# Alcohol consumption and risk of cutaneous basal cell carcinoma in women and men: 3 prospective cohort studies[1,2]

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## ABSTRACT

**Background:** Alcohol consumption has been associated with an increased prevalence of sunburn, which is an established skin cancer risk factor.

**Objective:** We investigated whether alcohol consumption is associated with risk of cutaneous basal cell carcinoma (BCC).

**Design:** We conducted a prospective analysis on alcohol consumption and risk of BCC on the basis of data from 167,765 women in the NHS (Nurses' Health Study) (1984–2010) and NHS II (1991–2011) and 43,697 men in the Health Professionals Follow-Up Study (1986–2010). Alcohol intake was repeatedly assessed every 2–4 y over the follow-up period. HRs and 95% CIs for BCC in association with alcohol intake were computed with the use of Cox proportional hazards models with adjustment for sun exposure and other skin cancer risk factors.

**Results:** A total of 28,951 incident BCC cases were documented over 3.74 million person-years of follow-up. Increased alcohol intake was associated with increased BCC risk in both women and men (both $P$-trend $< 0.0001$). Pooled multivariable-adjusted HRs over increasing cumulative averaged alcohol intake categories were 1.00 (reference) for nondrinkers, 1.13 (95% CI: 1.06, 1.20) for 0.1–9.9 g/d, 1.24 (95% CI: 1.14, 1.35) for 10.0–19.9 g/d, 1.27 (95% CI: 1.20, 1.35) for 20.0–29.9 g/d, and 1.22 (95% CI: 1.15, 1.30) for ≥30.0 g/d ($P$-trend $< 0.0001$, $P$-heterogeneity by study = 0.10 ). The association remained consistent when we used alcohol intakes over different latency periods (0–4, 4–8, 8–12, and 12–16 y) as exposures and over categories of sun exposure–related factors. In the individual alcoholic beverages, white wine and liquor were positively associated with BCC risk.

**Conclusion:** Alcohol consumption is associated with increased risk of cutaneous BCC in both women and men. *Am J Clin Nutr* 2015;102:1158–66.

**Keywords:** alcohol, basal cell carcinoma, cohort study, epidemiology, skin cancer, sun exposure

## INTRODUCTION

Basal cell carcinoma (BCC)[8] of the skin is the most prevalent cancer in the United States (1). It has been estimated that >2.5 million BCCs are diagnosed each year in the United States, which is a number greater than that of all other cancers combined (1, 2). As the major histologic type of skin cancer, BCC is responsible for substantial morbidity and billions of dollars of health care expenditures (3–5). Knowledge on the modifiable risk factors of BCC is required for the targeted prevention of cancer incidence. Existing evidence provides support that solar UV radiation is the major environmental risk factor for BCC, whereas studies have also suggested that BCC risk may be associated with other environmental and lifestyle factors, such as alcohol consumption and smoking (6, 7). Alcohol consumption is a well-known risk factor for human cancer and has been linked to a number of cancers including pharynx and larynx, esophagus, breast, prostate, pancreatic, and colon cancers (8–12). Alcohol use has been observed with an increased prevalence of severe sunburn (13), and it has been hypothesized that the combination of alcohol consumption and UV radiation can potentiate the skin carcinogenicity through the intermediate byproducts or metabolites of alcohol (e.g., acetaldehyde), which can serve as photosensitizers (14).

However, evidence for the association between alcohol consumption and BCC risk has been limited (8). Only a small number of epidemiologic studies have investigated this association. Although 2 earlier prospective studies reported an association between alcohol consumption and BCC risk (7, 15), a later prospective study and several case-control studies showed no association (16–19). Potential reasons for these heterogeneous results may include differences between study designs, an insufficient control for skin cancer risk factors, and the preference of alcoholic beverages consumed in different study populations. Notably, the numbers of BCC cases included in most of these

[1] Supported in part by the NIH (grants UM1 CA186107, P01 CA87969, UM1 CA176726, UM1 CA167552, and R01 CA137365).

[2] Supplemental Figure 1 and Supplemental Tables 1 and 2 are available from the "Online Supporting Material" link in the online posting of the article and from the same link in the online table of contents at http://ajcn.nutrition.org.

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[8] Abbreviations used: BCC, basal cell carcinoma; FFQ, food-frequency questionnaire; HPFS, Health Professionals Follow-Up Study; NHS, Nurses' Health Study.

Received May 12, 2015. Accepted for publication August 26, 2015.

First published online September 30, 2015; doi: 10.3945/ajcn.115.115196.

 

previous studies were relatively small (from dozens to a few thousands), which has thereby limited their ability to provide a comprehensive evaluation on this association. Specifically, a previous investigation on the basis of data in the first 8–10–follow-up years of 2 cohorts [the NHS (Nurses' Health Study) and HPFS (Health Professionals Follow-Up Study)] showed a nonmonotonic increasing BCC ($n = 6088$) risk over the alcohol intake range (15). However, the investigation did not examine the potential effect modification of this association by other skin cancer risk factors (e.g., sun exposure) and did not investigate the association of BCC risk with alcohol consumption in early adulthood, which has been associated with increased cancer risk in later life (9). In addition, most investigations included only one exposure assessment, which may have biased the results if long-term intake is relevant to cancer risk (20).

To address the hypothesis that alcohol consumption may be associated with increased BCC risk and the nature of this association, we conducted a more comprehensive prospective study with expanded follow-up data from the NHS (1984–2010) and HPFS (1986–2010) and data from an additional cohort of the NHS II (1991–2011), all of which had repeated assessments on alcohol intake over long durations.

## METHODS

### Study populations

The NHS was established in 1976 when 121,700 married, registered, female nurses between the ages of 30 and 55 y who were residing in the United States at the time of enrollment responded to a baseline questionnaire that included questions about their medical histories and lifestyle risk factors. The NHS II was established in 1989 when 116,430 registered female nurses aged 25–42 y were enrolled with the use of a mailed baseline questionnaire that inquired about medical histories and lifestyle practices. The HPFS was established in 1986 when 51,529 US male health professionals aged 40–75 y completed a baseline questionnaire on lifestyles, diets, and newly diagnosed diseases. The cohorts used similar standardized biennial questionnaires to collect data on disease outcomes and health-related factors of study participants. The overall follow-up rates generally exceeded 90% in all 3 cohorts. The institutional review boards of Brigham and Women's Hospital and Harvard School of Public Health approved the current study. We consider the participants' completion and return of the self-administered questionnaires as informed consent.

A total of 81,722 NHS women, 95,248 NHS II women, and 49,762 HPFS men completed a food-frequency questionnaire (FFQ) at baseline (NHS: 1984; NHS II: 1991; and HPFS: 1986). We excluded participants with a history of any cancer at baseline. After exclusions, a total of 167,765 women (75,209 women from the NHS and 92,556 from women the NHS II) and 43,697 men were included in the current study.

