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Alcohol And Early-Onset Basal Cell Carcinoma In A Case-Control Study

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ALCOHOL AND EARLY-ONSET BASAL CELL CARCINOMA IN A CASE-CONTROL STUDY

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ABSTRACT

Background Previous epidemiologic studies of overall alcohol intake and basal cell carcinoma (BCC) are inconsistent, with some evidence for differences by type of alcoholic beverage. While alcohol may enhance the carcinogenicity of ultraviolet (UV) light, this has not been evaluated in existing epidemiologic studies.

Objective To evaluate alcohol intake in relation to early-onset BCC, and explore potential interactions with UV exposure.

Methods BCC cases (n=380) and controls with benign skin conditions (n=390) under age 40 were identified through Yale Dermatopathology. Participants provided information on lifetime alcohol intake, including type of beverage during an in-person interview. Self-report data on indoor tanning and outdoor sunbathing were used to categorize UV exposure. We calculated odds ratios (OR) and 95% confidence intervals (CI) using unconditional multivariate logistic regression in the full sample and in women only.

Results There was no statistically significant association between lifetime alcohol intake and early-onset BCC overall (above median intake vs. no regular alcohol intake OR 1.10, 95% CI 0.69-1.73) or in women only (OR 1.21, 95% CI 0.73-2.01). Similarly, intake of red wine, white wine, beer or hard liquor and mixed drinks was not associated with early-onset BCC. However, in our full population, but especially in women, we observed a positive association between alcohol and BCC in those with the highest UV exposures (OR 3.09, 95% CI 1.26-7.59).

Conclusions Although we did not observe an association between lifetime alcohol intake and early-onset BCC, there was a positive association in those with relatively high UV exposures from indoor tanning/sunbathing.

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INTRODUCTION

Basal cell carcinoma (BCC), a type of non-melanoma skin cancer (NMSC), is the most common cancer.[1] Though rarely fatal, this malignancy causes considerable morbidity and places a high burden on health care systems.[2] BCC has been rising in incidence during the past several decades, with notable increases among young people, particularly females.[3] The rapidly changing incidence pattern suggests a role for lifestyle factors in BCC risk.

While evidence from epidemiologic studies and laboratory research indicates ultraviolet (UV) radiation is the primary environmental risk factor for melanoma and NMSC,[4] other behavioral and lifestyle factors are also of interest in relation to skin cancer. One such exposure, alcohol, has been investigated in relation to skin cancer in several epidemiologic studies. Alcohol intake has been linked to an increased risk of malignant melanoma in some research,[5-9] though other studies have not found an association.[10-12] Regarding NMSC, three prospective studies have reported an increased risk of BCC associated with alcohol,[13-15] while one other cohort study and several case-control studies found no association.[16-19] In addition to the inconclusive evidence of an association between BCC and total alcohol, there is also mixed evidence indicating risk may differ by type of alcoholic beverage consumed.[14, 15, 19]

There are several hypothesized mechanisms by which alcohol may impact skin carcinogenesis, including a potential role in enhancing the carcinogenicity of UV exposure. Research suggests this could be due to alcohol altering the antioxidant nutrient defense system in skin,[20] as well as interfering with immune function.[21] Compromised immune function is an established risk factor for BCC.[1] Although there are plausible pathways for UV exposure to

interact with alcohol to impact skin cancer risk, thus far, epidemiologic studies on alcohol intake and skin cancer have not evaluated this potential interaction.

Previous research on alcohol and skin cancer has focused on skin cancer among older individuals, who also may have different alcohol exposures than young adults. In addition, there is limited epidemiologic data on different types of alcoholic beverages in relation to BCC risk. Therefore, we evaluated lifetime alcohol intake (overall and by beverage type) in relation to early-onset BCC in the Yale Study of Skin Health in Young People and explored potential interactions with UV exposure.

