Short Communication

Intake of Alcohol and Alcoholic Beverages and the Risk of Basal Cell Carcinoma of the Skin[1]

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Abstract

We prospectively examined the intake of alcoholic beverages in relation to the risk of basal cell carcinoma BCC in two large cohorts of men and women. Alcohol intake was assessed with food frequency questionnaires every 2–4 years, and BCC was ascertained by self-report. We used a pooled logistic regression to model the association between alcohol intake and BCC adjusting for various health, sun exposure, and sun-sensitivity factors. During 8 years of follow-up in women (1986–1994) we recorded 3060 cases of BCC, and during 10 years (1986–1996), we recorded 3028 cases in men. Significant positive associations were observed between total alcohol intake (*P* for trend <0.0001), alcohol from liquor (*P* for trend = 0.003), and white wine (*P* for trend = 0.01) intake and risk of BCC. Compared with those who abstained, those who drank 0.1–4.9 g, 5.0–14.9 g, 15.0–14.9 g, and 30 g or more alcohol a day had multivariate relative risks of 1.11 [95% confidence interval (CI), 1.03, 1.19], 1.26 (95% CI, 1.12, 1.41), 1.29 (95% CI, 1.18, 1.42), and 1.12 (95% CI, 1.01, 1.26), respectively. Alcohol from beer had no association with BCC in either cohort, and red wine appeared to have an inverse association in women (*P* for trend = 0.004) but not in men. These associations remained unchanged after adjustment for individual vitamins, multivitamin use, outdoor walking, and exclusion of follow-up time after last physical examination among those who never had BCC. Alcohol intake was associated with BCC, but the association appeared to be different for each type of alcoholic beverage. Other studies are needed to confirm these results.

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Introduction

BCC[3] of the skin is the most common cancer in Caucasians (1). Although BCC is usually nonfatal, it nevertheless results in recurrence and disfigurement (2). Also, incidence may have increased over the past 20 years (3). Established risk factors include fair skin, light hair and eye color, a tendency to burn, and history of severe sunburns (4). Among these, only sun exposure is modifiable. Alcohol intake is a risk factor for several cancers, including hepatocellular carcinoma, oral, pharynx, esophagus, and breast cancer (5). A 9% increase in risk of breast cancer is observed with every 10-g increase in daily alcohol intake.

Human studies on alcohol consumption and risk of BCC are few. Two case-control studies did not find any association between alcohol intake and BCC, possibly because of crude classification of alcohol consumption and lack of adjustment for confounders (6, 7). In an unpublished study on fat intake and BCC, we observed a positive association with total alcohol when alcohol was included in regression models. Therefore, we conducted this exploratory analysis to assess the associations among intakes of total alcohol, specific alcoholic beverages, and risk of BCC in two large cohorts of men and women.

Materials and Methods

Study Cohorts

NHS. The NHS began in 1976 when 121,700 female nurses in 11 United States states ages 30–55 returned a questionnaire providing health and lifestyle data. Similar questionnaires were sent every 2 years to update information. Follow-up response was 95% of the potential person-years. For this analysis, women were eligible if they completed the 1986 semiquantitative FFQ with <70 missing items and a total energy intake between 500 and 3,500 kcal/day. We excluded women diagnosed previously with any cancer, including skin cancer, leaving 65,358 women for analysis.

HPFS. In 1986, >52,000 male health professionals, between 40 and 75 years of age were recruited for a prospective study of diet, lifestyle, and disease. A questionnaire similar to the NHS has been sent to participants every 2 years. Completion of questionnaire has been >90% at each cycle, and reports of health information were accurate (8). Members of the HPFS cohort were eligible for this analysis if they completed the 1986 FFQ with <70 missing items and total energy between 800 and 4,200 kcal/day. Men with any cancer, including any skin cancer, diagnosis at baseline were excluded, leaving 42,617 for analysis.

Assessment of Nutrient Intake

Dietary intake information was collected using a FFQ designed to assess average food intake over the previous year. Cohort

[3] The abbreviations used are: BCC, basal cell carcinoma; NHS, nurses health study; FFQ, food frequency questionnaire; HPFS, health professionals follow-up study; BMI, body mass index; RR, relative risk; CI, confidence interval.

members were asked to choose from nine possible responses, from "never" to "more than six times a day" for each food. Alcoholic beverage intake was obtained separately for beer, red and white wine, and liquor, then converted to grams of alcohol per day, with one 12-fluid-ounce drink of beer equal to 13 grams of alcohol, one 4-fluid-ounce drink of red or white wine equal to 11 grams, and one 2-fluid-ounce drink of liquor or spirits equal to 14 grams. Total alcohol intake was obtained by summing the amount from specific alcoholic beverages. Information on intake of vitamin and mineral supplements was also collected.