### Assessment of BCC cases

Information on BCC diagnosis was first asked in 1984 in the NHS, in 1989 in the NHS II, and in 1986 in the HPFS. A diagnosis on BCC was asked in all subsequent biennial questionnaires mailed to study participants. Medical records were not obtained for self-reported BCC. However, previous validation studies have shown a high validity of self-reported BCC in subgroups of NHS and HPFS participants, with 96% of women and 84% of men with confirmed BCC according to histopathologic findings or medical records (21, 22).

### Assessment of alcohol intake

On all FFQs, participants were asked how often, on average (i.e., from never to ≥6 times/d), during the previous year they had consumed beer, red wine, white wine, liquor, and other food items. We calculated the total alcohol intake in grams per day as the sum of the daily number of drinks multiplied by the average alcohol content per type of alcoholic beverage (12.8 g alcohol/355-mL serving of beer, 11.0 g alcohol/118-mL serving of wine, and 14.0 g/44-mL serving of liquor) (9). Alcohol intake measured by the FFQ was highly correlated with that calculated from detailed diet records ($r = 0.90$ for women and $r = 0.86$ for men) and with HDL concentrations ($r = 0.40$ for women and $r = 0.35$ for men) (23).

Detailed information on alcohol consumption was collected in 1984, 1986, 1990, 1994, 1998, 2002, and 2006 in the NHS; 1991, 1995, 1999, 2003, and 2007 in the NHS II; and 1986, 1990, 1994, 1998, 2002, and 2006 in the HPFS. In addition, information on alcohol consumption in an early life stage (ages 18–22 y) was asked in 1988 in the NHS and HPFS and 1989 in the NHS II.

### Assessment of covariates

In the biennial follow-up questionnaires, we inquired and updated information on anthropometric and lifestyle factors for chronic diseases including body height and weight, cigarette smoking, and physical activity. Data on the following phenotypic and sun exposure–related factors were also collected through the follow-up questionnaires (24, 25): ethnicities, family history of melanoma in first-degree relatives (parents and siblings), natural hair color, number of moles on arms (in the NHS and HPFS) or legs (in the NHS II), skin reaction to sun exposure ≥2 h as a child or adolescent, number of severe sunburns; time spent in direct sunlight per week over different ages; cumulative UV flux since baseline, and the use of sunscreen in summer months. A history of severe sunburn and the sunburn count on the body were asked in 1982 in the NHS, in 1989 in the NHS II, and in 1992 in the HPFS. We asked study participants (in the NHS in 2006, in the NHS II in 2005, and in the HPFS in 2008) the average hours per week that they spent outdoors in direct sunlight in the middle of the day (1000–1500), including during work and recreation, at each of the following periods: during summer months in high school, college, and nursing school and at ages 25–35, 36–59, and 60–65 y. Data were available for the first 2 periods only (high school, college, and nursing school and ages 25–35 y) in the NHS II, which consisted of a cohort of younger women. The average time spent in direct sunlight in the summer months was calculated as a weighted average of hours per week reported for different age periods and treated as a time-dependent variable during follow-up. The weight for each age period was determined according to the length (in number of years) of that age period, and only age periods relevant to the age of the participant were taken into account (e.g., for a participant at the age of 56 y, we calculated a weighted average on

the basis of hours per week reported for summer months in high school, college, and nursing school and at ages 25–35 and 36–59 y). The annual UV flux is a composite measure of a midrange UV radiation level on the basis of latitude, altitude, and cloud cover (24, 26, 27) and was estimated at every 2-y period over the cohort follow-up according to the state of residence that was known from mailing addresses of participants. The annual UV flux was measured in Robertson-Berger unit, and the gradient of UV flux across the continental United States has been documented elsewhere (28). A Robertson-Berger meter count of 440 may produce a typical sunburn reaction to untanned Caucasian skin. Associations of BCC risk with sunburn history and UV flux in the NHS and HPFS have been reported in our previous investigation (24). We also asked about information on tanning bed use in high school and college and at ages 25–35 y in 2005 in the NHS II (25).

### Statistical analysis

Study follow-up began when information on both exposure (alcohol intake) and the outcome disease (BCC) was available in the cohorts (in the NHS: June 1984; in the NHS II: June 1991; and in the HPFS: January 1986). Participants contributed to the follow-up time from the return month of the baseline questionnaire to the month of the first diagnosis of a cancer, the month of death, the time loss to follow-up, or the end of follow-up (in the NHS: June 2010; in the NHS II: June 2011; and in the HPFS: January 2010), whichever came first. We used Cox proportional hazards models to estimate age-adjusted and multivariable-adjusted HRs with 95% CIs of incident BCC in association with alcohol intakes. Multivariable analyses were conducted with adjustment for other known BCC risk factors and potential confounders. Missing data during any follow-up period were coded as a missing indicator category for categorical variables (e.g., smoking status) and with carried-forward values for continuous variables (e.g., BMI) (29). Trend tests across alcohol intake categories were conducted by assigning median values for these categories and treating the new variables as continuous terms in the models. Results from different study cohorts were pooled with the use of a random-effects model, and heterogeneity between study cohorts was examined with the use of the $Q$ statistic (30).

To create the best estimates of long-term alcohol intake, we calculated the cumulative averaged intake over time beginning at the baseline assessment on alcohol consumption. That is, at the beginning of every 2-y follow-up cycle, each intake was calculated as the mean of all reported intakes up to that time (31). To evaluate the latency between alcohol intake and BCC, we performed analyses with the use of varying lag times. For example, in the NHS, for a latency of 0–4 y before diagnosis (simple updated), we used alcohol intake in 1984 for follow-up from 1984 to 1986, intake in 1986 for follow-up from 1986 to 1990, intake in 1990 for follow-up from 1990 to 1994, and so forth. For a latency of 4–8 y, we used alcohol intake in 1984 for follow-up from 1988 to 1990, intake in 1986 for follow-up from 1990 to 1994, and so forth.

We fitted adjusted Cox proportional hazards models with the use of a restricted cubic spline regression analysis to examine the shapes of the dose-response relations between alcohol intake and risk of BCC (32). Observations with alcohol intakes >95% were excluded in the spline regression to avoid the influence of outliers. In addition, subgroup analyses were also performed according to adjusted variables to examine a potential effect modification by other variables. To address the concern about potential residual confounding by sun exposure, we performed an additional further subgroup analysis stratified by the total sun exposure score, which was a composite measure of sun-exposure history, duration, and intensity. This score was calculated with the use of cohort-derived HRs associated with each of the following 3 sun exposure–related factors: number of severe sunburns, average time spent in direct sunlight in summer months, and annual UV flux at residence. The score was calculated in each cohort separately to control for cohort heterogeneity in terms of sun exposure and adjusted for as quintiles in multivariable models in sensitivity analyses. The likelihood ratio test was used to examine interaction between alcohol and other variables. We used SAS software (version 9.2; SAS Institute Inc.) for all statistical analyses. All statistical tests were 2-tailed, and significance was set at $P < 0.05$.