METHODS

Yale Study of Skin Health in Young People

The Yale Study of Skin Health in Young People was a case-control study focusing on early-onset BCC and related lifestyle factors, conducted in Connecticut between July 2007 and December 2010. The study is described in detail elsewhere.[22] Sample size calculations were based on having at least 80% power to detect effect sizes ranging from 1.2 to 2.0 for hypothesized risk factors ranging in prevalence from 5% to 50% in controls. BCC cases were identified through Yale University's Dermatopathology database. Control subjects were individuals with non-UV related benign skin conditions randomly sampled from the same database and frequency matched to BCC cases on age at biopsy, gender, and biopsy site. A total of 389 cases (participation rate=72.8%) and 458 controls (participation rate=60.7%) enrolled in the study. Participants completed an in-person interview using a structured questionnaire, and several mailed self-administered questionnaires. Interviewers also collected a saliva sample for

buccal cell DNA from 98.9% of participants. Yale University's Institutional Review Board approved the study and participants (or guardians) provided written informed consent.

Data collection

The structured interview contained questions on self-reported phenotype characteristics (eye, skin and hair color; skin reaction to strong sunlight for the first time in summer for one hour without sunscreen; skin reaction after repeated and prolonged exposure to sunlight), outdoor UV exposure (general exposure, intentional sunbathing, outdoor activities), indoor tanning (ever/never, number of sessions), history of sunburns, sunscreen use, smoking, family history of skin cancer, as well as sociodemographic information. Interviewers were blinded to case-control status until the end of the interview, when participants were asked about their personal history of cancer.

Participants over 21 years of age (the legal drinking age in this location at the time of interview) were asked whether they consumed alcoholic drinks regularly, defined as at least once per week for 6 months or longer. Those who responded affirmatively to regular drinking were then asked about consumption of four types of alcoholic beverages, namely red wine, white wine, beer, and hard liquor or mixed drinks. Participants were asked to estimate the average number of drinks of each beverage type over a period of time of their choosing (per day, week, month or year), as well as the duration of the drinking behavior for two different age periods (before age 25 and age 25 to one year prior to interview). Cumulative numbers of drinks of each type of alcoholic beverage across the two time periods (before age 25 and age 25 to one year prior to interview) were calculated by multiplying average number of drinks by duration. Total lifetime number of alcoholic drinks was then calculated by summing across the four beverage

types across the two age periods. Individuals without regular alcohol consumption were assigned a zero value for lifetime drinks.

Statistical Analysis

Our analytic sample was limited to non-Hispanic whites: 380 (97.7%) cases and 390 (85.2%) controls. We further excluded three cases with Gorlin Syndrome, which predisposes individuals to multiple BCCs early in life, [23] six cases and five controls less than 21 years of age at the time of interview, and six cases and three controls missing data on frequency of alcohol intake. This left 747 individuals (365 cases and 382 controls) for analysis.

We used descriptive statistics (Chi-square test, Wilcoxon rank sum test, and t-test) to evaluate differences between cases and controls. Then using multivariate unconditional logistic regression, we calculated odds ratios (ORs) and 95% confidence intervals (CIs) for the association between lifetime alcohol intake and early-onset BCC in the whole sample, as well as in females only. Due to the limited sample of males in our population, we did not evaluate effects in that group alone. We categorized lifetime number of alcoholic drinks into three categories: no regular drinking, below or equal to median number of lifetime drinks, and above the median. Similar variables were created for total drinks consumed over the two age periods (before age 25 and 25 and older) and for the lifetime drinks of the individual beverage types. Median intake was based on consumption among regular drinking control subjects and individuals who did not regularly drink alcohol served as the reference group for these analyses.

All models were adjusted for study frequency matching variables (gender, age at diagnosis, and body site of biopsy), factors significantly associated with alcohol drinking in the analytic population (level of education, smoking status, hours spent outdoors in warm months, number of

sunburns, and family history of skin cancer), as well as variables related to skin cancer risk in our population (indoor tanning, skin color, and long-term skin reaction to sun exposure). The multivariate models for the individual alcoholic beverage types were also mutually adjusted for all other types of alcoholic beverages. We evaluated the linear trends using an ordinal categorical variable for each measure of alcohol intake.

