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Association of Tea Consumption and Cutaneous Squamous Cell Carcinoma

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Abstract

Background—Laboratory and epidemiologic studies suggest a protective effect of tea consumption on risk of cutaneous squamous cell carcinoma (SCC). We designed a case-control study to examine the association between putative protective exposures, including tea consumption, and SCC risk using a large health maintenance organization population.

Patient/Methods—Cases (n= 415) were defined as Kaiser Permanente Northern California (KPNC) members with a pathology-verified SCC in 2004 and controls (n=415) were age-, gender, and race-matched members with no previous history of skin cancer. Tea consumption and SCC risk factors were ascertained by questionnaire. Odds ratios (OR) and 95% confidence intervals (CI) were calculated using conditional logistic regression to estimate the association of SCC with regular use, as well as dose and duration of tea consumption. Risk factor adjusted models included education, smoking, hair and eye color, skin type, family history of skin cancer and history of freckling, sunburns, sun exposure and tanning bed use.

RESULTS—Adjusted analyses showed no reduction in SCC risk with regular consumption of tea (OR=1.11, 95% CI: 0.81–1.54). Examining duration, dose, and combined duration and dose exposure variables did not alter findings.

CONCLUSIONS—We found no evidence that tea consumption was associated with cutaneous SCC risk.

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INTRODUCTION

The natural ingredients in green and black tea, derived from the leaves of the *Camellia sinensis* plant, have anti-inflammatory and anti-carcinogenic activity. Recent evidence suggests that regular consumption of tea may be associated with lower rates of certain types of cancer, including skin cancer.[1–3] We conducted a case-control study to investigate whether tea consumption is associated with cutaneous squamous cell carcinoma (SCC) risk in members of the Kaiser Permanente Northern California (KPNC) health plan. KPNC electronic records include a comprehensive pathology database through which cutaneous SCCs can be accurately identified. We used a self-administered questionnaire to ascertain SCC risk factors and patterns of tea consumption (regular use, dose, duration). Based on the previously published literature,[1,3] we hypothesized that increased tea consumption would be associated with a reduction in SCC risk.

MATERIALS AND METHODS

Study Population

We conducted a case-control study within KPNC of 415 case subjects (ages 43 to 85) defined as having a pathology-confirmed cutaneous SCC diagnosed in 2004 and 415 control subjects with no prior history of skin cancer individually matched to cases by year of birth, sex and self-reported race. The cases were randomly chosen from a pool of over 4,000 members identified from KPNC electronic pathology records with a diagnosis of cutaneous (extra-genital, non-mucosal) SCC between January 1, 2004 and December 31, 2004. Control subjects were drawn from respondents to the 2005 Members Health Survey, a general health survey mailed to a random sample of KPNC adult members. We chose Members Health Survey participants because this survey asked questions on self-identified race and history of prior cancer. Each participant was contacted by mail and asked to complete a 3-page self-administered questionnaire regarding various personal characteristics, health behaviors including sun-protective measures, supplement use, and tea consumption, and skin cancer risk factors. The survey instrument was modeled off of a validated questionnaire to ascertain cancer risk in relation to supplement use developed for the Vitamins and Lifestyle Study.[4] The survey response rate for cases was 81% and 57% for controls. Detailed information about the study population and study design has been previously reported.[5] This study was approved by the Kaiser Foundation Research Institute Institutional Review Board and was conducted according to the Declaration of Helsinki principles.

Tea Exposure

The self-administered questionnaire inquired if participants drank “brewed green or black tea (not herbal) regularly (at least once-a-week).” Subjects who did not report regular tea consumption were defined as the reference group. If subjects indicated that they drank tea regularly, they were asked to quantify the amount. Amounts were presented in categories as follows: 1 cup per week, 2–6 cups per week, 1 cup per day, 2–3 cups per day and 4+ cups per day. Participants were also asked how long they had been exposed and were given the following categories to choose from: 1–4 years, 5–15 years, 15–30 years, > 30 years. The categories were then restructured based on distribution to create adequate cell sizes within each comparison. Frequency was recategorized as none, <1 cup per day, 1 cup per day, > 1 cup per day and duration recategorized as none, 1–4 years, 5–14 years, > 14 years. To simultaneously account for dose and duration, the variable “cup-years” was created by multiplying the number of cups per day by the years of use using the midpoint of each category, and the lower-bound for open ended categories. The cup-year variable was divided into 4 categories based on distribution of the data as follows: 0, >0 to ≤ 3, >3 to ≤ 10 and > 10 cup-years.

