of former drinkers who quitted drinking because of an illness (Shaper *et al*, 1988), the results remained very similar and are not presented.

Baseline and average lifetime consumption of total alcohol were modelled primarily as categorical variables based on the distribution of intake in EPIC (0, 0.1–4.9, 5–14.9, $\geqslant$15 g per day) after evaluating non-parametric lowess plots of alcohol on thyroid cancer risk for non-linearity. Alcohol consumption of 0.1–4.9 g per day was used as the reference category in all statistical models to allow for comparisons with the non-consumer category. In addition, non-consumers might be a biased group as some participants may have stopped drinking due to ill health. However, when different cutpoints of alcohol consumption were used (0, 0.1–4.9, 5–14.9, 15–29.9, $\geqslant$30 or 0, 0.1–2.9, 3–9.9, 10–19.9, $\geqslant$20 g per day or quartiles based on the distribution in the whole cohort or in each EPIC centre) or when the non-consumers were the reference category, the results were very similar and are not presented. Alcohol consumption was also evaluated using a continuous variable per 10 g per day or 3 g per day, depending upon the range of intake of each alcoholic beverage, after adjusting for consumer *vs* non-consumer status using an indicator variable or after performing analyses only among consumers. Alcohol consumption of 10 g per day equals approximately to a small glass of wine (100 ml), a can of beer (330 ml) or a shot of spirit (30 ml). Separate analyses were performed by type of alcohol consumption (beer, wine, spirits) after mutually adjusting each time for energy obtained from the other two types of beverages. Non-consumers were defined here as participants who did not consume the alcoholic beverage under evaluation, but could consume other alcoholic beverages.

To evaluate whether the association of alcohol intake with thyroid cancer risk differed by age at recruitment ($<$50 *vs* $\geqslant$50 years), sex, smoking status (never, former, current smokers), BMI ($<$25 *vs* $\geqslant$25 kg m^{-2}) and diabetes (no *vs* yes), interaction terms were incorporated in the multivariable models and its significance assessed with Wald tests. Country-specific analyses were also performed, and heterogeneity of associations across countries (and by type of alcoholic beverage) were assessed using Cochran's *Q*-test and the I^2 metric of inconsistency (Higgins *et al*, 2003). A sensitivity analysis was conducted excluding the first two years of follow-up to limit the likelihood that the observed associations were due to change of alcohol consumption produced by extant cancers, but the results were very similar to the main analysis and are not shown. All *P*-values (*P*) were two-sided and all analyses were performed using STATA version 12 (College Station, TX, USA).

RESULTS

Table 1 describes the distribution of participant characteristics at recruitment by country in the EPIC study. The mean age at enrolment in the cohort was 51 years and 70% of the participants were women. The majority of the 556 differentiated thyroid carcinoma cases, 90% ($n=499$) of which occurred in women, were identified in France ($n=202$) followed by Italy ($n=82$) and Germany ($n=79$). Of the 477 263 total participants, 14% were non-consumers of alcohol at baseline (17% in women and 7% in men), and 25% consumed 15 or more grams of alcohol per day (16% in women and 45% in men), a percentage that ranged from 1% in Norway (100% of Norwegian participants were women) to 46% in Denmark (52% of Danish participants were women). The mean baseline alcohol consumption among consumers was 13.5 g per day (9.5 g per day in women and 21.8 g per day in men), whereas it was almost 14 g per day when alcohol consumption during lifetime was considered. Overall, the female participants in EPIC had a low-to-moderate alcohol consumption with very few heavy drinkers in the data set (only 5% of the female population had alcohol intake of $>$33.5 g per day and 1% of the population had intake of $>$56.9 g per day at recruitment). Men consumed on average more alcohol than women with $\sim$25% consuming more than 31 g per day at recruitment.

Table 2 presents sex-specific frequencies of selected baseline characteristics by categories of baseline alcohol intake adjusted for country and age at recruitment. Compared with women consuming no alcohol, alcohol consumers had on average a higher level of education, were more likely to be current or ever smokers, were more physically active, were more likely to be ever users of hormone replacement therapy and oral contraceptives, were less likely to be postmenopausal and have diabetes and were on average leaner. These associations generally increased linearly with increasing alcohol consumption. Similar but smaller in magnitude differences were observed among men with the exception of mean BMI, which was similar across alcohol consumption categories.

