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Tea consumption and basal cell and squamous cell skin cancer: results of a case control study

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Abstract

Background— Tea constituents, including polyphenols, are hypothesized to have chemopreventive properties, and inhibit the induction of skin cancers in animal models.

Objective— To explore the association between regular tea consumption (≥ 1 cup/day for ≥ 1 month) and the incidence of squamous cell (SCC) and basal cell (BCC) carcinomas.

Methods— A population based case control study of 770 individuals with BCC, 696 with SCC, and 715 age- and sex-matched controls.

Results— After adjustment for age, sex and lifetime history of painful sunburns, ever having consumed tea regularly was associated with a significantly lower risk of SCC (OR=0.70; 95% CI 0.53–0.92), especially among long-term drinkers (≥ 47 years consumption, SCC OR=0.49; 95% CI 0.29–0.83; P for trend=0.008) and among those consuming ≥ 2 cups/day (OR=0.65; 95% CI 0.44–0.96; P for trend=0.013). After adjustment for age and sex, ever having consumed tea regularly was weakly associated with BCC risk (OR=0.79; 95% CI 0.63–0.98).

Limitations— Our case control study was susceptible to recall bias and to confounding by unknown cancer risk factors associated with tea consumption.

Conclusions— Our findings support the existence of an inverse association between tea consumption and skin carcinogenesis.

In the past two decades, a dramatic increase has been noted in the incidence of non melanoma skin cancer (NMSC) ¹. It has been estimated that over a million cases of NMSC will be diagnosed in the United States in 2005 ². In view of the considerable health care resources

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needed to treat NMSC³, the identification of methods to prevent them is becoming increasingly important.

The major environmental influence on the development of NMSC is exposure to ultraviolet (UV) radiation⁴, which generates reactive oxygen species and free radicals that damage a variety of cellular molecules⁵. In animal models of chemical and ultraviolet-induced carcinogenesis, green and black tea demonstrate anti-tumor activity even when administered after UVB exposure^{6, 7}. Green and black tea are derived from the same plant, *Camellia sinensis*, after the leaves are “fermented” for different lengths of time⁸. Both contain polyphenols, anti-oxidants that scavenge reactive oxygen and nitrogen species, and bind proteins. Green tea contains a lower proportion of caffeine than black tea, and a higher proportion of polyphenols, of which epigallocatechin-3-gallate (EGCG) may have the greatest antioxidant activity⁹. In contrast, black tea contains primarily theaflavins, which are responsible for tea flavor and aroma, thearubigens, and a higher concentration of caffeine.

Although animal models of skin cancer provide compelling data regarding the antioxidant and other potentially anti-carcinogenic ingredients in black and green tea, few studies have examined their effects in humans. A population-based case control study of SCC in southeastern Arizona identified a possible reduction in SCC risk associated with hot black tea consumption¹⁰, whereas two case-control studies of BCC found no association with tea consumption^{11, 12}. In light of the paucity of epidemiologic data on this issue, we explored tea consumption in relation to both SCC and BCC of the skin in a large population-based case-control study in New Hampshire.

METHODS

We identified cases of primary invasive SCC and BCC through a collaboration with dermatologists and pathologists serving the population of New Hampshire^{1, 13}. From this survey, we selected New Hampshire residents aged between 25 and 74 years who were diagnosed with SCC or BCC between July 1, 1993 and June 30, 1995 (series 1) and between July 1, 1997 and March 30, 2000 (series 2). To be eligible, participants were required to have an identifiable telephone number and speak English. For efficiency, we selected all potentially eligible cases of SCC and a randomly selected sample of BCC cases in a ratio of approximately two to one in the first series and one to one in the second series. The selection of BCC cases was achieved by random selection of BCCs within strata of age, gender and anatomic site to ensure representativeness of the entire BCC group. Potential controls less than 65 years of age were selected from the New Hampshire Department of Transportation driver's license files of state residents, and those 65 years and older were identified through the Center for Medicare and Medicaid Services files of New Hampshire residents enrolled in Medicare. Controls were randomly selected within sex and age strata (categories: 25–35, 36–45, 46–50, 51–59, 60–64, 65–69, and 70–74 years) using the frequency distribution of the combined BCC and SCC cases to achieve frequency matching of controls to cases. Participation rates for individuals selected for enrollment were 78% for cases and 66% for controls in the first phase and 80% for cases and 73% for controls in the second phase.