We also tested the interaction between total alcohol intake and UV exposure in relation to risk by including cross-product terms in the multivariate models. We first evaluated the interaction with continuous measures of exposure (lifetime alcoholic drinks and lifetime indoor tanning sessions; lifetime alcoholic drinks and lifetime sunbathing sessions). We then evaluated the interaction between categories of alcohol and UV, with the former as a three-level categorical variable (no regular drinking, below or equal to median number of lifetime drinks, and above the median) and the later categorized in two ways: ever versus never indoor tanning, and a combined three-level categorical variable that incorporated UV exposure from both indoor tanning and outdoor sunbathing. For the three-level UV variable, participants were classified into "below or equal to median for both indoor tanning and outdoor sunbathing," "mixed - above the median for either indoor tanning or outdoor sunbathing," and "above the median for both indoor tanning and outdoor sunbathing;" median cut-points were derived from the distribution of these exposures in exposed controls. Stratified analyses were conducted for any p-value for interaction less than 0.10. Subgroup analyses were not adjusted for multiple comparisons considering the exploratory nature of these analyses. All analyses were conducted using SAS software (SAS, Version 9.3, SAS Institute Inc., Cary, NC) and reported p-values are two-sided.

RESULTS

69.6% of the study participants were female and the median age at skin biopsy was approximately 36 years. Compared to controls, BCC cases were more likely to have a higher level of education, lower BMI, fairer complexion, burn rather than tan with sun exposure and a family history of skin cancer (Table 1). The majority of study participants regularly consumed alcoholic drinks (76.3% of cases and 72.0% of controls). The median number of lifetime drinks was 3064 for cases, and 2270 for controls. Number of lifetime drinks differed by gender, with a median of 5086 drinks for male participants and 2064 for female participants ($p<0.001$, data not shown).

Multivariate risk estimates were calculated for BCC in relation to lifetime total alcohol intake and the individual alcoholic beverage types in the overall population and in women only (Table 2). No statistically significant association was found between lifetime alcohol intake and early-onset BCC (OR for above median intake vs. not regular drinker=1.10, 95% CI=0.69-1.73). There also was no evidence of an association in women only (OR=1.21, 95% CI=0.73-2.01). Similarly, intake of red wine, white wine, beer or hard liquor and mixed drinks were not associated with early-onset BCC in the full sample or women alone.

There were non-significant associations by age of consumption, with above median total intake under age 25 positively associated with BCC (OR=1.59, 95% CI=0.65-3.86), but above median total intake over age 25 inversely associated with risk (OR = 0.72, 95% CI = 0.30-1.75) (data not shown). A similar pattern was observed among females as well (OR for above median alcohol intake under age 25=1.83, 95% CI= 0.66-5.05; OR for above median alcohol intake over age 25=0.57, 95% CI=0.20-1.60).

We explored whether alcohol and UV exposures interacted to affect risk of BCC (Table 3). Among females, we observed statistically significant effect modification of the association of alcohol with BCC by never/ever indoor tanning in females. More specifically, we observed an increased risk of BCC with higher alcohol intake for female indoor tanners, but an inverse association with higher alcohol intake among females who never indoor tanned, though both risk estimates were not statistically significant. Similarly, there was evidence of an interaction between alcohol and the three-level combined indoor tanning and outdoor sunbathing UV exposure variable for males and females combined and females alone. Again, there was evidence of a positive association between alcohol and BCC among those with high UV exposure, but an inverse association for low UV. Despite these findings for categorical measures of UV exposure and alcohol, we did not observe any statistically significant effect modification by indoor tanning or sunbathing when both UV exposure and alcohol were examined as continuous variables (data not shown).

DISCUSSION

In this study of BCC among young people, we did not observe an association between lifetime alcohol intake and risk of early-onset BCC. There was also no clear evidence of an association between early-onset BCC and individual alcoholic beverage types or alcohol intake by age of consumption (under/over age 25). We did observe some evidence for effect modification of the association between lifetime alcohol and BCC by ever/never indoor tanning status among women, and by a combined measure of indoor tanning and outdoor sunbathing UV exposure in the overall population and in women. However, when alcohol and UV exposure were assessed on a continuous scale, there was no statistically significant interaction.