Table 3 reports hazard ratios (HRs) and 95% confidence intervals (CIs) for the associations of baseline and lifetime alcohol intake with differentiated thyroid carcinoma risk. Compared with men and women consuming 0.1–4.9 g of alcohol per day at recruitment, individuals consuming 15 or more grams per day had a 24% lower risk of differentiated thyroid carcinoma (HR = 0.76; 95% CI = 0.60–0.97) in age, sex and centre stratified models. Further adjustment for smoking, education, BMI, physical activity, diabetes, energy from non-alcohol sources, hormone replacement therapy, oral contraceptives, age at menarche, number of full-term pregnancies and menopausal status yielded an identical association (HR = 0.77; 95% CI = 0.60–0.98). Non-consumers of alcohol at recruitment were at a similar risk for thyroid carcinoma (HR = 0.97; 95% CI = 0.76–1.25) compared with consumers of 0.1–4.9 g per day. For every 10 g of alcohol consumed per day among consumers, the risk of thyroid carcinoma was lowered by 9% (HR = 0.91; 95% CI = 0.84–0.98). Very similar and statistically significant associations were observed for intake of alcohol from wine (HR per 10 g per day among consumers = 0.91 (0.82–0.99)). The risk estimates were smaller and not statistically significant for beer (HR per 3 g per day among consumers = 0.96; 95% CI = 0.90–1.03) and spirits intake (HR per 3 g per day among consumers = 0.99; 95% CI = 0.89–1.10), but overall the associations by type of alcoholic beverage did not differ from each other (*P*-heterogeneity = 0.38; $I^2=0\%$).

When analyses were performed for lifetime alcohol intake, similar associations with the alcohol at baseline analyses were observed, but the risk estimates for total alcohol and alcohol from wine intake and thyroid carcinoma risk were attenuated and were not statistically significant anymore (Table 3). The HR per 10 g per day of total lifetime alcohol intake among consumers was 0.93 (95% CI = 0.84–1.02). Moreover, similar results were observed for baseline and lifetime alcohol intake and risk of papillary thyroid carcinoma (Supplementary Table 1) as well as by thyroid carcinoma stage (Supplementary Tables 2 and 3).

No statistically significant interactions were observed for total baseline or lifetime alcohol consumption and thyroid

carcinoma risk according to age at recruitment, sex, BMI, smoking status or diabetes (Table 4). When analysis was performed by EPIC-participating country, the risk estimates were relatively homogeneous (alcohol intake at baseline: *P*-heterogeneity = 0.35; $I^2 = 10\%$; average lifetime alcohol intake: *P*-heterogeneity = 0.63; $I^2 = 0\%$).

DISCUSSION

In this large prospective study involving 477 263 participants and 556 incident differentiated thyroid carcinoma cases, we observed that moderate alcohol intake at recruitment was associated with a statistically significant lower risk of thyroid carcinoma. These findings did not materially differ by whether baseline or lifetime alcohol consumption was considered, although the risk estimates for lifetime alcohol and thyroid carcinoma were not nominally statistically significant, by type of alcoholic beverage, by thyroid carcinoma histology and stage, or according to age, sex, BMI, smoking status and diabetes.

In parallel to our findings, several large cohort (Galanti *et al*, 1997; Navarro Silvera *et al*, 2005; Allen *et al*, 2009; Meinhold *et al*, 2009; Kabat *et al*, 2012; Kitahara *et al*, 2012) and case–control (Rossing *et al*, 2000; Mack *et al*, 2003) studies have also reported suggestive inverse associations for moderate alcohol intake at recruitment and risk of thyroid carcinoma. The Million Women Study enrolled 1 280 296 women in the United Kingdom, 491 of which developed incident thyroid cancer during an average of 7.2 years of follow-up. Compared with women consuming less than two drinks per week, those consuming more than 15 drinks per week had a statistically significant 46% lower risk (HR = 0.54; 95% CI = 0.31–0.92; Allen *et al*, 2009). The Women's Health Initiative cohort study, which included 159 340 post-menopausal women with 331 incident thyroid cancer cases, reported a borderline significant inverse association comparing women consuming at least seven drinks per week *vs* none (HR = 0.66; 95% CI = 0.44–1.01; Kabat *et al*, 2012). A pooled analysis of five prospective studies from the United States (Kitahara *et al*, 2012) that included 384 443 men, 361 664 women and 1003 incident thyroid cancers showed a HR of 0.72 (95% CI = 0.58–0.90) for an alcohol intake of $\geqslant 7$ drinks per week *vs* zero, that is, an inverse association of similar magnitude to the one we observed in EPIC.