FFQs were used to calculate total energy intake and intakes of other nutrients. Dietary data were collected in 1986 and 1990 for the NHS, and in 1986, 1990, and 1994 for the HPFS. Previous validation studies among members of the NHS and HPFS cohorts revealed good correlations between alcohol intake from FFQ and food records (9, 10). In the NHS, correlations coefficients were 0.81 for beer, 0.83 for wine, and 0.80 for liquor. In HPFS, correlations between dietary records and FFQ were 0.88 for beer, 0.83 for red wine, 0.78 for white wine, and 0.85 for liquor.

Case Ascertainment

The first diagnosis of BCC was obtained by self-report, shown previously to be 96% accurate in a sample of NHS (11). In NHS, the duration of case accrual was 8 years (1986–1994). In HPFS, 84% confirmation of self-reported BCC by medical records was obtained (12). The duration of case accrual was 10 years (1986–1996) in HPFS.

Statistical Analysis

We assessed the effect of total alcohol intake as well as alcohol from each specific beverage. We expressed intakes as cumulative averages to reduce within-person variation and to represent long-term intake. For example, in men, the average of 1986 and 1990 intake was used to model rates between 1990 and 1992, and so forth. The alcohol and BCC association was modeled with multivariate pooled logistic regression with 2-year intervals (13) and cubic regression splines separately for each cohort. In the NHS, we adjusted for tendency to tan (5 categories), tendency to sunburn (5 categories), natural hair color (5 categories) at age 20, major ancestry (8 categories), and number of lifetime blistering sunburns (4 categories) and the use of sunscreen (yes, no, or "does not go out"), both assessed in 1980. We also adjusted for state of residence at age 15, a proxy for sun exposure in childhood, and current state of residence, a proxy for recent sun exposure. In the HPFS, we adjusted for major ancestry (6 categories), natural hair color at age 18 (5 categories), eye color (3 categories), tendency to burn or tan in adolescence (3 categories), state of residence at age 15, and current state of residence. In both cohorts, we also adjusted for age and BMI. Data from our group and others have shown BMI to have an independent inverse association with BCC (12, 14). As failure to return FFQs may be associated with lifestyle behavior related to BCC risk, we created and adjusted for "missing FFQ" indicator variables. We also adjusted for smoking status, which may be a marker for general health-related behavior.

To investigate possible differential associations of alcohol intake and BCC by overall BCC risk profile, we computed a composite BCC multivariate risk score for each cohort member based on the adjusted effect estimates of potential confounders (15). We then tested for interaction between alcohol intake and tertiles of the composite score. We also explored the role of timing of alcohol intake by allowing variable lag times between dietary assessment and BCC incidence.

After separate analyses for each cohort, the relative risks were pooled using a random effects model to provide a combined risk estimate (16). We also tested for heterogeneity of the relative risks. Tests of trend were performed by assigning to each participant the median of the quintile to which they belonged and modeling this variable as a single continuous variable. Statistical analyses were performed with SAS, and all of the P are two-sided (17).

Results

Between 1986 and 1994 in the NHS, we recorded 3060 cases of BCC. Between 1986 and 1996 in the HPFS, we obtained 3028 cases of BCC. Thirty-two percent of NHS and 24% of HPFS participants were abstainers from alcohol in 1986. Women with higher intakes of alcohol tended to be leaner, except for the highest intake level (Table 1). Heavy drinkers also tended to be smokers. In the HPFS, liquor or spirits had the highest percentage of heavy drinkers, with 6.1% reporting drinking <2 drinks a day. A "U"-shaped relationship was seen among alcoholic beverage, consumption, and obesity (Table 1).

After pooling the relative risks from both cohorts, total alcohol was associated positively with BCC (P for trend <0.0001; Table 2). In cubic spline regression analyses, the general shape of the spline curves and the magnitude of association were similar to results from categorical analyses, and the associations were significantly nonlinear in both cohorts (data not shown).

Different trends were observed for specific alcoholic beverages. Alcohol from beer had no association with BCC in either cohort, but a positive association was observed with liquor in both. This positive trend was stronger in men. Those who consumed >30 grams of alcohol from liquor were 25% more likely to have a BCC than abstainers. Red wine may have an inverse association in women (P for trend $= 0.004$), but no association was observed in men (P for heterogeneity of trend $= 0.04$). A significant positive association was observed between white wine and BCC in the pooled analysis (P for trend $= 0.01$; RR, 1.24; and 95% CI, 0.97, 1.60 among those who consumed >15 grams of alcohol from white wine). When we compared the trends among the different alcoholic beverages, we did not observed statistically significant differences in the direction of association in men (data not shown). In women, however, the directions of association were significantly different between red and white wines (inverse *versus* positive association), red wine and liquor (inverse *versus* no association), white wine and beer (positive *versus* no association), and white wine and liquor (positive *versus* no association).