While we did not observe an association between alcohol and early-onset BCC, several cohort studies have found a moderately increased risk of BCC associated with greater alcohol consumption. In a cohort of Danish females, a 10 gram increase in daily alcohol intake was associated with a statistically significant relative risk of 1.05 for BCC.[15] Similarly, in a cohort study among US radiological technologists, there was a 30 and 40% increased risk of BCC for individuals who consumed 3-6 drinks per week and 7-14 drinks per week, respectively, compared to nondrinkers.[13] Another US cohort study observed a 29% increased risk of BCC for people who drank 15-29.9 g alcohol per day.[14] However, the data are not entirely consistent, as one other cohort study and several case-control studies found no statistically significant associations between overall alcohol intake and BCC.[16-19, 24] It is important to consider that because our outcome is early-onset BCC only, the alcohol association could be different for this specific BCC outcome as opposed to the existing cohort studies in which most BCC cases are older. If the effects seen in the majority of the cohorts are real, it is possible that the association between alcohol intake and BCC may have a long latency period, such that an association with early-onset BCC would not be present.

Evidence from studies that examined beverage type-specific effects of alcohol on BCC has also been mixed. Red wine was inversely associated with BCC among women, but not men, in a US cohort study, while white wine was associated with an increased risk of BCC risk in the overall population and women only.[14] In the same study, liquor was associated with an increased risk of BCC in the overall population and in men only.[14] In a Danish population, intake of wine and spirits was related to marginal increases in BCC in both men and women, while intake of beer was associated with a decreased risk.[15] In our investigation, no statistically significant

relationship was found for different types of alcoholic drinks with BCC; however, our power to examine these associations was more limited than for our measure of total alcohol.

The significant interactions we observed between categorical measures of UV exposure and alcohol intake and risk of BCC are intriguing. We saw evidence of an inverse relationship between alcohol and BCC in people who never tanned indoors, whereas there was a suggestion of an increased risk of BCC in indoor tanners. We observed a similar pattern of increased risk among those with higher UV exposure in the test of interaction of alcohol intake and a combined categorical variable of indoor tanning and outdoor sunbathing. However, these results should be interpreted with caution, as we did not observe a significant main effect of alcohol nor did we observe a significant interaction when alcohol and UV exposure were evaluated as continuous variables. While the interaction may be real, it is also possible that the group of people who consumed greater alcohol and engaged in indoor tanning/outdoor sunbathing may have differed in other unmeasured factors potentially related to skin cancer risk as compared with those who did not drink, never tanned indoors and sunbathed infrequently. Additional larger studies are required to further investigate this possible interaction, especially as there is some evidence from mechanistic research supporting the hypothesis that alcohol may enhance the carcinogenicity of UV exposure.[20, 21]

To our knowledge, the present study is the first to evaluate alcohol and early-onset BCC and to explore the potential modifying effect of UV exposure on the association between alcohol consumption and BCC. With detailed assessment of alcohol consumption, we were able to explore the association by different types of alcoholic beverages, as well as the effect of alcohol intake at different ages. In addition, with extensive information on major skin cancer risk factors

and UV related activities, we evaluated and adjusted for numerous potential confounders. Finally, since there has not been an established association between alcohol intake and skin cancer covered in the popular media, reporting of alcohol intake was unlikely to differ by case-control status.

Despite these strengths, the present study had several limitations. Firstly, the retrospective nature inherent in case-control studies limits the accuracy of self-reported information on alcohol intake, indoor tanning history and outdoor sunbathing history. Although alcohol intake was by self-report, as expected it was correlated with pack-years of smoking in our study population, providing some internal validation of the self-report measure. Secondly, based on the wording of our questionnaire, we could only assess number of lifetime alcoholic drinks and were not able to calculate a measure of average alcohol consumption (per week/per day); the measure used by many studies that had food frequency questionnaires. Thus far, only one cohort study has assessed lifetime alcohol consumption, and in that study, as in ours, there was no overall association between alcohol and BCC.[15] Consequently, the ability to compare our results with previous studies of alcohol and BCC is somewhat limited. Third, we did not have sufficient power to examine the association of alcohol and UV exposure in men, and our investigations of risk by alcoholic beverage type were limited by lower intake of certain beverages. Finally, our study population was limited to one state, Connecticut, and our sample was reasonably well-educated which could limit the generalizability of our results to a broader population.