Covariates

Participants also answered questions on variables known to influence SCC risk including skin type, history of freckling (yes/no), eye color, natural hair color, education, family history of skin cancer, history of sunburns, regular peak-time outdoor sun exposure (yes/no), regular peak-time occupational sun exposure (yes/no), tanning bed use (yes/no), high-risk exposures including ultraviolet (UV) light treatment, burn scar, non-healing ulcers, radiation treatment, arsenic exposure, exposure to industrial chemicals (yes/no), and smoking (current vs. former/never).

Statistical Analysis

Differences in distributions of categorical covariates between cases and controls were analyzed using Pearson chi-square tests. For the matched case-control analysis, we used conditional logistic regression to estimate unadjusted and adjusted odds ratios and Wald 95% confidence intervals for regular use, dose, duration, and cup-years exposure measures. The referent category for analyses involving regular use and duration were non-regular users (tea consumption < once-a-week). For the adjusted models, we adjusted for all ascertained SCC risk factors (fully adjusted model), and, to ensure that our multivariate analyses were not over-adjusted, we created a model limiting the variables to those that were associated with both tea exposure and SCC risk at the $p<0.20$ level (parsimonious model). *P* values were two-sided. All statistical analyses were performed using SAS, version 9.1, (SAS Institute Inc., Cary, NC).

RESULTS

The average age of participants at index date was 72.5 years ± 8.6 SD (range: 43–85 years). The majority of participants were male (n=514, 61.9%). Compared to controls, cases were more likely to have red or blond hair, blue or grey eyes, and lighter skin types. Cases were also more likely to report current smoking, a family history of skin cancer, a history of childhood freckles, routine sun exposure and severe sunburns, and exposure to other SCC high risk factors (Table 1).

Regular consumption of tea (at least once a week) was reported by 34% of study participants and was not associated with a reduction in SCC risk (parsimonious adjusted OR=1.11, 95% CI: 0.80–1.54). Furthermore, SCC risk was not associated with amount of tea consumed (dose), years of use (duration), or a composite measure of dose and duration (cup-years) in either the parsimonious or fully adjusted models (Table 2). We tested for interaction between regular peak-time sun exposure and tea consumption in parsimonious models and found no evidence of interaction (all p-values on the interaction term were >0.50; data not shown).

DISCUSSION

Results from this case-control study do not support the hypothesis that tea consumption is inversely associated with risk of SCC. There was no effect of dose, duration, or combined dose-duration variables for tea consumption on risk of SCC.

Previously published case-control studies of tea consumption and SCC risk have yielded mixed results.[1–3] A case-control study drawing on subjects from the Southeastern Arizona Health Study, (n=450) reported that while there was no association between any tea consumption and SCC risk, there was a protective effect for hot black tea after adjusting for brewing time (OR=0.33, 95% CI 0.12–0.87).[1] Antioxidant activity as well as the content of the polyphenols in tea has been shown to increase with the brewing time.[6] A follow-up study using the same source population[2] reported that compared to non-tea drinkers, hot tea

drinkers had a *lower*, but statistically non-significant risk of cutaneous SCC (adjusted OR = 0.63, 95% CI 0.36–1.10) whereas iced tea drinkers were at a slightly *higher*, non-statistically significant risk (OR = 1.02, 95% CI 0.64–1.63). Finally, a population based case-control study of 696 individuals with primary invasive SCC and 715 age- and sex-matched controls showed that ever having regularly consumed tea (≥ 1 cup/day for ≥ 1 month) was associated with a significantly lower risk of SCC (OR = 0.70, 95% CI 0.53–0.92).[3] There was further risk reduction with increased duration and dose of tea consumption.