We did not observe any significant difference in the association between total alcohol intake and BCC at different tertiles of the composite risk factor score (data not shown), nor a clear difference in association with different durations of lag time. These associations remained after additional adjustments for walking outdoors (additional sun exposure information), and vitamin intake, or excluding those with missing FFQ. They were also not affected by excluding person-time after the last physical examination among those who never became a case to minimize detection bias. The results also did not differ with or without controlling for smoking. In addition, excluding past heavy drinkers who later abstained did not change the results.

Discussion

In this analysis, we observed positive associations among total alcohol, alcohol from liquor, and white wine and risk of BCC.

Table 1 Age-adjusted lifestyle characteristics (%) of NHS in 1984 and HPFS participants by selected levels of alcohol intake in 1986

Alcohol	Drinks per day[a]	% Drinkers	% BMI >25	% Tend to burn[b]	% Red or blond/light hair	% High current ambient sun[c]
Total NHS	0	31.7	49	37	14	20
	5.0–14.9	21.4	32	34	16	20
	30+	5.5	31	33	16	24
Total HPFS	0 g	23.8	40	50	9	39
	5.0–14.9	16.8	35	53	10	31
	30+	11.6	37	54	11	38
Beer NHS	0 g	79.4	41	36	15	19
	0.5–1	2.0	30	33	17	20
	4+	0.2	36	31	14	21
Beer HPFS	0	44.5	39	51	9	35
	0.5–1	8.3	32	56	11	36
	4+	0.8	39	55	14	37
Liquor NHS	0	63.5	42	36	15	20
	0.5–1	5.9	30	32	17	19
	4+	0.3	38	39	15	24
Liquor HPFS	0	47.9	36	52	9	36
	0.5–1	9.4	39	54	11	34
	4+	0.8	43	50	11	37
Red wine NHS	0	73.1	42	36	15	20
	0.5–1	1.5	27	35	14	22
	4+	0.1	29	46	17	39
Red wine HPFS	0	59.5	37	52	10	36
	0.5–1	2.4	36	55	9	39
	4+	0.1	30	48	9	37
White wine NHS	0	51.4	45	37	15	18
	0.5–1	5.3	23	34	17	28
	4+	0.2	31	38	13	45
White wine HPFS	0	45.2	40	51	10	35
	0.5–1	4.5	31	57	11	42
	4+	0.1	35	47	3	42

[a] Except for total alcohol-grams.
[b] Tend to burn painfully or burn with blister on 2 h of sun exposure in childhood.
[c] Current state of residence with high ambient sun radiation.

An inverse association between alcohol from red wine and BCC was seen among women only. However, a clear monotone-increasing or monotone-decreasing response relationship was not observed with total alcohol intake.

To our knowledge, this study is the first long-term prospective evaluation of alcohol consumption and risk of BCC. Our results are not in agreement with the few existing human studies. In a case-control study of men, current, past and non-alcohol drinkers did not differ in skin cancer incidence (6). However, information bias was possible in this study, as both the cases and the interviewers were aware of the disease status. Also, this analysis did not appear to account for possible confounders. In another case-control study matched on age, sex, and skin type, there was no difference in consumption status (i.e., > or <15 years of use) between the cases with aggressive BCC and the controls (7). Response rate was 46%, and the analysis was not additionally adjusted for potential confounders.

In various animal and *in vitro* models, alcohol was shown to have tumor-promoting effects and can generate free radicals (18). Immunosuppression is a skin cancer risk factor as transplant patients have elevated risk for skin cancers, including BCC (19). Alcohol may impair cell-mediated and humoral immunity (20). Chronic alcohol consumption in rats resulted in thymus atrophy accompanied by a reduction of the antioxidant glutathione (20).

The different associations observed among different alcoholic beverages may be attributable to a combination of effects from ethanol and other substances in the specific beverages. Wine contains phenolic compounds, and many of them have antioxidant activities (21). Red wine has higher amounts of phenolic compounds than white wines and can acutely increase serum antioxidant activity after ingestion (22). On the other hand, lower antioxidant activity is found in beer and distilled spirits (23). Because phenolic compounds have anticarcinogenic effects in cell cultures and animal models (24), this may account for the lack of increased risk that we observed with red wine in women.

The prospective nature of this analysis and the high follow-up rate render information and selection bias unlikely. Our repeated measures of intake reduced random within-person variation. Heavy drinkers may under-report alcohol intake, and this would underestimate any true association. If there were substantial under-reporting among heavy drinkers, then we would expect a flattened curve rather than an inverted "U" for total alcohol intake. In addition, the validity of alcohol intake assessment from our FFQ has shown to be highly valid and well correlated with plasma high-density lipoprotein cholesterol (9, 10).

