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Research article

Joint effects of citrus peel use and black tea intake on the risk of squamous cell carcinoma of the skin

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Abstract

Background: Differences in tea drinking habits and/or citrus peel use are likely to vary by populations and could contribute to the inconsistencies found between studies comparing their consumption and cancer risk.

Methods: A population-based case-control study was used to evaluate the relationships between citrus peel use and black tea intake and squamous cell carcinoma (SCC) of the skin. Moreover, we assessed the independent and interactive effects of citrus peel and black tea in the development of SCC.

Results: Hot and iced teas were consumed by 30.7% and 51.8% of the subjects, respectively. Peel consumption was reported by 34.5% of subjects. Controls were more likely than were cases to report citrus peel use (odds ratio (OR) = 0.67) and hot tea intake (OR = 0.79). After adjustment for hot and iced tea intake, the ORs associated with citrus peel use were 0.55 and 0.69, respectively, whereas the corresponding adjusted ORs for hot and iced tea intake after adjustment for citrus peel use were 0.87 and 1.22 respectively. Compared with those who did not consume hot black tea or citrus peel, the adjusted ORs associated with sole consumption of hot black tea or citrus peel were 0.60 and 0.30, respectively. Subjects who reported consumption of both hot black tea and citrus peel had a significant marked decrease (OR= 0.22; 95% CI = 0.10 – 0.51) risk of skin SCC.

Conclusion: These results indicate that both citrus peel use and strong (hot) black tea have independent potential protective effects in relation to skin SCC.

Introduction

Non-melanoma skin cancer, which includes squamous cell carcinoma (SCC) and basal cell carcinoma (BCC), is the most common type of cancer in the United States and results in substantial morbidity and treatment costs. It is estimated that 1.2 million new cases of non-melanoma skin cancer occur each year in the United States, and the majority of these are believed to result from heavy exposure to ultraviolet (UV) light from the sun [1]. The incidence of skin cancer is predicted to increase even further because of the depletion of the stratospheric ozone layer [2]. The development of chemopreventive strategies for skin cancer is thus a high public health priority. Residents of Arizona experience a three to seven times greater incidence of non-melanoma skin cancer than the general population in the United States [3]. Our goal is

the development of oral agents that will complement primary skin cancer prevention.

Black tea has been shown to have a preventative effect against skin carcinogenesis in animal models [4–9]. Of particular interest are the accumulating data that reflect similar potential health benefits associated with both the epicatechins of green tea and the theaflavins of black tea [10,11]. Several mechanisms may be responsible for the anti-initiation and anti-promotion properties of black tea [5,10–15]

Citrus, in addition to providing an ample supply of vitamin C, folic acid, potassium, and pectin, contains a host of active phytochemicals. The mutagenicity-reducing activity per weight of peels of citrus fruits was considerably higher than that of their juices [16]. The two main compositional differences between peel and juice components are that the peel contains a higher concentration of ascorbic acid than the juice, and that the peel also contains higher concentrations of active components (d-limonene, hesperidin, naringin, and auraptene) than do the juice and pulp.

d-Limonene, which comprises > 90% of citrus peel oil, has demonstrated chemopreventive activity against a variety of chemically induced rodent cancers [17–22]. Several mechanisms of action may account for the antitumor activities of d-limonene [23–25]. Among citrus bioflavonoids, hesperidin and naringin have been tested as potential chemopreventive agents [26,27]. In our previous studies, we showed that citrus peel use [28] and consumption of hot (strong) black tea [29] were each independently associated with reduced risk of skin SCC. Neither study, however, explored the potential for a joint or synergistic effect of tea and citrus consumption. Therefore, the present study sought to examine the independent and interactive roles of citrus peel use and black tea consumption in skin SCC in Arizona, a population at high risk of skin SCC.

Subjects & Methods
Study population
Subjects and methods of the Southeastern Arizona Health Study (SEAHS) have been described previously [28,29]. Briefly, SEAHS is a population-based case-control study that was conducted from 1994–1996 with cases of SCC of the skin randomly selected from persons identified through the Southeastern Arizona Skin Cancer Registry. Cases were eligible if they were ≥ 30 years of age, had a histo-pathologically confirmed, non-metastatic SCC of the skin diagnosed within the past 4 months, with no prior history of a skin cancer. Control subjects were recruited through a random-digit dialing process to reflect the age and gender distribution of the cases. One

control per household was invited to participate using modified Waksberg criteria [30]. Control subjects were considered eligible if they had no prior history of skin cancer, lived within the Tucson region, and were within the age, gender, and ethnicity grouping. All subjects (404 cases and 391 controls) completed an extensive interview for demographic, behavioral, and past ultraviolet exposure information. A subset of the total study population (n = 566), namely those who also completed 24-hour dietary recalls, were asked to complete the citrus and tea consumption questionnaires, yielding 450 subjects (234 cases and 216 controls) in this study (tea & citrus).