The evidence for an association between alcohol consumption and risk of differentiated thyroid carcinoma in men is sparse, because this disease is much more common among women. In EPIC, we observed that moderate alcohol consumption at baseline or during the lifetime was associated with a lower but not statistically significant risk of differentiated thyroid carcinoma in men. Studies that have reported results in men and women have generally not observed significantly different findings by sex (Galanti *et al*, 1997; Guignard *et al*, 2007; Meinhold *et al*, 2009; Kitahara *et al*, 2012), in agreement with our findings. Moreover, other studies have also not observed great differences in the associations of alcohol and thyroid carcinoma by type of alcoholic beverage, by thyroid carcinoma histology, by age, BMI or smoking status at recruitment (Galanti *et al*, 1997; Allen *et al*, 2009; Meinhold *et al*, 2009; Kabat *et al*, 2012; Kitahara *et al*, 2012), in agreement with findings in EPIC.

The mechanisms explaining the potential link between alcohol consumption and differentiated thyroid carcinoma risk are not well known and are potentially complex. Some studies have described thyroid dysfunction in alcoholic individuals, and have suggested either a direct toxic effect of alcohol on the thyroid or a disturbance on the hypothalamus–pituitary–thyroid axis (Hegedus *et al*, 1988; Zoeller *et al*, 1996). However, the potential effects of low-to-moderate alcohol consumption on the thyroid are much less studied and should be considered speculative. Alcohol metabolism results in generation of free radicals, which has been hypothesised to induce oxidative stress in tissues poorly metabolising alcohol, such as the thyroid, and subsequently lead to hypothalamus–pituitary–thyroid axis dysfunction and reduction of peripheral thyroid hormone concentrations (Valeix *et al*, 2008). However, a recent nested case–control study in EPIC did not find an association between pre-diagnostic concentrations of total or free T3 and T4 with differentiated thyroid carcinoma risk, although Tg and TSH concentrations were significantly associated with the disease in a positive and negative manner, respectively (Rinaldi *et al*, 2014).

The present study has a number of strengths, including its prospective nature that precludes reverse causation to a large extent, and the large size of the EPIC cohort that gave rise to the largest number of differentiated thyroid carcinoma cases to date by any single cohort study. In addition, information on the histological subtype and stage of thyroid cancer and on drinking habits at recruitment and over lifetime as well as data on a wide

Table 1. Distribution of participant characteristics at recruitment in the EPIC cohort by country