## RESULTS

Over a total of 3.74 million person-years of follow-up, we documented a total of 28,951 BCC cases in 3 study cohorts. There were 13,666 BCC cases in the NHS (1.52 million person-years), 6013 cases in the NHS II (1.48 million person-years), and 9272 cases in the HFPS (0.74 million person-years). The median follow-up time was 25, 19, and 20 y in the 3 cohorts, respectively. **Table 1** shows the characteristics of study participants by total alcohol intake categories. Compared with nondrinkers, participants with high alcohol intake were more likely to exercise and smoke, more likely to have a red or blonde hair color, less likely to have moles on the arms and legs and a painful burn or blister skin reaction under sun exposure as a child and adolescent, and more likely to use sunscreen and have a higher number of severe sunburns. Heavy drinkers with alcohol intake ≥30 g/d were more likely to drink beer or liquor than red or white wine.

Increased alcohol intake was significantly associated with increased BCC risk in all 3 study cohorts, although risk estimates appeared to be slightly higher in women than in men (all $P$-trend $< 0.0001$, $P$-heterogeneity by study = 0.10) (**Table 2**). Risk estimates were higher for cumulative averaged intake than were those for simple updated (0–4-y lag) intake. Results of the spline regression suggested that the dose-response relations between alcohol intake and BCC risk were primarily linear over the major intakes in both women and men (**Supplemental Figure 1**). Analyses that used alcohol intakes over other latency periods (4–8, 8–12, and 12–16 y) suggested generally similar associations between alcohol and BCC risk, although the linear trend over intake categories was most apparent when alcohol intake of a 12–16-y latency was used as the exposure (**Table 3**). An additional analysis that used alcohol intake at baseline as the exposure revealed a similar association pattern with the main analyses (data not shown). Sensitivity analyses adjusted for tanning bed use (in the NHS II) and total sun exposure score (in quintiles) instead of 3 sun-exposure variables (number of severe sunburns, average time spent in direct sunlight in summer months, and annual UV flux at residence) also yielded essentially the same results (data not shown).

Stratified analyses by sun exposure–related factors (i.e., history of severe sunburns, annual UV flux at residence, average time spent in direct sunlight in summer months, and use of

**TABLE 1**
Baseline characteristics of study participants according to alcohol intake in the NHS, NHS II, and HPFS[1]

| | Total alcohol consumption, g/d | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | NHS (1984) | | | NHS II (1991) | | | HPFS (1986) | | |
| | None | 10.0–19.9 | ≥30.0 | None | 10.0–19.9 | ≥30.0 | None | 10.0–19.9 | ≥30.0 |
| Participants, *n* | 23,791 | 10,583 | 4177 | 39,685 | 6026 | 974 | 10,416 | 8606 | 5214 |
| Age, y | 50.6 ± 7.3[2] | 50.5 ± 7.0 | 51.5 ± 6.7 | 36.2 ± 4.6 | 36.5 ± 4.7 | 37.6 ± 4.3 | 53.8 ± 9.8 | 53.4 ± 9.4 | 54.7 ± 9.4 |
| BMI, kg/m$^2$ | 26.0 ± 5.4 | 23.9 ± 3.8 | 24.0 ± 3.9 | 25.5 ± 5.9 | 23.3 ± 4.0 | 23.8 ± 4.5 | 25.1 ± 5.2 | 24.9 ± 5.0 | 25.0 ± 5.0 |
| Physical activity, metabolic equivalents, h/wk | 12.1 ± 19.1 | 15.8 ± 22.4 | 14.2 ± 19.9 | 18.4 ± 25.3 | 25.1 ± 30.2 | 23.6 ± 32.0 | 18.6 ± 27.0 | 23.1 ± 31.9 | 21.0 ± 29.5 |
| Current smoking, % | 19.1 | 29.8 | 46.8 | 9.2 | 20.2 | 37.9 | 7.0 | 9.7 | 20.3 |
| Caffeine intake, mg/d | 287 ± 242 | 357 ± 225 | 368 ± 227 | 195 ± 207 | 315 ± 214 | 371 ± 234 | 190 ± 227 | 246 ± 224 | 304 ± 244 |
| Family history of melanoma, % | 7.8 | 7.7 | 7.6 | 12.1 | 13.2 | 12.8 | 3.7 | 4.1 | 3.8 |
| Red/blonde hair, % | 14.3 | 16.3 | 16.4 | 18.5 | 22.2 | 22.8 | 12.5 | 13.5 | 14.7 |
| Arm with moles, % | 36.4 | 35.6 | 33.9 | 50.6 | 51.0 | 48.8 | 31.4 | 31.6 | 29.6 |
| Painful burn/blisters skin reaction as a child/adolescent, % | 15.8 | 13.2 | 13.2 | 25.3 | 19.9 | 23.1 | 25.3 | 21.9 | 21.4 |
| Severe sunburns, *n* | 7.9 ± 6.8 | 9.0 ± 7.1 | 9.2 ± 7.2 | 1.8 ± 2.2 | 2.0 ± 2.4 | 2.2 ± 2.6 | 12.3 ± 11.9 | 12.9 ± 12.2 | 13.6 ± 12.7 |
| Annual UV flux, $\times 10^{-4}$ RB count | 122.6 ± 24.9 | 122.1 ± 24.5 | 124.4 ± 25.9 | 125.6 ± 24.5 | 127.1 ± 25.6 | 130.3 ± 26.3 | 132.2 ± 27.1 | 128.7 ± 27.0 | 131.3 ± 28.1 |
| Time spent in direct sunlight in summer months, h/wk | 5.2 ± 3.0 | 5.6 ± 2.9 | 5.7 ± 3.0 | 4.3 ± 1.7 | 4.7 ± 1.5 | 4.7 ± 1.5 | 10.1 ± 6.1 | 10.5 ± 5.9 | 10.6 ± 6.2 |
| Use of sunscreen in summer months, % | 20.0 | 27.3 | 25.1 | 77.7 | 86.5 | 81.0 | 50.4 | 62.8 | 57.0 |
| Alcoholic beverage preference,[3] drinks/wk | | | | | | | | | |
| Beer | 0.0 ± 0.0 | 1.1 ± 2.0 | 5.2 ± 8.9 | 0.0 ± 0.0 | 3.3 ± 2.7 | 11.4 ± 10.8 | 0.0 ± 0.0 | 2.5 ± 2.3 | 8.8 ± 9.9 |
| Red wine | 0.0 ± 0.0 | 1.1 ± 1.8 | 2.0 ± 4.9 | 0.0 ± 0.0 | 0.9 ± 1.5 | 1.9 ± 4.7 | 0.0 ± 0.0 | 1.0 ± 1.5 | 2.0 ± 4.6 |
| White wine | 0.0 ± 0.0 | 2.6 ± 2.5 | 4.8 ± 7.8 | 0.0 ± 0.0 | 2.1 ± 2.3 | 4.8 ± 7.7 | 0.0 ± 0.0 | 1.6 ± 1.9 | 2.8 ± 5.5 |
| Liquor | 0.0 ± 0.0 | 2.7 ± 2.7 | 11.3 ± 9.3 | 0.0 ± 0.0 | 1.3 ± 1.9 | 5.3 ± 8.2 | 0.0 ± 0.0 | 2.6 ± 2.4 | 10.8 ± 9.8 |