Citrus & tea questionnaires
Citrus (CQ) and tea (TQ) questionnaires were developed after a series of focus groups. Both questionnaires were tested for short and long term reliability as well as relative validity (diet methods). CQ asked detailed information on consumption of each type of citrus fruit and juice. In addition, the questionnaire asked how the juice was stored, i.e. types of containers, and whether citrus juices and citrus peel were added during food preparation and/or food serving [28]. TQ asked about usual tea intake over the past year, as well as a lifetime consumption pattern and how the past year intake differed from the lifetime pattern (amount or type or preparation techniques). Detailed information was collected for the past year's tea intake for each type of tea consumed (black, green or herbal and hot or iced) [29].

Other variables
All participants completed a structured interview detailing personal, behavioral, and demographic characteristics. This interview instrument sought information on: skin characteristics, sunburns and tanning history, use of suntan lotions and sunscreens, residential history, UV exposure during past year, family history of skin cancer, past medical history, tobacco and alcohol use, physical characteristics, and demographic information. All subjects also completed four 24-hour dietary recalls, which included 4 randomly selected days within two weeks of the clinic visit. Daily mean nutrient intakes were calculated with the use of the Minnesota Nutrition Data System [31].

Quality control
All interviews were conducted by trained, experienced interviewers. One interviewer conducted over 90% of the personal interviews and 100% of the dietary recalls, and citrus and tea questionnaires. At the time of CQ and TQ, the interviewer was unaware of the case-control status of the subjects. She was given a computer-generated list that included only names and phone numbers of subjects. After each interview, questionnaires were reviewed for completeness and coded. Data entry was through

screen-based entry programs that included range checks.

Data analyses

Distribution of demographic characteristics and potential risk factors were compared between cases and controls using *t* tests for continuous variables and Chi-square $(X)^2$ tests for categorical variables. Chi-square $(X)^2$ tests for trend were also calculated. To assess the risk of skin SCC with citrus peel use and black tea intake, crude and adjusted odds ratios (ORs) with their 95 percent confidence intervals (C.I.) were estimated with logistic regression models.

We assessed the potential confounding effects of age, sex, education, energy intake (kcal/day), fat intake (mean percent of kcal as fat), retinol and carotenoids (ug/day), vitamin C (mg/day), α-tocopherol (mg/day), foods rich in carotenoids (servings/week), alcohol intake (mean alcohol intake/day), smoking history (never, former smoker, and current smoker), body mass index (kg/ht in m^2), daily hours of sun exposure during the past year, history of actinic skin damage (self-reported physician-diagnosed actinic keratosis), self-reported ability to tan after prolonged sun exposure (no suntan, mildly tan, moderately tan, and deeply tan), and number of current freckles on the arms. The initial adjusted model included age, sex. Inclusion of energy intake, fat intake, antioxidant vitamins (vitamin A, E and C) or carotenoid intake, alcohol intake, smoking status, education, and daily hours of sun exposure did not alter any of the results and were excluded from the final model.

Age, sex, inability to tan after prolonged sun exposure, number of current freckles on the arms, and history of diagnosed and treated actinic keratosis (AK) were included in the final multivariate model. All statistical analyses were done using STATA computer software [32].

Results

A total of 263 men and 187 women who had participated in the SEAHS are included in this current study. Since this evaluation of citrus peel and tea consumption in relation to skin SCC was completed in a subset of the original participants, we compared subjects who participated in this study with those who did not participate. We found no statistically significant difference between the two groups in relation to case-control status, gender, education, smoking, average hours in sun per day in past year, and tanning ability. Participants in the current study did report more AK history than subjects who did not participate in the study, with the increase being consistent for cases and controls.

Table 1 shows the distribution of cases and controls according to sex, age, smoking status, alcohol intake, reported tanning ability, history of AK, number of current freckles on the arms, and daily hours of sun exposure during the past year. Information from CQ and TQ, as citrus peel use, hot and iced black tea consumption, are also included. The study population is an older educated Southwestern United States population with 68.8% of cases and 66.2% of controls having some college education. There was no difference between the cases and controls in antioxidants intake (retinol in μg/day, β-carotene in μg/day, α-carotene in μg/day, lycopene in μg/day, α-tocopherol in mg/day, and vitamin C in mg/day). There were also no differences between the cases and controls in the number of years they have lived in Arizona, and in the reported usual hours spent in the sun. Cases reported spending in the past year, on average, 1.38 hours in the sun during peak hours compared to 1.49 hours for controls. Only tanning ability, history of AK, number of current freckles on the arms, citrus peel use and hot black tea consumption showed a significant difference between cases and controls.