In conclusion, we did not observe a clear or consistent association between lifetime total alcohol intake or intake of specific types of alcoholic beverages and risk of early-onset BCC. However, our findings suggest an association in those exposed to higher levels of UV exposure

via indoor tanning and outdoor sunbathing. Replication in large, prospective studies with both alcohol and UV exposure data are needed to clarify this potential relationship.

Table 1. Selected characteristics of BCC cases and controls in Yale Study of Skin Health in Young People

Characteristics	Cases, N= 365 N[1] (%)	Controls, N=382 N[1] (%)	P value[2]
Age (y), Median (IQR)	36.4 (33.6-38.5)	36.8 (32.9-38.5)	0.966
Female	253 (69.3%)	270 (70.7%)	0.684
Body site of skin biopsy			<0.001
Head	195 (53.4%)	160 (41.9%)	
Extremity	71 (19.5%)	123 (32.2%)	
Trunk	99 (27.1%)	99 (25.9%)	
Lifetime alcoholic drinks, median (IQR)	3064 (104-6736)	2270 (0-5824)	0.096
Education			0.009
≤ Some college	98 (26.9%)	139 (36.4%)	
College graduate	112 (30.7%)	115 (30.1%)	
≥ Some graduate school	155 (42.5%)	128 (33.5%)	
Hair color			<0.001
Black/dark brown	100 (27.5%)	157 (41.1%)	
Light brown	127 (34.9%)	153 (40.1%)	
Blonde/fair	98 (26.9%)	62 (16.2%)	
Red	39 (10.7%)	10 (2.6%)	
Skin color (inner upper arm)			<0.001
Olive	15 (4.1%)	74 (19.4%)	
Fair	203 (55.6%)	232 (60.7%)	
Very fair	147 (40.3%)	76 (19.9%)	
Skin reaction with first summer sun exposure			<0.001
Turn brown, no burn/ mild burn then tan	138 (37.8%)	226 (59.3%)	
Painful burn/ Severe burn	227 (62.2%)	155 (40.7%)	
Skin reaction with prolonged sun exposure			<0.001
Deeply tanned/ moderately tanned	201 (55.1%)	289 (75.7%)	
Mildly tanned / freckled without tan	164 (44.9%)	93 (24.3%)	
Family history of skin cancer	240 (65.8%)	148 (38.7%)	<0.001
Body mass index, kg/m^2			<0.001
≤ 25.0	238 (65.2%)	202 (52.9%)	
25-29.9	87 (23.8%)	106 (27.8%)	
≥30.0	40 (11.0%)	74 (19.4%)	
Smoking status			<0.001
Never	226 (61.9%)	197 (51.6%)	
Former	109 (29.9%)	121 (31.7%)	
Current	30 (8.2%)	64 (16.8%)	
Outdoor sun exposure in warm months (h), mean ± SD	9017 ± 3392	8365 ± 3177	0.007 [3]
Sunburns (n), median (IQR)	7 (1- 17)	3 (1- 9)	<0.001

Abbreviation: BCC, basal cell carcinoma; IQR, Interquartile range

[1]May not sum to total due to missing data.

[2]Chi-square test for categorical variables, Wilcoxon rank sum test for continuous variables.

[3]T-test.