	All	Denmark	France	Germany	Greece	Italy	Netherlands	Norway	Spain	Sweden	UK
	(*n* = 477 263)	(*n* = 55 006)	(*n* = 67 375)	(*n* = 48 576)	(*n* = 26 028)	(*n* = 44 533)	(*n* = 36 502)	(*n* = 35 167)	(*n* = 39 997)	(*n* = 48 682)	(*n* = 75 397)
Mean age, years	50.7	56.2	52.2	50.1	52.6	50	48.5	47.6	48.7	51.5	48.8
Female, *n* (%)	335 018 (70.2)	28 715 (52.2)	67 375 (100)	27 405 (56.4)	15 223 (58.5)	30 506 (68.5)	26 864 (73.6)	35 167 (100)	24 852 (62.1)	26 370 (54.2)	52 543 (69.7)
Person years	5 414 700	625 248	704 066	495 537	251 145	515 726	443 810	351 003	493 373	669 902	864 889
No. of cases, *n*	556	23	202	79	24	82	12	30	51	24	29
Baseline alcohol intake, n (%)											
Non-consumer	66 664 (14.0)	1235 (2.2)	9484 (14.0)	2217 (4.6)	6485 (24.9)	7435 (16.7)	5763 (15.8)	7254 (20.6)	15 346 (38.4)	6814 (14.0)	4631 (6.1)
0.1–4.9	164 560 (34.5)	10 654 (19.4)	21 683 (32.2)	15 375 (31.7)	9249 (35.5)	13 658 (30.6)	12 526 (34.3)	20 778 (59.1)	7587 (18.9)	22 206 (45.6)	30 844 (41.0)
5.0–14.9	127 520 (26.7)	18 041 (32.8)	18 980 (28.2)	13 482 (27.7)	5304 (20.4)	9828 (22.1)	8734 (23.9)	6768 (19.2)	5993 (15.0)	13 222 (27.2)	27 168 (36.0)
$\geqslant$15	118 519 (24.8)	25 076 (45.6)	17 228 (25.6)	17 502 (36.0)	4990 (19.2)	13 612 (30.6)	9479 (26.0)	367 (1.1)	11 071 (27.7)	6440 (13.2)	12 754 (16.9)
Mean, g per d[a]	13.5	21.1	12.7	16.6	12.6	16.3	13.1	3.5	21.5	7.9	9.6
Lifetime alcohol intake, n (%)											
Non-consumer	37 949 (8.0)	1750 (3.2)	9924 (14.8)	722 (1.5)	5680 (21.8)	4934 (11.1)	1835 (5.0)	NA	10 389 (26.0)	NA	2715 (3.6)
0.1–4.9	120 726 (25.3)	11 712 (21.3)	28 409 (42.2)	16 561 (34.1)	8396 (32.3)	12 756 (28.6)	6318 (17.3)	NA	9042 (22.6)	NA	27 532 (36.5)
5.0–14.9	109 502 (22.9)	22 081 (40.1)	19 639 (29.1)	15 297 (31.5)	5096 (19.6)	10 140 (22.8)	5101 (14.0)	NA	6911 (17.3)	NA	25 237 (33.5)
$\geqslant$15	95 022 (19.9)	19 217 (40.0)	8445 (12.5)	15 995 (32.9)	6856 (26.3)	11 566 (26.0)	2158 (5.9)	NA	13 407 (33.5)	NA	17 378 (23)
Unknown	114 06 (23.9)	246 (0.4)	958 (1.4)	1 (0)	NA	5137 (11.5)	21 090 (57.8)	35 167 (100)	248 (0.6)	48 682 (100)	2535 (3.4)
Mean, g per d[a]	13.9	15.1	7.9	16.3	18.9	14.3	8.2	NA	25.4	NA	11.0

Abbreviations: EPIC = European Prospective Investigation into Cancer and Nutrition; UK = United Kingdom; NA = not available.
[a]Mean values of alcohol consumption only among alcohol consumers.

Table 2. Country and age-adjusted participant characteristics by categories of baseline alcohol intake and sex in the EPIC cohort[a]

	Baseline alcohol intake (g per day)			
Characteristics	**Non-consumers**	**0.1–4.9**	**5.0–14.9**	**⩾15**
Women (n = 335 018)				
Mean age (s.d.), years	51.8 (9.9)	49.6 (9.9)	50.1 (9.9)	51.2 (9.9)
University graduate, %	12.1	19.0	26.0	29.4
Current smoker, %	18.8	17.5	18.3	27.6
Ever smoker, %	34.2	40.6	45.8	56.8
Physically active, %	23.5	32.9	39.7	43.0
Ever hormone replacement therapy users,%	17.4	23.2	25.5	27.6
Ever oral contraceptive users, %	42.0	57.6	65.9	69.2
Parous, %	90.3	87.9	85.4	84.1
Postmenopausal (naturally or surgically), %	45.4	42.3	39.3	38.1
Diabetes, %	3.6	2.0	1.3	1.3
Mean body mass index (s.d.), kg m^{-2}	26.6 (4.14)	25.2 (4.13)	24.6 (4.12)	24.4 (4.15)
Mean energy from non-alcohol (s.d.), kcal per day	1811 (554)	1847 (553)	1895 (552)	1913 (555)
Men (n = 142 245)				
Mean age (s.d.), years	53.5 (9.9)	50.7 (9.9)	51.3 (9.9)	51.9 (9.9)
University graduate, %	15.3	22.4	29.7	29.9
Current smoker, %	30.2	22.0	23.4	33.8
Ever smoker, %	63.7	55.2	60.3	73.4
Physically active, %	41.7	46.0	48.9	52.2
Diabetes, %	4.9	3.4	2.5	2.6
Mean body mass index (s.d.), kg m^{-2}	26.8 (4.12)	26.3 (4.12)	26.3 (4.12)	26.7 (4.14)
Mean energy from non-alcohol (s.d.), kcal per day	2297 (552)	2243 (552)	2293 (554)	2322 (554)