[1]Values were standardized (except for the age variable) to the age distribution of the study population. HPFS, Health Professionals Follow-Up Study; NHS, Nurses' Health Study; RB, Robertson-Berger.
[2]Mean ± SD (all such values).
[3]Serving sizes of one drink were as follows: beer, 355 mL; wine, 118 mL; and liquor, 44 mL.

sunscreen in summer months) showed generally consistent associations over different subgroups of the study population. Although there were borderline significant interactions between alcohol intake and annual UV flux at residence and use of sunscreen in women ($P$-interaction $< 0.10$), there were no appreciable differences in risk estimates over different categories of sun exposure–related factors (**Supplemental Table 1**). An additional subgroup analysis that was stratified by the median of the total sun exposure score also suggested essentially similar associations over subgroups with low and high exposure scores, and additional interaction tests for alcohol intake and total sun exposure score divided by medians or categorized into tertiles did not reveal any appreciable interaction (all $P$-interaction $> 0.40$). The association between alcohol intake and BCC risk appeared to be stronger in never smokers in both women and men ($P$-interaction $< 0.0001$ in women and $P$-interaction $= 0.16$ in men) (Supplemental Table 1). Nevertheless, the association between alcohol intake and BCC risk was significant in both never smokers and ever smokers.

Of the individual alcoholic beverages, white wine showed the most-consistent association with increased BCC risk, followed by liquor (both $P$-trend $< 0.0001$) (**Table 4**). Beer and red wine were generally not associated with BCC risk.

Alcohol intake between ages 18 and 22 y was also significantly associated with BCC risk in all 3 cohorts (**Supplemental Table 2**). After additional adjustment for cumulative averaged alcohol intake in adulthood in the model, this association persisted in women but not in men. Nevertheless, the pooled analysis still supported a modest association between alcohol intake during ages 18–22 y and BCC risk ($P$-trend $= 0.0007$).

## DISCUSSION

In the current study, we provided a comprehensive evaluation on the association between alcohol consumption and risk of cutaneous BCC on the basis of data from 3 large prospective cohorts of women and men. We showed that alcohol consumption was associated with increased risk of BCC in both women and men, and the association was generally consistent over the 3 cohorts. Additional analyses suggested that the association was consistent over different latency periods of alcohol intake and over subgroups divided by sun exposure–related factors. White

**TABLE 2**
HRs of incident basal cell carcinoma according to alcohol intake in the NHS (1984–2010), NHS II (1991–2011), and HPFS (1986–2010)[1]

| | Simple updated (0–4-y lag) | | | | Cumulative average | | | |
|---|---|---|---|---|---|---|---|---|
| Alcohol intake | Cases, *n* | Person-years, thousands | Age-adjusted HR (95% CI) | Multivariable-adjusted HR (95% CI) | Cases, *n* | Person-years, thousands | Age-adjusted HR (95% CI) | Multivariable-adjusted HR (95% CI) |
| NHS | | | | | | | | |
| None | 4995 | 607 | 1.00 | 1.00 | 2818 | 383 | 1.00 | 1.00 |
| 0.1–9.9 g/d | 5535 | 621 | 1.19 (1.15, 1.24) | 1.13 (1.09, 1.18) | 7573 | 831 | 1.23 (1.18, 1.28) | 1.16 (1.11, 1.21) |
| 10.0–19.9 | 2002 | 183 | 1.38 (1.31, 1.45) | 1.26 (1.19, 1.33) | 1983 | 183 | 1.46 (1.38, 1.55) | 1.31 (1.23, 1.39) |
| 20.0–29.9 g/d | 449 | 41 | 1.42 (1.29, 1.56) | 1.27 (1.15, 1.40) | 720 | 63 | 1.50 (1.38, 1.62) | 1.32 (1.22, 1.44) |
| ≥30.0 g/d | 685 | 65 | 1.32 (1.22, 1.43) | 1.22 (1.12, 1.32) | 572 | 56 | 1.39 (1.27, 1.52) | 1.27 (1.16, 1.39) |
| *P*-trend | — | — | <0.0001 | <0.0001 | — | — | <0.0001 | <0.0001 |
| NHS II | | | | | | | | |
| None | 1948 | 596 | 1.00 | 1.00 | 1373 | 473 | 1.00 | 1.00 |
| 0.1–9.9 g/d | 2895 | 697 | 1.24 (1.17, 1.31) | 1.15 (1.08, 1.22) | 3826 | 864 | 1.27 (1.19, 1.35) | 1.17 (1.10, 1.25) |
| 10.0–19.9 g/d | 829 | 137 | 1.47 (1.35, 1.59) | 1.28 (1.17, 1.39) | 592 | 108 | 1.48 (1.34, 1.63) | 1.27 (1.14, 1.40) |
| 20.0–29.9 g/d | 145 | 26 | 1.34 (1.13, 1.58) | 1.14 (0.96, 1.35) | 148 | 25 | 1.49 (1.26, 1.77) | 1.28 (1.08, 1.52) |
| ≥30.0 g/d | 196 | 28 | 1.47 (1.27, 1.70) | 1.29 (1.11, 1.50) | 74 | 14 | 1.42 (1.12, 1.79) | 1.24 (0.98, 1.57) |
| *P*-trend | — | — | <0.0001 | <0.0001 | — | — | <0.0001 | <0.0001 |
| HPFS | | | | | | | | |
| None | 2139 | 182 | 1.00 | 1.00 | 1501 | 139 | 1.00 | 1.00 |
| 0.1–9.9 g/d | 3302 | 280 | 1.05 (1.00, 1.11) | 1.02 (0.96, 1.07) | 3956 | 326 | 1.12 (1.06, 1.19) | 1.06 (0.99, 1.12) |
| 10.0–19.9 g/d | 2041 | 148 | 1.18 (1.11, 1.26) | 1.09 (1.03, 1.16) | 1980 | 144 | 1.26 (1.17, 1.34) | 1.15 (1.07, 1.23) |
| 20.0–29.9 g/d | 656 | 46 | 1.22 (1.12, 1.33) | 1.11 (1.02, 1.22) | 824 | 54 | 1.33 (1.22, 1.45) | 1.22 (1.11, 1.33) |
| ≥30.0 g/d | 1134 | 80 | 1.20 (1.12, 1.29) | 1.15 (1.07, 1.24) | 1011 | 73 | 1.23 (1.13, 1.33) | 1.18 (1.08, 1.28) |
| *P*-trend | — | — | <0.0001 | <0.0001 | — | — | <0.0001 | <0.0001 |
| Meta-analysis, women in the NHS and NHS II | | | | | | | | |
| None | 6943 | 1203 | 1.00 | 1.00 | 4191 | 856 | 1.00 | 1.00 |
| 0.1–9.9 g/d | 8430 | 1318 | 1.21 (1.17, 1.25) | 1.14 (1.10, 1.18) | 11,399 | 1695 | 1.24 (1.20, 1.28) | 1.16 (1.12, 1.21) |
| 10.0–19.9 g/d | 2831 | 320 | 1.41 (1.33, 1.50) | 1.26 (1.21, 1.32) | 2575 | 291 | 1.47 (1.39, 1.54) | 1.30 (1.23, 1.37) |
| 20.0–29.9 g/d | 594 | 67 | 1.40 (1.29, 1.52) | 1.23 (1.12, 1.35) | 868 | 88 | 1.49 (1.39, 1.61) | 1.32 (1.22, 1.42) |
| ≥30.0 g/d | 881 | 93 | 1.37 (1.24, 1.51) | 1.23 (1.15, 1.33) | 646 | 70 | 1.39 (1.28, 1.51) | 1.27 (1.16, 1.38) |
| *P*-trend | — | — | <0.0001 | <0.0001 | — | — | <0.0001 | <0.0001 |
| Meta-analysis, women and men in the NHS, NHS II, and HPFS | | | | | | | | |
| None | 9082 | 1385 | 1.00 | 1.00 | 5692 | 995 | 1.00 | 1.00 |
| 0.1–9.9 g/d | 11,732 | 1598 | 1.16 (1.06, 1.26) | 1.10 (1.02, 1.18) | 15,355 | 2021 | 1.20 (1.13, 1.29) | 1.13 (1.06, 1.20) |
| 10.0–19.9 g/d | 4872 | 468 | 1.34 (1.18, 1.51) | 1.20 (1.09, 1.33) | 4555 | 435 | 1.39 (1.25, 1.55) | 1.24 (1.14, 1.35) |
| 20.0–29.9 g/d | 1250 | 113 | 1.32 (1.19, 1.46) | 1.17 (1.07, 1.29) | 1692 | 142 | 1.43 (1.31, 1.55) | 1.27 (1.20, 1.35) |
| ≥30.0 g/d | 2015 | 173 | 1.31 (1.18, 1.44) | 1.19 (1.13, 1.26) | 1657 | 143 | 1.32 (1.19, 1.45) | 1.22 (1.15, 1.30) |
| *P*-trend | — | — | <0.0001 | <0.0001 | — | — | <0.0001 | <0.0001 |
| Per 10-g/d increase | — | — | 1.09 (1.04, 1.15) | 1.06 (1.03, 1.08) | — | — | 1.11 (1.04, 1.17) | 1.06 (1.03, 1.10) |