The study was approved by the Institutional Review Board of Dartmouth College, and participants in the case-control study provided informed consent. Participants were interviewed, usually at their home, to obtain information about various skin-related factors, including sensitivity to sun exposure, pigmentation characteristics and history of sunburn; medical data including history of cancer, ultraviolet or radiation therapy along with personal data such as educational background, marital status, and smoking history. Questions relating to tea consumption were added about one year after the study began, in 1995. We asked participants whether they regularly consumed tea, defined as at least one cup per day, on

average, for at least one month. Those who responded positively were asked when they began drinking tea regularly. If they were not currently drinking tea regularly, we asked when they had stopped. Further, we asked whether there were intervening periods in which they stopped drinking tea, and if so, for how long.

Statistical analysis

Odds ratios and 95% confidence intervals were derived from logistic regression models, which included factors found to relate to both tea consumption and risk for BCC or SCC. We examined daily tea consumption in categories (0, 1–2 or ≥ 3 cups) and as a continuous variable. We also evaluated the duration of tea consumption in categories based on quartiles among tea drinking controls, and also as a continuous variable. In addition, we examined the odds ratios for tea consumption according to anatomic site of the tumor (i.e. the head and neck, or only on other parts of the body). Participants with tumors in both anatomic sites were excluded from analyses involving tumor site.

In addition to age and sex, we evaluated the potentially confounding effects of skin type classified according to reported skin reaction to the first strong summer sun (dichotomized to “burners”: painful or severe sunburn with blistering or peeling versus “tanners”: mild or no sunburn with tanning). We also evaluated the potentially confounding effects of level of education (college education or less) and number of severe sunburns during the participant’s lifetime (0, 1–2 or 3+) and history of cigarette smoking (ever smoked regularly and never smoked). Because we found that tea consumption was unrelated to skin type or level of education, we did not retain these variables in the final models. Also, adjustment for chronic sun exposure and history of cigarette smoking did not have an impact on the odds ratios, and these variables were also dropped from the final models. However, the number of painful sunburns contributed significantly to the final model for SCC. Considering these factors, our final model for SCC included age, sex and lifetime painful sunburns, and the final model for BCC included age and sex.

We further evaluated the potential modifying effect of skin type (groupings), history of cigarette smoking (groupings), and lifetime number of painful sunburns (groupings) in addition to age (groups) and sex. To identify interaction effects, we included the following variables in the final models as well as their interaction term with tea drinking status (ever/never): age (quintiles), smoking (dichotomous), chronic sun exposure (dichotomous), and number of painful sunburns (tertiles). Only the latter suggested a possible interaction, which was then investigated with a stratified analysis. Statistical analyses were performed using Stata Version 9.0 (Stata Statistical Software, College Station, TX: StataCorp LP).

RESULTS

We ascertained tea consumption history for a total of 770 participants with BCC, 696 with SCC, and 715 controls; these comprised 94% (2181/2327) of those included in the study after the tea consumption questions were added in 1995. The characteristics of participants who did or did not provide tea data were similar with respect to age, gender, smoking history, education level, and tendency to sunburn. Among those who provided data on tea consumption, 58% were male, and the mean ages in the BCC, SCC and control groups were 58, 64 and 61 years respectively. Of those for whom the data were available, 31% had ever consumed tea regularly; 37% had a college level education; 36% had never smoked; 40% had skin that tended to burn; and 49% had ≥ 3 painful sunburns during their lifetime (Table I).