Abbreviations: EPIC = European Prospective Investigation into Cancer and Nutrition; s.d. = standard deviation.
[a]Country and age at recruitment-adjusted means with standard deviations are presented for continuous variables and percentage for categorical variables using linear and logistic regression models, respectively.

Table 3. Association of alcohol intake and differentiated thyroid carcinoma in the EPIC cohort

	Intake at baseline			Average lifetime intake[a]		
	Cases/cohort	**HR[b] (95% CI)**	**HR[c] (95% CI)**	**Cases/cohort**	**HR[b] (95% CI)**	**HR[c] (95% CI)**
Total alcohol (g per day)						
0	98/66 566	0.98 (0.76–1.26)	0.97 (0.76–1.25)	81/37 868	1.16 (0.89–1.52)	1.16 (0.89–1.52)
0.1–4.9	224/164 336	1.00 (reference)	1.00 (reference)	201/120 525	1.00 (reference)	1.00 (reference)
5–14.9	127/127 393	0.76 (0.61–0.94)	0.76 (0.61–0.95)	125/109 377	0.86 (0.68–1.08)	0.86 (0.69–1.08)
⩾15	107/118 412	0.76 (0.60–0.97)	0.77 (0.60–0.98)	76/94 946	0.90 (0.68–1.21)	0.90 (0.67–1.21)
Per 10 g per day[d]	458/410 141	0.91 (0.84–0.98)	0.91 (0.84–0.98)	402/324 848	0.93 (0.84–1.02)	0.93 (0.84–1.02)
Alcohol from wine (g per day)						
0[e]	124/98 185	0.95 (0.75–1.21)	0.94 (0.75–1.19)	102/63 771	1.07 (0.83–1.38)	1.07 (0.83–1.37)
0.1–4.9	244/194 805	1.00 (reference)	1.00 (reference)	232/161 738	1.00 (reference)	1.00 (reference)
5–14.9	116/116 785	0.80 (0.63–0.99)	0.81 (0.64–1.01)	110/91 736	0.94 (0.74–1.19)	0.94 (0.75–1.19)
⩾15	72/66 932	0.74 (0.56–0.97)	0.75 (0.57–0.99)	112/159 462	0.81 (0.56–1.17)	0.81 (0.56–1.17)
Per 10 g per day[d]	458/410 141	0.90 (0.82–0.99)	0.91 (0.82–0.99)	402/324 848	0.96 (0.84–1.09)	0.96 (0.84–1.09)
Alcohol from beer (g per day)						
0[f]	321/213 960	1.10 (0.88–1.38)	1.09 (0.87–1.37)	255/150 311	1.01 (0.79–1.28)	1.00 (0.79–1.28)
0.1–0.9	118/89 139	1.00 (Reference)	1.00 (Reference)	109/70 825	1.00 (Reference)	1.00 (Reference)
1.0–2.9	54/71 768	0.77 (0.55–1.07)	0.77 (0.55–1.07)	60/55 400	0.97 (0.70–1.34)	0.98 (0.71–1.35)
⩾3	63/101 840	0.90 (0.65–1.26)	0.90 (0.64–1.25)	59/86 180	1.06 (0.74–1.53)	1.07 (0.74–1.54)
Per 3 g per d[d]	458/410 141	0.96 (0.90–1.03)	0.96 (0.90–1.03)	402/324 848	0.99 (0.92–1.07)	0.99 (0.92–1.07)
Alcohol from spirits (g per day)						
0[g]	384/273 418	1.10 (0.86–1.41)	1.10 (0.86–1.41)	312/179 769	1.27 (0.97–1.66)	1.28 (0.98–1.68)
0.1–0.9	106/102 921	1.00 (Reference)	1.00 (Reference)	79/63 692	1.00 (Reference)	1.00 (Reference)
1.0–2.9	38/44 975	0.89 (0.61–1.29)	0.88 (0.60–1.29)	52/55 831	1.17 /0.82–1.68)	1.16 (0.81–1.66)
⩾3	28/55 393	0.82 (0.53–1.27)	0.81 (0.52–1.25)	40/63 424	1.25 (0.82–1.91)	1.21 (0.79–1.84)
Per 3 g per d[d]	458/410 141	1.00 (0.90–1.10)	0.99 (0.89–1.10)	402/324 848	0.92 (0.81–1.03)	0.91 (0.80–1.03)
P-heterogeneity by type of beverage[d]; I^2		0.38; 0%				0.42; 0%