In conclusion, we observed a modest positive association between total alcohol intake and risk of BCC in both men and women. However, a clear monotonic association was not present, and the associations with the specific alcoholic beverages varied. These findings suggest that alcohol per se may not be a causal factor, but rather that the findings may be attributable to other constituents of alcoholic beverages or to unmeasured confounding variables. UV radiation remains the strongest modifiable risk factor for BCC, and first-line prevention strategies should focus on minimizing sun exposure.

Table 2 Multivariate[a] RRs of BCC with 95% CIs by categories of alcohol intakes per day

Alcohol	Nondrinkers	0.1–4.9 g/day	5.0–14.9 g/day	15.0–29.9 g/day	30+ g/day	*P* for trend
Total alcohol						
Women	1	1.13 (1.03, 1.24)	1.33 (1.20, 1.47)	1.33 (1.15, 1.52)	1.06 (0.89, 1.28)	0.001
Men	1	1.07 (0.96, 1.20)	1.18 (1.06, 1.32)	1.27 (1.12, 1.44)	1.16 (1.01, 1.34)	0.002
Pooled	1	1.11 (1.03, 1.19)	1.26 (1.12, 1.41)	1.29 (1.18, 1.42)	1.12 (1.01, 1.26)	0.0001
Beer						
Women	1	0.97 (0.87, 1.07)	1.00 (0.84, 1.19)	1.05 (0.54, 2.04)	0.82 (0.53, 1.27)	0.50
Men	1	1.08 (0.98, 1.19)	1.14 (1.02, 1.28)	1.00 (0.72, 1.38)	0.92 (0.73, 1.17)	0.95
Pooled	1	1.02 (0.92, 1.14)	1.09 (0.96, 1.23)	1.01 (0.75, 1.35)	0.90 (0.73, 1.10)	0.78
Liquor						
Women	1	1.09 (1.00, 1.20)	1.20 (1.07, 1.34)	1.31 (0.95, 1.80)	0.97 (0.77, 1.23)	0.13
Men	1	1.12 (1.02, 1.24)	1.24 (1.10, 1.38)	1.11 (0.94, 1.31)	1.25 (1.06, 1.47)	0.01
Pooled	1	1.11 (1.03, 1.18)	1.22 (1.12, 1.32)	1.15 (0.99, 1.33)	1.12 (0.88, 1.42)	0.003
Red wine						
Women	1	0.91 (0.83, 1.00)	0.78 (0.58, 1.05)	0.56 (0.29, 1.08)		0.004
Men	1	0.90 (0.82, 0.98)	0.97 (0.78, 1.20)	1.00 (0.67, 1.49)		0.64
Pooled	1	0.90 (0.85, 0.96)	0.89 (0.73, 1.09)	0.79 (0.45, 1.39)		0.23[b]
White wine						
Women	1	1.19 (1.09, 1.30)	1.31 (1.13, 1.52)	1.39 (1.11, 1.73)		0.0002
Men	1	1.03 (0.93, 1.13)	1.13 (0.95, 1.34)	1.07 (0.79, 1.45)		0.24
Pooled	1	1.11 (0.96, 1.27)	1.22 (1.06, 1.41)	1.24 (0.97, 1.60)		0.01

[a] Adjusted for age (5-year categories), missing FFQ, current state of residence, BMI (<21, 21–22.9, 23–24.9, 25–28.9, 29+, missing), childhood state of residence (high, medium, and low ambient sun radiation), total calories (quintiles), beer (nondrinker, 0.1–4.9 g, 5–14.9 g, 15–29 g, 30+ g per day), liquor (same categories as beer), wine (same categories as beer), smoking (never, past, current but unknown quantity, 1–14 cigarettes, 15–24 cigarettes, 25–34 cigarettes, 35+ cigarettes per day, missing). For women, also adjusted for lifetime blistering sunburn (never, 1–2 times, 3–5 times, 6+ times, missing), childhood tanning ability (no or light tan, average or deep tan, missing), childhood sun reaction (no burn, red, burn, painful burn, blistering burn, missing), sunscreen use (yes, no, does not go out), ancestry (nonwhites, southern European, Scandinavian, other Caucasian, other ancestry, native Americans, missing), hair color (red, blonde, light brown, dark brown, black, missing). For men, also adjusted for hair color (red/light, blonde, light brown, black, missing), eye color (dark/brown, green/medium, blue/light, missing), ancestry (Scandinavian, southern European, other Caucasian, other ancestry, non-whites, missing), tendency to burn in childhood (burn/peel, burn/tan, tan, missing), and childhood sun exposure in swimsuit (<1/week, 1/week, 2/week, several/week, daily, missing).

[b] Test for heterogeneity was significant, $P = 0.04$.

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