[1]Multivariable analyses in Cox proportional hazards models were adjusted for age, BMI (in kg/m$^2$; <18.5, 18.5–24.9, 25.0–29.9, 30.0–34.9, or ≥35.0), smoking status (never, past, or current with 1–14, 15–24, or ≥25 cigarettes/d), physical activity (quintiles), caffeine intake (quintiles), ethnicities (Southern European, Scandinavian, other Caucasian, nonwhite, or other ancestry), family history of melanoma (yes or no), natural hair color (red, blonde, light brown, dark brown, or black), number of moles on arms or legs (none, 1–2, 3–5, 6–9, or ≥10), skin reaction to sun exposure as a child/adolescent (none/some redness, burn, or painful burn/blisters), number of severe sunburns (none, 1–2, 3–4, 5–9, or ≥10), cumulative UV flux since baseline (quintiles), average time spent in direct sunlight in summer months (<2, 2–5, or ≥6 h/wk), and use of sunscreen in summer months (yes or no). Results in different cohorts were pooled with the use of a random-effects model. HPFS, Health Professionals Follow-Up Study; NHS, Nurses' Health Study.

wine and liquor may be the 2 individual alcoholic beverages that contributed to increased BCC risk. In addition, alcohol consumption in early adulthood (ages 18–22 y) was also associated with increased BCC risk particularly in women.

Several biological mechanisms have been proposed for increased risk of skin cancer associated with alcohol. Acetaldehyde is a major metabolite of ethanol and is known to have direct mutagenic and carcinogenic effects (33). As a highly reactive chemical, acetaldehyde serves as a photosensitizer and generates reactive oxygen species and related intermediates on exposure to UV radiation. Reactive oxygen species generated by this process further induce oxidative DNA damage, enhance the binding of acetaldehyde to DNA (genetic effect), and activate signal-transduction cascades and prostaglandin synthesis (an epigenetic effect), thereby leading to skin carcinogenicity (14). Alcohol also has immunosuppressive effects that may alleviate the immune surveillance on mutated cells and, thus, increase the propensity to develop cancer (34). In combination with UV radiation, alcohol can also induce skin tumors with a broader mutational spectrum in a critical tumor-suppressor gene (i.e., *p53*) in mice (35).

**TABLE 3**
HRs of incident basal cell carcinoma according to alcohol intake of different lags in the NHS (1984–2010), NHS II (1991–2011), and HPFS (1986–2010)[1]