Abbreviations: EPIC = European Prospective Investigation into Cancer and Nutrition; HR = hazard ratio; CI = confidence interval.
[a]This information was missing for participants from the EPIC centres of Naples, Bilthoven, Umea, Malmo and Norway.
[b]From Cox proportional hazard models stratified by centre and age at recruitment; alcohol intake of one alcoholic beverage is mutually adjusted for the intake of the other two beverages.
[c]From Cox proportional hazard models stratified by centre and age at recruitment and adjusted for cigarette smoking intensity, education, body mass index, physical activity, diabetes, energy from non-alcohol sources, hormone replacement therapy, oral contraceptives, age at menarche, number of full-term pregnancies and menopausal status; alcohol intake of one alcoholic beverage is mutually adjusted for the intake of the other two beverages.
[d]Among consumers of alcoholic beverages only. When we performed analyses including both consumers and non-consumers of alcoholic beverages but after adjusting for being a consumer or not, the results were identical.
[e]This group includes participants who did not consume wine, but consumed other alcoholic beverages.
[f]This group includes participants who did not consume beer, but consumed other alcoholic beverages.
[g]This group includes participants who did not consume spirits, but consumed other alcoholic beverages.

Table 4. Association of alcohol intake (per 10 g per day among consumers) and differentiated thyroid carcinoma by subgroups in the EPIC cohort

	Intake at baseline		Average lifetime intake[a]	
Subgroups	**Cases/cohort**	**HR[b] (95% CI)**	**Cases/cohort**	**HR[b] (95% CI)**
Country				
Denmark	22/53 749	1.02 (0.81–1.27)	22/52 988	0.97 (0.66–1.43)
France	174/57 717	0.91 (0.81–1.03)	166/56 327	0.92 (0.77–1.10)
Germany	76/46 283	0.79 (0.62–0.99)	79/47 774	0.84 (0.65–1.09)
Greece	17/19 526	1.04 (0.76–1.41)	17/20 331	0.71 (0.41–1.22)
Italy	63/37 035	0.96 (0.81–1.13)	57/34 405	0.99 (0.81–1.22)
Norway	27/27 886	0.54 (0.15–1.99)	NA	NA
Spain	23/24 628	1.06 (0.75–1.50)	28/29 332	1.08 (0.92–1.27)
Sweden	18/41 850	0.77 (0.35–1.67)	NA	NA
The Netherland	11/30 728	0.11 (0.02–0.81)	7/13 570	0.96 (0.35–2.64)
United Kingdom	27/70 739	0.84 (0.54–1.29)	26/70 121	0.79 (0.50–1.25)
P-heterogeneity; I^2		0.35; 10%		0.63; 0%
Age at recruitment (years)				
<50	222/175 102	0.90 (0.80–1.02)	191/125 040	0.86 (0.73–1.00)
$\geqslant 50$	236/235 039	0.91 (0.82–1.01)	211/191 352	0.97 (0.87–1.09)
P-interaction		0.94		0.24
Sex				
Male	52/132 480	0.94 (0.82–1.09)	46/102 326	0.94 (0.82–1.07)
Female	406/277 661	0.89 (0.81–0.98)	356/214 066	0.91 (0.80–1.04)
P-interaction		0.80		0.86
Body mass index				
$<25\,kg\,m^{-2}$	259/210 776	0.88 (0.79–0.99)	223/160 200	0.88 (0.75–1.03)
$\geqslant 25\,kg\,m^{-2}$	199/199 365	0.93 (0.84–1.04)	179/156 192	0.96 (0.85–1.08)
P-interaction		0.43		0.26
Smoking status				
Never smoker	244/192 158	0.83 (0.72–0.95)	223/155 952	0.80 (0.66–0.98)
Former smoker	118/115 574	0.90 (0.77–1.03)	104/88 406	0.99 (0.87–1.14)
Current smoker	84/94 199	0.99 (0.87–1.12)	66/67 058	0.92 (0.77–1.10)
P-interaction		0.11		0.60
Diabetes				
No	440/386 254	0.90 (0.83–0.98)	392/301 062	0.93 (0.84–1.02)
Yes	8/9353	1.17 (0.82–1.66)	8/8026	0.97 (0.64–1.46)
P-interaction		0.78		0.41