After adjusting for age, sex and lifetime painful sunburns (0, 1–2, ≥ 3), we found that the risk of SCC was statistically significantly lower among participants who had ever drunk tea regularly (OR=0.70; 95% CI 0.53–0.92) and specifically among current drinkers (OR=0.62;

95% CI 0.45–0.86) (Table II). The association was strongest among those who consumed two or more cups per day (OR=0.65; 95% CI 0.44–0.96; *P* for trend=0.013); and among those with the longest duration of tea consumption (≥ 47 years; OR=0.49; 95% CI 0.29–0.83; *P* for trend=0.008). On a continuous scale, the odds ratio for SCC for every additional 10 years of tea consumption was 0.90 (95% CI 0.84–0.98). After adjustment for age and sex, the risk of BCC was statistically significantly lower among those who had ever drunk tea regularly (OR=0.79; 95% CI 0.63–0.98), but not more so among current tea drinkers (OR=0.79; 95% CI 0.61–1.01). The odds ratio for BCC also was lowest among long term tea drinkers (≥ 47 years, OR=0.66; 95% CI 0.43–1.01) but no statistically significant trends were identified for either duration or cups per day (Table II).

After adjustment for age and sex, the odds ratio for SCC associated with tea consumption was lower among those who had never burned (OR=0.49; 95% CI 0.28–0.84) compared to those with 1–2 painful sunburns (OR=0.59; 95% CI 0.35–1.01) and ≥ 3 painful sunburns (OR=0.97; 95% CI 0.63–1.48). The equivalent results for BCC were OR=0.76 (95% CI 0.45–1.30); OR=0.53 (0.30–0.94); and OR=1.02 (0.67–1.54). Tea consumption largely was related to a lower risk of head and neck SCCs (after adjustment for age, sex and painful sunburns, OR=0.55; 95% CI 0.39–0.77); for those with tumors of non head and neck sites, tea appeared to be unrelated to SCC risk (OR=0.93; 95% CI 0.65–1.33). We did not observe any appreciable differences in associations between NMSC and tea consumption by age, gender, skin type or smoking status (data not shown).

DISCUSSION

Our results suggest that regular tea consumption is associated with a reduced risk of SCC of the skin. The strongest inverse associations were seen between SCC and tea consumption in the highest categories of duration of consumption and daily amount of consumption. A weaker inverse association was observed for BCC, with no apparent trends by duration or amount of tea consumption.

Our findings are consistent with the case-control study of SCC from Arizona that detected an inverse relationship with hot black tea consumption, which was strongest after adjustment for brewing time¹⁰. A subsequent report of the same study found that use of citrus peel in tea also related to a reduced SCC risk. Thus, it is possible that some of the effect we found in our study was due to citrus peel rather than tea consumption itself; however, we did not collect this information. For BCC, a smaller Mediterranean study¹² had a similar odds ratio to ours, but it did not reach statistical significance. In contrast, a small Finnish twin pair study of BCC found no association with >1 cup tea consumption compared to rare or no consumption¹¹.

The constituents of tea have been investigated for their activity against a variety of diseases and cancers¹⁴. In animal models of skin cancer and related *in vitro* studies, the catechins, theaflavins and caffeine have been shown to be chemopreventive^{14, 15}, but the most potent appear to be polyphenols such as epigallocatechin-3-gallate⁹. Topical EGCG has been shown to reduce erythema and the infiltration of leukocytes in UVB-exposed human skin^{16, 17}. Thus it is conceivable that the stronger inverse relation between tea consumption and SCC among participants with only head and neck tumors is due to a protective effect of tea against oxidative damage caused by moderate sun exposure, whereas the lack of protective effect among participants with more lifetime painful sunburns may reflect lack of protection by tea against the more extreme effects of sun exposure such as DNA damage.

A limitation of our study was the retrospective recall of tea consumption and thus its susceptibility to recall bias, a possibility in all case control studies. We would expect that the estimation of the amount or duration of tea consumption is prone to misclassification; but the

tea drinking status (i.e., ever, current, former and non tea drinker) may be more readily recalled. It is also possible that another, unidentified NMSC risk factor to which tea consumption is related may be responsible for its apparent inverse association with these cancers. However, the fact that this association is also supported by a variety of laboratory data suggests that further investigation in human populations is warranted. Our study had the advantages of population-based case and control ascertainment to minimize selection bias; and the use of in-person interviews to obtain detailed histories in relation to sun and other relevant exposures which we took into account in the analysis.