| | 4–8-y lag | | | 8–12-y lag | | | 12–16 y-lag | | |
|---|---|---|---|---|---|---|---|---|---|
| Alcohol intake | Cases, *n* | Person-years, thousands | Multivariable-adjusted HR (95% CI) | Cases, *n* | Person-years, thousands | Multivariable-adjusted HR (95% CI) | Cases, *n* | Person-years, thousands | Multivariable-adjusted HR (95% CI) |
| NHS | | | | | | | | | |
| None | 4048 | 477 | 1.00 | 3221 | 361 | 1.00 | 2430 | 257 | 1.00 |
| 0.1–9.9 g/d | 4968 | 514 | 1.16 (1.11, 1.21) | 4279 | 409 | 1.17 (1.11, 1.22) | 3470 | 303 | 1.19 (1.12, 1.25) |
| 10.0–19.9 g/d | 1653 | 145 | 1.26 (1.19, 1.34) | 1319 | 111 | 1.24 (1.16, 1.33) | 1034 | 82 | 1.24 (1.15, 1.34) |
| 20.0–29.9 g/d | 379 | 34 | 1.23 (1.10, 1.37) | 342 | 27 | 1.30 (1.16, 1.46) | 258 | 20 | 1.24 (1.09, 1.41) |
| ≥30.0 g/d | 584 | 51 | 1.29 (1.18, 1.41) | 455 | 38 | 1.28 (1.15, 1.41) | 392 | 28 | 1.38 (1.24, 1.54) |
| *P*-trend | — | — | <0.0001 | — | — | <0.0001 | — | — | <0.0001 |
| NHS II | | | | | | | | | |
| None | 1855 | 457 | 1.00 | 1600 | 328 | 1.00 | 1373 | 204 | 1.00 |
| 0.1–9.9 g/d | 2711 | 528 | 1.16 (1.09, 1.23) | 2427 | 374 | 1.23 (1.15, 1.31) | 1962 | 231 | 1.18 (1.10, 1.27) |
| 10.0–19.9 g/d | 617 | 93 | 1.24 (1.12, 1.36) | 453 | 59 | 1.29 (1.16, 1.44) | 324 | 33 | 1.25 (1.11, 1.42) |
| 20.0–29.9 g/d | 116 | 18 | 1.18 (0.97, 1.42) | 75 | 11 | 1.09 (0.87, 1.38) | 61 | 6 | 1.29 (0.99, 1.67) |
| ≥30.0 g/d | 130 | 17 | 1.31 (1.10, 1.58) | 72 | 10 | 1.24 (0.97, 1.57) | 46 | 5 | 1.08 (0.80, 1.45) |
| *P*-trend | — | — | <0.0001 | — | — | 0.0001 | — | — | 0.0008 |
| HPFS | | | | | | | | | |
| None | 1724 | 142 | 1.00 | 1306 | 104 | 1.00 | 947 | 71 | 1.00 |
| 0.1–9.9 g/d | 2859 | 223 | 1.05 (0.98, 1.11) | 2368 | 168 | 1.11 (1.03, 1.19) | 1716 | 115 | 1.09 (1.00, 1.18) |
| 10.0–19.9 g/d | 1683 | 115 | 1.12 (1.04, 1.20) | 1283 | 84 | 1.13 (1.04, 1.22) | 887 | 55 | 1.09 (0.99, 1.20) |
| 20.0–29.9 g/d | 527 | 35 | 1.14 (1.03, 1.26) | 394 | 25 | 1.18 (1.05, 1.32) | 282 | 16 | 1.17 (1.02, 1.34) |
| ≥30.0 g/d | 895 | 61 | 1.15 (1.06, 1.25) | 644 | 43 | 1.12 (1.01, 1.23) | 499 | 29 | 1.18 (1.06, 1.32) |
| *P*-trend | — | — | <0.0001 | — | — | 0.02 | — | — | 0.004 |
| Meta-analysis, women in the NHS and NHS II | | | | | | | | | |
| None | 5903 | 934 | 1.00 | 4821 | 689 | 1.00 | 3803 | 461 | 1.00 |
| 0.1–9.9 g/d | 7679 | 1042 | 1.16 (1.12, 1.20) | 6706 | 783 | 1.19 (1.13, 1.25) | 5432 | 534 | 1.18 (1.13, 1.24) |
| 10.0–19.9 g/d | 2270 | 238 | 1.25 (1.19, 1.32) | 1772 | 170 | 1.26 (1.19, 1.33) | 1358 | 115 | 1.24 (1.17, 1.33) |
| 20.0–29.9 g/d | 495 | 52 | 1.22 (1.11, 1.33) | 417 | 38 | 1.23 (1.05, 1.44) | 319 | 26 | 1.25 (1.11, 1.41) |
| ≥30.0 g/d | 714 | 68 | 1.30 (1.20, 1.41) | 527 | 48 | 1.27 (1.16, 1.39) | 438 | 33 | 1.27 (1.01, 1.60) |
| *P*-trend | — | — | <0.0001 | — | — | <0.0001 | — | — | <0.0001 |
| Meta-analysis, women and men in the NHS, NHS II, and HPFS | | | | | | | | | |
| None | 7627 | 1076 | 1.00 | 6127 | 793 | 1.00 | 4750 | 532 | 1.00 |
| 0.1–9.9 g/d | 10,538 | 1265 | 1.12 (1.05, 1.20) | 9074 | 951 | 1.17 (1.11, 1.23) | 7148 | 649 | 1.16 (1.10, 1.22) |
| 10.0–19.9 g/d | 3953 | 353 | 1.20 (1.11, 1.30) | 3055 | 254 | 1.21 (1.13, 1.31) | 2245 | 170 | 1.19 (1.09, 1.30) |
| 20.0–29.9 g/d | 1022 | 87 | 1.18 (1.10, 1.26) | 811 | 63 | 1.22 (1.12, 1.33) | 601 | 42 | 1.22 (1.11, 1.33) |
| ≥30.0 g/d | 1609 | 129 | 1.23 (1.13, 1.35) | 1171 | 91 | 1.20 (1.09, 1.32) | 937 | 62 | 1.25 (1.09, 1.43) |
| *P*-trend | — | — | <0.0001 | — | — | 0.001 | — | — | <0.0001 |
| Per 10-g/d increase | — | — | 1.06 (1.02, 1.10) | — | — | 1.06 (1.01, 1.10) | — | — | 1.06 (1.03, 1.10) |

[1]Multivariable analyses in Cox proportional hazards models were adjusted for age, BMI (in kg/m$^2$; <18.5, 18.5–24.9, 25.0–29.9, 30.0–34.9, or ≥35.0), smoking status (never, past, or current with 1–14, 15–24, or ≥25 cigarettes/d), physical activity (quintiles), caffeine intake (quintiles), ethnicities (Southern European, Scandinavian, other Caucasian, nonwhite, or other ancestry), family history of melanoma (yes or no), natural hair color (red, blonde, light brown, dark brown, or black), number of moles on arms or legs (none, 1–2, 3–5, 6–9, or ≥10), skin reaction to sun exposure as a child/adolescent (none/some redness, burn, or painful burn/blisters), number of severe sunburns (none, 1–2, 3–4, 5–9, or ≥10), cumulative UV flux since baseline (quintiles), average time spent in direct sunlight in summer months (<2, 2–5, or ≥6 h/wk), and use of sunscreen in summer months (yes or no). Results in different cohorts were pooled with the use of a random-effects model. HPFS, Health Professionals Follow-Up Study; NHS, Nurses' Health Study.

**TABLE 4**
HRs of incident basal cell carcinoma according to cumulative averaged alcoholic beverage intake in the NHS (1984–2010), NHS II (1991–2011), and HPFS (1986–2010)[1]