Abbreviations: EPIC = European Prospective Investigation into Cancer and Nutrition; HR = hazard ratio; CI = confidence interval; NA = not applicable.
[a]This information was missing for participants from the EPIC centres of Naples, Bilthoven, Umea, Malmo, and Norway.
[b]From Cox proportional hazard models stratified by centre and age at recruitment and adjusted for cigarette smoking intensity, education, body mass index, physical activity, diabetes, energy from non-alcohol sources, hormone replacement therapy, oral contraceptives, age at menarche, number of full-term pregnancies and menopausal status.

range of potential confounders is important and unique aspects of this study.

However, the study also has limitations. First, most women in the EPIC cohort, and in most other published epidemiological studies, were consuming low to moderate amounts of alcohol at enrolment or over their lifetimes, which did not allow investigating the association of heavy sustained drinking on subsequent risk of thyroid carcinoma. Second, information on alcohol consumption at baseline and over the lifetime was self-reported, but due to the prospective nature of the study this is likely to lead to non-differential misclassification (by thyroid carcinoma cases and non-cases) and bias, if any, our results towards the null. However, the information on alcohol consumption at recruitment in EPIC has been shown to be adequately reliable and valid compared with repeat food frequency questionnaires and multiple 24-h diet recalls (Kaaks *et al*, 1997). Third, data on ionizing radiation exposure and medical history of benign thyroid diseases, the most well-established risk factors for thyroid cancer were not available in EPIC and confounding due to these variables could not be assessed. However, adjustment for radiation and benign thyroid conditions in a prior publication had little influence on the associations (Kitahara *et al*, 2012). In addition, all of our risk estimates were adjusted for several confounding factors with relatively small difference to the risk estimates compared with unadjusted models. Besides that we cannot rule out the possibility of residual confounding by other unmeasured factors. Finally, individuals with a healthy lifestyle who may consume little or no alcohol might be prone to have their thyroids examined or removed surgically, and thus maybe have an incidental finding of a small localised thyroid cancer without clinical relevance, which could explain the weak inverse association observed in this study. However, this potential detection bias is unlikely to have driven our findings, because risk estimates did not differ between analyses for localised and advanced thyroid carcinomas.

In conclusion, our prospective study provides some support to the hypothesis that moderate alcohol consumption may be associated with a lower risk of differentiated thyroid carcinoma. However, more studies are needed to fully characterise the nature and mechanisms underlying this association. Given that many studies have reported an increased risk of various forms of cancer with alcohol intake, the findings of this study do not change the current public health recommendation that if alcoholic beverages are consumed, consumption should be limited to no more than two drinks a day for men and one drink a day for women (World Cancer Research Fund/American Institute for Cancer Research, 2007).