These conflicting findings may be explained, in part, by differences in the source populations, including differences in mean age (younger mean age in other published studies compared to our study), skin type (skin with tendency to burn: 23% of participants in our study vs. 25%[1–2] and 40%[3] in previously published studies), tea consumption patterns (iced tea consumption was more prominent in the Arizona population), and sun exposure history (due to geographic variability). The photoprotective effects of tea may be modified by skin type such that effects are more pronounced in source populations that consist of people with lighter complexions.

Strengths of this study include a large sample size (n=830), thorough measurement of exposure including overall use, dose, and duration and adjustment for SCC risk factors such a skin type and sun exposure history, which could potentially modify the effects. There are several potential limitations to this study, including the possibility of recall bias, selection bias, and limitations of generalizability. Differential misclassification would result if the cancer diagnosis served as a stimulus for cases to recall tea consumption exposures more or less thoroughly than controls, but this is not likely given that the cutaneous chemopreventive effects of tea consumption are not widely recognized, and tea drinking was only one of several different exposures ascertained in questionnaire. The generalizability of our study may be limited because we only studied KPNC members, although previous studies have shown that the KPNC membership is highly representative of the surrounding region except for the tail ends of the income distribution.[7–8] Finally, we did not collect information on tea consumption patterns such as hot versus cold tea consumption, green versus black tea, or brewing time, which may impact antioxidant potency.

In this case-control study, we did not detect any consistent relationships between tea consumption and SCC risk. Amount and duration of tea consumption did not appear to alter risk of SCC. Given the differences in conclusions depending on the population studied, further studies may be warranted.

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Table 1

SCC Risk Factors among Cases and Controls

Covariates	SCC n = 415 n (%)	Controls n = 415 n (%)	p value[1]
Pigmentation Variables			
Hair color (red/blond)[2]	102 (24.6)	67 (16.2)	0.003
Eye color (blue/grey)	191 (46.1)	165 (40.0)	0.073
Skin type[3]			
1	58 (14.0)	20 (4.8)	
2	76 (18.3)	40 (9.6)	
3	244 (58.8)	253 (61.0)	<0.001
4	36 (8.7)	90 (21.7)	
Missing	1 (0.2)	12 (2.9)	
Childhood freckles (yes)	224 (54.5)	111 (27.2)	<0.001
UV Exposure Variables			
Sunburns (> 2 severe sunburns)	263 (63.5)	184 (44.7)	<0.001
Occupational sun exposure[4] (yes)	96 (23.2)	85 (20.6)	0.365
Regular peak-time sun exposure[5] (yes)	312 (75.2)	284 (68.6)	0.035
Tanning bed use (yes)	49 (11.8)	36 (8.7)	0.137
Other Variables			
Education (≥ 4-year college degree)	158 (38.1)	176(42.5)	0.193
Cigarette smoking (current)	29 (7.0)	16 (3.9)	0.046
Family history of skin cancer[6]			
No	172 (41.6)	315 (75.9)	
Yes	136 (32.9)	59 (14.2)	<0.001
Don't Know	106 (25.6)	41 (9.9)	
High-risk exposures[7]	177 (42.7)	150 (36.1)	0.055

[1] Pearson Chi-squared test for proportions

[2] Ascertained as "adult natural hair color (prior to graying, if applicable)"

[3] Reaction of skin after exposure to 1 hour of mid-day sun for the first time in the summer with 1=painful or blistering sunburn with no tan, 2=painful sunburn followed by a light tan, 3= mild sunburn followed by a moderate tan, 4= no sunburn followed by a deep tan

[4] At least 2 hours/day of sun-exposure between 10am–4 pm for primary occupation

[5] At least 2 hours/day once-a-week of sun-exposure between 10am–4 pm in the past 10 years

[6] Including natural parents, brothers, and sisters only

[7] UV light treatment, burn scar, non-healing ulcers, radiation treatment, arsenic exposure, exposure to industrial chemicals (yes/no)