CONCLUSIONS

Our population-based case control study supports recent hypotheses that regular tea consumption may be associated with a reduced risk of non melanoma skin cancers, especially SCC. Further, the accumulating epidemiologic and experimental data concerning the effects of tea on cancer risk could ultimately lead to a better understanding of the etiology and potential prevention of these malignancies.

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Table 1

Selected baseline characteristics among 2181 participants with basal cell carcinoma (BCC), squamous cell carcinoma (SCC) and controls for whom tea consumption data were available

Demographic Factors	BCC (n=770)*	SCC (n=696)*	Controls (n=715)*
Age (years)			
<55	285 (50%)	119 (21%)	171 (30%)
55–59	104 (38%)	77 (28%)	93 (34%)
60–64	110 (36%)	100 (33%)	97 (32%)
65–69	132 (27%)	169 (35%)	181 (38%)
70–74	139 (26%)	231 (43%)	173 (32%)
Gender			
Male	429 (34%)	432 (34%)	410 (32%)
Female	341 (37%)	264 (29%)	305 (34%)
Education			
College level or higher	304 (38%)	248 (31%)	244 (31%)
No college	466 (34%)	448 (32%)	470 (34%)
Smoking status			
Never	312 (39%)	223 (28%)	256 (32%)
Former or current	457 (33%)	473 (34%)	459 (33%)
Skin reaction to 1 hour sun exposure first time in summer			
Painful or severe sunburn with blistering or peeling	342 (39%)	299 (34%)	229 (26%)
Mild or no sunburn with tanning	428 (33%)	396 (30%)	484 (37%)
Lifetime number of painful sunburns [†]			
0	122 (31%)	135 (34%)	139 (35%)
1–2	102 (30%)	118 (34%)	123 (36%)
3 or more	269 (37%)	271 (37%)	184 (25%)
Location of tumors present at time of interview [‡]			
Head & neck only	468 (54%)	395 (46%)	
Sites other than head & neck only	282 (50%)	279 (50%)	

* Denominators vary where data are missing

[†] Data available for participants in series 2 only

[‡] Participants with tumors in both sites are omitted

Table II
Tea consumption and risk of basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) of skin

	BCC participants (N=770)*		SCC participants (N=696) [†]		Controls (N=715)
	N	OR (95% CI)	N	OR (95% CI)	N
Tea consumption					
Never	545	1.00 (Reference)	489	1.00 (Reference)	466
Ever	225	0.79 (0.63–0.98)	207	0.70 (0.53–0.92)	249
Current	163	0.79 (0.61–1.01)	136	0.62 (0.45–0.86)	185
Former	62	0.80 (0.55–1.17)	70	0.91 (0.59–1.42)	64
Average daily tea consumption (cups per day) while drinking tea regularly					
0	538	1.00 (Reference)	488	1.00 (Reference)	465
1	101	0.67 (0.50–0.89)	116	0.75 (0.53–1.06)	135
2 or more	122	0.98 (0.74–1.31)	88	0.65 (0.44–0.96)	110
OR per cup (continuous)		P for trend=0.349		P for trend=0.013	
Duration of tea consumption (years)		0.99 (0.90–1.07)		0.94 (0.84–1.04)	
0	546	1.00 (Reference)	491	1.00 (Reference)	476
>0 to <10	53	0.94 (0.62–1.43)	38	0.83 (0.48–1.43)	46
10 to <29	60	0.78 (0.53–1.13)	60	0.93 (0.58–1.51)	64
29 to <47	65	0.95 (0.65–1.38)	52	0.72 (0.45–1.15)	61
47 years or more	39	0.66 (0.43–1.01)	46	0.49 (0.29–0.83)	63
OR per 10 years (continuous)		P for trend =0.064		P for trend=0.008	
		0.95 (0.89–1.01)		0.90 (0.84–0.98)	

* BCC models adjusted for age and sex

[†] SCC models adjusted for age, sex and lifetime number of painful sunburns (0, 1–2 or ≥3)