| | Beer | | | Red wine | | | White wine | | | Liquor | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Alcohol intake | Cases, *n* | Person-years, thousands | Multivariable-adjusted HR (95% CI) | Cases, *n* | Person-years, thousands | Multivariable-adjusted HR (95% CI) | Cases, *n* | Person-years, thousands | Multivariable-adjusted HR (95% CI) | Cases, *n* | Person-years, thousands | Multivariable-adjusted HR (95% CI) |
| NHS | | | | | | | | | | | | |
| None | 9246 | 1057 | 1.00 | 6797 | 812 | 1.00 | 4292 | 574 | 1.00 | 6393 | 793 | 1.00 |
| <2.5 g/d | 3362 | 340 | 0.98 (0.94, 1.02) | 5671 | 589 | 0.97 (0.93, 1.01) | 6282 | 667 | 1.13 (1.08, 1.19) | 4330 | 456 | 1.08 (1.03, 1.13) |
| 2.5–4.9 g/d | 465 | 46 | 0.95 (0.87, 1.05) | 757 | 72 | 0.99 (0.91, 1.07) | 1548 | 144 | 1.25 (1.17, 1.34) | 798 | 76 | 1.10 (1.02, 1.19) |
| 5.0–9.9 g/d | 351 | 41 | 0.93 (0.84, 1.04) | 285 | 28 | 0.92 (0.81, 1.04) | 863 | 75 | 1.23 (1.13, 1.33) | 935 | 84 | 1.20 (1.12, 1.29) |
| ≥10.0 g/d | 242 | 33 | 0.84 (0.74, 0.96) | 156 | 16 | 1.00 (0.85, 1.18) | 681 | 57 | 1.35 (1.24, 1.37) | 1210 | 108 | 1.20 (1.12, 1.28) |
| *P*-trend | — | — | 0.001 | — | — | 0.74 | — | — | <0.0001 | — | — | <0.0001 |
| NHS II | | | | | | | | | | | | |
| None | 3100 | 867 | 1.00 | 4054 | 1078 | 1.00 | 2233 | 713 | 1.00 | 3519 | 1010 | 1.00 |
| <2.5 g/d | 1992 | 414 | 1.06 (0.99, 1.12) | 1601 | 339 | 0.99 (0.93, 1.06) | 2921 | 624 | 1.09 (1.02, 1.16) | 2063 | 398 | 1.10 (1.04, 1.17) |
| 2.5–4.9 g/d | 475 | 92 | 1.10 (0.99, 1.21) | 240 | 47 | 0.91 (0.80, 1.05) | 514 | 93 | 1.20 (1.08, 1.34) | 252 | 34 | 1.43 (1.25, 1.64) |
| 5.0–9.9 g/d | 288 | 72 | 1.00 (0.88, 1.14) | 92 | 16 | 0.96 (0.77, 1.18) | 217 | 34 | 1.15 (0.99, 1.34) | 109 | 26 | 1.01 (0.83, 1.22) |
| ≥10.0 g/d | 158 | 39 | 1.13 (0.96, 1.33) | 26 | 5 | 0.88 (0.59, 1.29) | 128 | 21 | 1.18 (0.98, 1.42) | 70 | 15 | 1.07 (0.84, 1.36) |
| *P*-trend | — | — | 0.29 | — | — | 0.44 | — | — | 0.009 | — | — | 0.17 |
| HPFS | | | | | | | | | | | | |
| None | 3058 | 262 | 1.00 | 3939 | 337 | 1.00 | 2982 | 262 | 1.00 | 3449 | 310 | 1.00 |
| <2.5 g/d | 3290 | 251 | 1.03 (0.97, 1.09) | 3904 | 300 | 0.97 (0.92, 1.03) | 4512 | 347 | 1.02 (0.96, 1.08) | 2708 | 215 | 1.06 (1.01, 1.13) |
| 2.5–4.9 g/d | 971 | 64 | 1.07 (0.99, 1.16) | 862 | 61 | 0.98 (0.90, 1.07) | 1078 | 80 | 1.03 (0.94, 1.11) | 667 | 46 | 1.05 (0.96, 1.14) |
| 5.0–9.9 g/d | 1091 | 86 | 1.07 (0.98, 1.16) | 374 | 24 | 1.01 (0.90, 1.13) | 433 | 29 | 1.07 (0.95, 1.19) | 1037 | 73 | 1.15 (1.06, 1.24) |
| ≥10.0 g/d | 862 | 73 | 1.06 (0.97, 1.15) | 193 | 14 | 1.00 (0.86, 1.17) | 267 | 18 | 1.10 (0.96, 1.25) | 1411 | 93 | 1.15 (1.07, 1.23) |
| *P*-trend | — | — | 0.38 | — | — | 0.94 | — | — | 0.08 | — | — | 0.002 |
| Meta-analysis, women in the NHS and NHS II | | | | | | | | | | | | |
| None | 12,346 | 1924 | 1.00 | 10,851 | 1890 | 1.00 | 6525 | 1287 | 1.00 | 9912 | 1803 | 1.00 |
| <2.5 g/d | 5354 | 754 | 1.01 (0.94, 1.09) | 7272 | 928 | 0.97 (0.94, 1.01) | 9203 | 1291 | 1.12 (1.07, 1.16) | 6393 | 854 | 1.09 (1.05, 1.13) |
| 2.5–4.9 g/d | 940 | 138 | 1.02 (0.89, 1.17) | 997 | 119 | 0.97 (0.90, 1.04) | 2062 | 237 | 1.24 (1.17, 1.31) | 1050 | 110 | 1.25 (0.96, 1.61) |
| 5.0–9.9 g/d | 639 | 113 | 0.96 (0.89, 1.04) | 377 | 44 | 0.93 (0.83, 1.03) | 1080 | 109 | 1.21 (1.12, 1.30) | 1044 | 110 | 1.13 (0.95, 1.34) |
| ≥10.0 g/d | 400 | 72 | 0.97 (0.73, 1.29) | 182 | 21 | 0.98 (0.85, 1.14) | 809 | 78 | 1.30 (1.15, 1.46) | 1280 | 123 | 1.19 (1.12, 1.27) |
| *P*-trend | — | — | 0.67 | — | — | 0.51 | — | — | <0.0001 | — | — | <0.0001 |
| Meta-analysis, women and men in the NHS, NHS II, and HPFS | | | | | | | | | | | | |
| None | 15,404 | 2186 | 1.00 | 14,790 | 2227 | 1.00 | 9507 | 1549 | 1.00 | 13361 | 2113 | 1.00 |
| <2.5 g/d | 8644 | 1005 | 1.01 (0.97, 1.06) | 11176 | 1228 | 0.97 (0.94, 1.00) | 13,715 | 1638 | 1.08 (1.01, 1.15) | 9101 | 1069 | 1.08 (1.05, 1.11) |
| 2.5–4.9 | 1911 | 202 | 1.04 (0.96, 1.13) | 1859 | 180 | 0.97 (0.92, 1.03) | 3140 | 317 | 1.16 (1.02, 1.31) | 1717 | 156 | 1.17 (1.00, 1.37) |
| 5.0–9.9 g/d | 1730 | 199 | 1.01 (0.92, 1.10) | 751 | 68 | 0.96 (0.89, 1.04) | 1513 | 138 | 1.15 (1.05, 1.26) | 2081 | 183 | 1.16 (1.08, 1.24) |
| ≥10.0 g/d | 1262 | 145 | 1.00 (0.85, 1.17) | 375 | 35 | 0.99 (0.89, 1.10) | 1076 | 96 | 1.22 (1.06, 1.40) | 2691 | 216 | 1.17 (1.12, 1.23) |
| *P*-trend | — | — | 0.71 | — | — | 0.67 | — | — | <0.0001 | — | — | <0.0001 |
| Per 10- g/d increase | — | — | 0.99 (0.92, 1.06) | — | — | 0.99 (0.94, 1.04) | — | — | 1.10 (1.06, 1.15) | — | — | 1.05 (1.03, 1.07) |