Table 2

Association of Tea Consumption and SCC risk

Exposure	Cases n (%)N=415	Controls n (%)N=415	Crude OR (95%CI)	Parsimoniously Adjusted OR[1] (95% CI)	Fully Adjusted OR[2] (95% CI)
Overall use					
Not regular[3]	271 (65.3)	278 (67.0)	1.0 (referent)	1.0 (referent)	1.0 (referent)
Regular	144 (34.7)	137 (33.0)	1.08 (0.81, 1.44)	1.11 (0.80, 1.54)	1.20 (0.82, 1.75)
Dose (cups)[4]					
None	271(65.3)	278 (67.0)	1.0 (referent)	1.0 (referent)	1.0 (referent)
< 1 per day	60 (14.5)	53 (12.8)	1.17 (0.77, 1.79)	1.10 (0.68, 1.77)	1.22 (0.71, 2.11)
1 per day	42 (10.1)	37 (8.9)	1.15 (0.73, 1.83)	1.24 (0.73, 2.12)	1.48 (0.81, 2.73)
>1 per day	42 (10.1)	47 (11.3)	0.91 (0.58, 1.44)	1.00 (0.60, 1.67)	0.98 (0.55, 1.73)
Test for Trend			**p-value 0.70**	**p-value 0.88**	**p-value 0.89**
Duration (years)[4]					
None	271(65.3)	278 (67.0)	1.0 (referent)	1.0 (referent)	1.0 (referent)
1–4	44 (10.6)	44 (10.6)	1.03 (0.66, 1.59)	1.03 (0.63, 1.70)	1.20 (0.67, 2.13)
5–14	39 (9.4)	34 (8.2)	1.19 (0.72, 1.99)	1.30 (0.73, 2.28)	1.29 (0.67, 2.47)
≥ 15	61 (14.7)	59 (14.2)	1.06 (0.71, 1.58)	1.06 (0.66, 1.68)	1.14 (0.67, 1.95)
Test for Trend			**p-value 0.64**	**p-value 0.62**	**p-value 0.60**
Cup-Years[4,5]					
0	271 (65.3)	278 (67.0)	1.0 (referent)	1.0 (referent)	1.0 (referent)
>0 to ≤ 3	52 (12.5)	50 (12.1)	1.07 (0.70, 1.62)	1.08 (0.68, 1.88)	1.26 (0.73, 2.17)
>3 to ≤ 10	41 (9.9)	36 (8.7)	1.17 (0.72, 1.90)	1.06 (0.60, 1.86)	1.14 (0.60, 2.19)
> 10	51 (12.3)	51 (12.3)	1.03 (0.68, 1.57)	1.16 (0.72, 1.74)	1.18 (0.68, 2.03)
Test for Trend			**p-value 0.80**	**p-value 0.61**	**p-value 0.68**

[1] Adjusted for variables associated with both tea exposure and SCC risk at the p<0.20 level including eye color (blue/grey vs. other), natural hair color (red/blond vs. other), skin type (reaction of skin after exposure to 1 hour of mid-day sun for the first time in the summer with 1=painful or blistering sunburn with no tan, 2=painful sunburn followed by a light tan, 3= mild sunburn followed by a moderate tan, 4= no sunburn followed by a deep tan), education (4-year college or above vs. not), history of sunburns (> 2 severe vs. ≤ 2 severe), regular (at least once-a-week for at least 2 hours) peak-time sun exposure (yes/no), and history of smoking (current vs. former/none). Dummy variables were created for all missing values. 95% CI values are Wald estimates.

[2]Adjusted for all SCC risk factors including eye color (blue/grey vs. other), natural hair color (red/blond vs. other), skin type (reaction of skin after exposure to 1 hour of mid-day sun for the first time in the summer with 1=painful or blistering sunburn with no tan, 2=painful sunburn followed by a light tan, 3= mild sunburn followed by a moderate tan, 4= no sunburn followed by a deep tan), education (4-year college or above vs. not), history of sunburns (> 2 severe vs. ≤ 2 severe), history of high-risk exposures such as UV light, burn scar, non-healing ulcers, radiation treatment, arsenic exposure, exposure to industrial chemicals (yes/no), history of smoking (current vs. former/none), history of freckling (yes/no), outdoor sun exposure (> 2 hours per week between 10am and 4 pm) (yes/no), occupational sun exposure (yes/no), tanning bed use (yes/no), and family history of skin cancer (yes/no). Dummy variables were created for all missing values. 95% CI values are Wald estimates.

[3]Less than once/week for one year

[4]Test for trend is not significant (all p-values > 0.60)

[5]Number of cups per week × years of use using the midpoint of each dose and duration category, and the lower bound for top categories