Table 2. Adjusted ORs for early-onset BCC among all subjects (n=736) and women (n=515) according to cumulative lifetime alcoholic drinks

	Total alcohol	Red wine	White wine	Beer	Liquor
Overall					
Median among controls	4314	520	487	2248	816
No regular alcohol consumption					
cases/controls	88/106	163/179	186/206	110/134	141/156
OR (95% CI)[1]	1.00	1.00	1.00	1.00	1.00
Below median					
cases/controls	131/135	104/96	97/85	119/121	117/109
OR (95% CI)[1]	1.04(0.67-1.59)	1.07 (0.66-1.75)	1.08 (0.48-1.34)	1.04 (0.62-1.76)	0.90 (0.59-1.59)
Above median					
cases/controls	140/136	92/102	76/86	130/122	101/112
OR (95% CI)[1]	1.10 (0.69-1.73)	1.07 (0.65-1.76)	0.80 (0.48-1.34)	1.18 (0.68-2.04)	0.90 (0.55-1.46)
P-trend	0.434	0.341	0.348	0.849	0.203
Women					
Median among controls	3234	520	520	1560	780
No regular alcohol consumption					
cases/controls	69/82	115/133	117/137	88/109	104/117
OR (95% CI)[1]	1.00	1.00	1.00	1.00	1.00
Below median					
cases/controls	100/112	66/63	71/60	95/100	82/77
OR (95% CI)[1]	0.93 (0.57-1.51)	1.10 (0.61-1.99)	1.19 (0.66-2.15)	0.91 (0.49-1.69)	1.02 (0.56-1.85)
Above median					
cases/controls	80/72	68/70	61/69	66/57	63/72
OR (95% CI)[1]	1.21 (0.73-2.01)	1.24 (0.70-2.21)	0.86 (0.47-1.57)	1.18 (0.64-2.19)	0.86 (0.49-1.50)
P-trend	0.635	0.295	0.501	0.748	0.683

[1]Adjusted for age, gender (for overall sample model), body site of biopsy (head, extremity, trunk), indoor tanning (never, ever), skin color (olive, fair, very fair), education (some college or less, college graduate, some graduate school), smoking status (never, former, current), hours spent outdoors in warm months (continuous), sunburns (continuous), and family history of skin cancer (yes, no) in all models; and mutually adjusted for the other subtypes of alcohol in models for beverage subtype.

Table 3. Stratified analyses for cumulative lifetime total alcohol and early-onset BCC by indoor tanning status, and indoor tanning and outdoor sunbathing

	Indoor tanning status		Indoor tanning and outdoor sunbathing		
	Never	Ever	Low	Mixed	High
Overall	(n=736)		(n=731)		
No regular alcohol consumption					
cases/controls	32/29	56/77	33/32	28/34	26/40
OR (95% CI)[1]	1.00	1.00	1.00	1.00	1.00
Below median					
cases/controls	44/45	87/90	46/47	39/38	44/47
OR (95% CI)[1]	0.68 (0.30-1.53)	1.13 (0.67-1.89)	0.69 (0.29-1.63)	0.90 (0.40-1.99)	1.54 (0.74-3.21)
Above median					
cases/controls	43/57	97/79	37/53	41/35	63/48
OR (95% CI)[1]	0.45 (0.18-1.11)	1.42 (0.82-2.47)	0.36 (0.14-0.92)	1.03 (0.42-2.55)	1.92 (0.91-4.03)
$P_{interaction}$	0.100		0.023		
Women	(n=515)		(n=510)		
No regular alcohol consumption					
cases/controls	21/18	48/64	20/15	24/27	24/40
OR (95% CI)[1]	1.00	1.00	1.00	1.00	1.00
Below median					
cases/controls	18/23	59/69	17/24	26/30	33/36
OR (95% CI)[1]	0.63 (0.22-1.86)	1.06 (0.60-1.88)	0.60 (0.24-1.48)	0.78 (0.31-2.01)	2.01 (0.80-5.08)
Above median					
cases/controls	7/24	96/68	10/18	25/23	68/50
OR (95% CI)[1]	0.30 (0.09-1.04)	1.68 (0.94-3.00)	0.36 (0.12-1.08)	1.28 (0.50-3.26)	3.09 (1.26-7.59)
$P_{interaction}$	0.003		0.008		

[1]Adjusted for age, gender (for overall sample model), body site of biopsy (head, extremity, trunk), indoor tanning (never, ever), skin color (olive, fair, very fair), education (some college or less, college graduate, some graduate school), smoking status (never, former, current), hours spent outdoors in warm months (continuous), sunburns (continuous), and family history of skin cancer (yes, no).

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