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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[1]*Department of Hygiene and Epidemiology, University of Ioannina School of Medicine, Ioannina 45110, Greece;* [2]*Department of Public Health and General Practice, Faculty of Medicine, Norwegian University of Science and Technology, NTNU, Trondheim N-7491, Norway;* [3]*Cancer Epidemiology Unit, University of Oxford, Oxford, UK;* [4]*Department of Epidemiology and Biostatistics, School of Public Health, Imperial College London, London, UK;* [5]*Clinical Trial Service Unit and Epidemiological Studies Unit, University of Oxford, Oxford, UK;* [6]*International Agency for Research on Cancer, Lyon, France;* [7]*Department of Surgery, University Hospital Lund, Lund, Sweden;* [8]*Malmö Diet and Cancer Study, University Hospital Malmö, Malmö, Sweden;* [9]*Section for Epidemiology, Department of Public Health, Aarhus University, Aarhus, Denmark;* [10]*Danish Cancer Society Research Center, Copenhagen, Denmark;* [11]*Inserm, Centre for research in Epidemiology and Population Health (CESP), Nutrition, Hormones and Women's Health team, Villejuif, France;* [12]*Université Paris Sud, Villejuif, France;* [13]*Institut Gustave Roussy, Villejuif, France;* [14]*Cancer Epidemiology Centre, Cancer Council of Victoria, Melbourne, Victoria, Australia;* [15]*Centre for Epidemiology and Biostatistics, School of Population and Global Health, University of Melbourne, Melbourne, Victoria, Australia;* [16]*German Cancer Research Center (DKFZ), Heidelberg, Germany;* [17]*Department of Epidemiology, German Institute of Human Nutrition Potsdam-Rehbrueke, Nuthetal, Germany;* [18]*Hellenic Health Foundation, Athens, Greece;* [19]*Department of Hygiene, Epidemiology and Medical Statistics, University of Athens Medical School, Athens, Greece;* [20]*Bureau of Epidemiologic Research, Academy of Athens, Athens, Greece;* [21]*Department of Epidemiology, Harvard School of Public Health, Boston, MA, USA;* [22]*Molecular and Nutritional Epidemiology Unit, Cancer Research and Prevention Institute—ISPO, Florence, Italy;* [23]*Department of Preventive and Predictive Medicine, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy;* [24]*Dipartimento Di Medicina Clinica E Chirurgia, Federico Ii University, Naples, Italy;* [25]*Ragusa Cancer Registry, Azienda Ospedaliera "Civile M.P. Arezzo", Ragusa, Italy;* [26]*Human Genetics Foundation (HuGeF), Torino, Italy;* [27]*Department for Determinants of Chronic Diseases (DCD), National Institute for Public Health and the Environment (RIVM), Bilthoven, The Netherlands;* [28]*Department of Gastroenterology and Hepatology, University Medical Centre, Utrecht, The Netherlands;* [29]*Department of Social and Preventive Medicine, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia;* [30]*Julius Center for Health Sciences and Primary Care, Epidemiology, University Medical Center, Utrecht, The Netherlands;* [31]*Department of Nutrition, Institute of Basic Medical Sciences, University of Oslo, Oslo, Norway;* [32]*Department of Community Medicine, Faculty of Health Sciences, University of Tromsø, Arctic University of Norway, Tromsø, Norway;* [33]*Department of Research, Cancer Registry of Norway, Oslo, Norway;* [34]*Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden;* [35]*Genetic Epidemiology Group, Folkhälsan Research Center, Helsinki, Finland;* [36]*Public Health Directorate, Asturias, Spain;* [37]*Unit of Nutrition and Cancer, Cancer Epidemiology Research Program, IDIBELL, Catalan Institute of Oncology-ICO, L'Hospitalet de Llobregat, Barcelona, Spain;* [38]*Escuela Andaluza de Salud Pública, Instituto de Investigación Biosanitaria, Hospitales Universitarios de Granada/Universidad de Granada, Granada, Spain;* [39]*CIBER de Epidemiología y Salud Pública (CIBERESP), Spain;* [40]*Public Health Division of Gipuzkoa, Instituto BIO-Donostia, Basque Government, San Sebastian, Spain;* [41]*Department of Epidemiology, Murcia Regional Health Council, IMIB-Arrixaca, Murcia, Spain;* [42]*Navarre Public Health Institute, Pamplona, Spain;* [43]*Department of Surgery, University Hospital Malmö, Malmö, Sweden;* [44]*Department of Surgical and Perioperative Sciences, Umeå University, Umeå, Sweden;* [45]*Department for Radiation Sciences, Umeå University, Umeå, Sweden;* [46]*School of Clinical Medicine, Addenbrooke's Hospital, University of Cambridge, Cambridge, UK and* [47]*MRC Epidemiology Unit, Institute of Metabolic Science, University of Cambridge, Cambridge, UK*