[1]Multivariable analyses in Cox proportional hazards models were adjusted for age, BMI (in kg/m$^2$; <18.5, 18.5–24.9, 25.0–29.9, 30.0–34.9, or ≥35.0), smoking status (never, past, or current with 1–14, 15–24, or ≥25 cigarettes/d), physical activity (quintiles), caffeine intake (quintiles), ethnicities (Southern European, Scandinavian, other Caucasian, nonwhite, or other ancestry), family history of melanoma (yes or no), natural hair color (red, blonde, light brown, dark brown, or black), number of moles on arms or legs (none, 1–2, 3–5, 6–9, or ≥10), skin reaction to sun exposure as a child/adolescent (none/some redness, burn, or painful burn/blisters), number of severe sunburns (none, 1–2, 3–4, 5–9, or ≥10), cumulative UV flux since baseline (quintiles), average time spent in direct sunlight in summer months (<2, 2–5, or ≥6 h/wk), use of sunscreen in summer months (yes or no), and the other alcoholic beverages listed in the table (e.g., analyses for consumption of beer were adjusted for consumption of red wine, white wine and liquor, and vice versa). Results in different cohorts were pooled with the use of a random-effects model. HPFS, Health Professionals Follow-Up Study; NHS, Nurses' Health Study.

In support of alcohol's photosensitizing effect, an early survey reported that individuals who consumed alcohol at the beach had more-severe sunburns than did nondrinkers (13), and an additional large population-based survey with 300,000 participants also showed that excessive drinking was associated with higher rates of sunburn (36). A history of sunburn is a strong predictor of skin cancer and has been associated with increased risk of BCC (24). Several epidemiologic studies have also investigated the association between alcohol and BCC risk (7, 15–19), of which 4 studies showed no association (16–19). However, most of these studies were case-control studies and did not account for several important skin cancer risk factors including UV exposure and pigmentation traits (e.g., number of nevi and moles, hair color, and skin sensitivity to prolonged sun exposure). Numbers of BCC cases included in these studies were also relatively small and, thus, may have deterred from their ability to detect a modest association.

Two early population-based investigations reported a nonlinear association between alcohol and BCC risk (7, 15), including one study that used the NHS and HPFS data that was published more than a decade ago (15). With a much longer follow-up (24–26 y) and many more BCC cases in the NHS and HPFS cohorts and the addition of the third cohort the NHS II, we accumulated a sufficiently large sample for a comprehensive evaluation of the association between alcohol and BCC risk. In the current study, we were also able to control for UV exposure in a finer manner than was done in the previous study by adjusting for sun-exposure variables more extensively (e.g., annual UV flux at residence and average time spent in direct sunlight). The nonmonotonic association between alcohol and BCC risk has also been reported in another cohort study (United States Radiological Technologists) (7). However, the study was not able to examine the association of BCC with specific alcoholic beverages.

Our findings of BCC risk with different alcoholic beverages are somewhat consistent with results of a recent Danish study with 2409 BCC cases (6). The Danish study did not find a significant association between total alcohol intake and BCC risk but identified increased BCC risk associated with intakes of wine and spirits (liquor) and decreased risk with intake of beer. However, the study was not able to differentiate between red wine and white wine, which were shown to be differently associated with BCC risk in the current study. The different associations for specific beverages may be explained by potential combined effects of ethanol and other chemicals contained in the alcoholic beverages. Wine contains phenolic compounds, many of which have antioxidant activities (37). Compared with white wine, red wine contains higher amounts of phenolic compounds and can increase the serum antioxidant capacity more apparently after ingestion (38). In recent years, in vitro and in vivo experiments have provided a growing body of evidence for the anticarcinogenic effects of phenolic compounds (39). Therefore, the different associations of BCC risk with red and white wines may be explained by the different amounts of phenolic compounds contained in the wines. Liquor (spirits) has the highest alcohol by volume because of distillation and lower amounts of phenolic compounds than in wines (40) and, thus, may also possess the ability to elicit cutaneous carcinogenic effects. A previous in vivo study showed that nonalcoholic extracts of beer have inhibitory effects on heterocyclic amine–induced DNA adduct formation in mice and, thus, are protective against genotoxic effects of heterocyclic amines associated with tumorigenesis (41). Whether the nonalcoholic extracts of beer also have inhibitory effects against skin tumorigenesis is unknown. However, if these effects are confirmed in future studies, they may help explain the null association of beer and BCC risk.

The strengths of our study included its prospective design, large sample size, long-term follow-up over 20–26 y, repeated assessments of dietary and lifestyle factors, the ability to differentiate between major alcoholic beverages, and the ability to control for a number of skin cancer risk factors and potential confounders on the basis of detailed cohort follow-up information. Our study also had several limitations. First, the studied cohorts comprised well-educated health professionals and, therefore, were not a representative sample of the US population. However, the restriction of the sample to health professionals also reduced potential residual confounding from socioeconomic status, which has been implicated in the assessment of health risk associated with alcohol consumption (42). Second, the outcome disease of BCC was accessed on the basis of self-reports. Nevertheless, our study participants were well-educated health professionals who were more likely to have a better understanding of BCC than other populations do, and previous pilot studies also showed a high validity of self- reported BCC in subgroups of the cohort participants (21, 22). Therefore, a misclassification in BCC would be expected to be minimal and would not have biased any association materially. In addition, almost all of our findings were consistent over different study cohorts, and therefore, the validity of the study findings was ensured. Third, although we adjusted for a number of potential confounders including sun-exposure measures in the analysis, it was possible that residual confounding by sun exposure and other unmeasured factors such as personal behaviors related to alcohol use may have still existed in the current study. Nevertheless, our study was one of the few prospective studies that had extensive data on sun-exposure information. and whether the association between alcohol and BCC risk is causal could be further investigated with more data from future studies.

In conclusion, our findings support increased BCC risk in association with alcohol consumption that was independent of sun exposure and other potential confounders on the basis of data from 3 large cohorts. The identified association was consistently positive in both women and men with the use of different approaches of analyses. White wine and liquor may be the major alcoholic beverages that contribute to increased BCC risk. In addition, alcohol consumption in early adulthood (ages 18–22 y) was also associated with modest BCC risk after adjustment for alcohol intake in adulthood, particularly in women. Because of the prevalent alcohol consumption and high incidence of BCC in the population, our findings may help advance the understanding of the disease cause and be potentially useful for the prevention of cutaneous BCC. Nevertheless, additional studies are needed to replicate our findings in other populations and to explore the exact mechanisms behind the increased risk of BCC associated with alcohol consumption.

The authors' responsibilities were as follows—SW: drafting of the manuscript; AAQ and EC: administrative, technical, or material support (i.e., reporting or organizing data, constructing databases); SW and EC: study supervision; and all authors: study concept and design; development of methodology; acquisition of the data (e.g., provided animals, acquired and managed patients, and provided facilities); analysis and interpretation of the

data (e.g., statistical analysis, biostatistics, and computational analysis); writing, review, and/or revision of the manuscript; and full responsibility for analyses and interpretation of the data. AAQ serves as a consultant for Abbott, Centocor, Novartis, and the CDC. SW, W-QL, and EC reported no conflicts of interest related to the study.

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