In this Arizona population, 66.4% and 34.5% reported some tea drinking and some citrus peel use, respectively, during the past year. Controls were more likely than were cases to report citrus peel use (39.2% versus 30.2%, with an OR of 0.67) and hot tea intake (35.7% versus 26.1%, with an OR of 0.79).

Table 2 shows the ORs for citrus peel use and tea intake controlling for the other variables. The OR of skin SCC associated with any citrus peel use was 0.67 (95%CI = 0.45 − 0.99). Adjustment for hot tea intake resulted in a decrease in the OR to 0.55 (95%CI = 0.34 − 0.91), while adjustment for iced tea consumption did no change the OR (OR = 0.69; 95%CI = 0.45 − 1.05). Further adjustment for age, gender, AK, tanning ability and number of current freckles on the arms resulted in marked decrease in ORs to 0.34 (95%CI = 0.18 − 0.62) and 0.54 (95%CI = 0.33 − 0.89) among hot and iced tea drinkers respectively.

Taking non-tea drinkers as the reference group, the OR of skin SCC was 0.79 (95% CI = 0.49 − 1.26) for drinkers of hot tea compared to 1.14 (95%CI = 0.76 − 1.72) for drinkers of iced tea. After adjustment for citrus peel use, the ORs increased to 0.87 (95%CI = 0.54 − 1.39) and 1.22 (95% CI = 0.81 − 1.84) for drinkers of hot and iced tea respectively. However, in the final model the ORs of skin SCC decreased to 0.65 (95%CI = 0.37 − 1.15) and 1.06 (95%CI = 0.37 − 1.15) among hot and iced tea drinkers respectively.

Table 1: Selected characteristics of skin SCC cases and control participating in SEAH study

		Cases N = 234 Mean + SD or %	Controls N= 216 Mean + SD or %	P
Age (mean + SD)		66.6 + 10.4	66.2 + 11.1	0.75
Male (%)		59.0%	57.9%	0.81
Alcohol [a]	Yes	78.7%	81.8%	0.53
Smoking :	Never	36.8%	37.5%	
	Former	51.7%	46.8%	
	Current	11.5%	15.7%	0.36
Hours in Sun [d]	(h/day)	1.38 + 0.1	1.49 + 0.1	0.35
AK [a]	Yes	78.2%	37.0%	0.000
Tanning [b]	Yes	68.8%	81.0%	0.001
Freckles [c]	No	50.6%	61.5%	0.005
Citrus peel use:	Yes	30.2%	39.2%	0.045
Hot tea intake:	Yes	26.1%	35.7%	0.028
Iced tea intake	Yes	53.4%	50.0%	0.47
Kcal/day (mean +	SD)	1499.9 + 396.3	1531.8 + 433.5	0.41
Antioxidants (mean + SD)				
Retinol (μg/day)		474.5 + 23.2	449.4 + 23.8	0.45
β-Carotene (μg/day)		92.4 + 7.1	87.6 + 7.8	0.65
α-Carotene (μg/day)		722.9 + 52.3	777.9 + 63.0	0.50
Lycopene (μg/day)		5882.9 + 359.7	5440.2 + 419.4	0.42
α-Tocopherol (mg/day)		7.1 + 1.1	6.4 + 0.5	0.57
Vitamin C (mg/day)		110.7 + 4.5	109.5 + 4.0	0.84

a: Based on 4–24 hour dietary recalls; b : History of treated actinic keratosis c: Moderate to deep tanning ability after prolonged sun exposure; d: Number of current freckles on the arms; e: Average hours per day during past year spent outside during peak sun expressed as mean (SD).

Table 2: Odds ratios and 95% confidence intervals from multivariate analyses for skin SCC

Model		Citrus peel OR (95% C.I.)	Black tea OR (95% C.I.)
Hot Black tea			
-	Citrus peel	0.67 (0.45 – 0.99)	—
-	Hot tea	—	0.79 (0.49 – 1.26)
-	Citrus peel + hot tea	0.55 (0.34 – 0.91)	0.87 (0.54 – 1.39)
-	The above + age & gender	0.54 (0.32 – 0.90)	0.84 (0.52 – 1.36)
-	The above + SCC risk factors [*]	0.34 (0.18 – 0.62)	0.65 (0.37 – 1.15)
Iced Black tea			
-	Citrus peel	0.67 (0.45 – 0.99)	—
-	Iced tea	—	1.14 (0.76 – 1.72)
-	Citrus peel + iced tea	0.69 (0.45 – 1.05)	1.22 (0.81 – 1.84)
-	The above + age & gender	0.69 (0.45 – 1.07)	1.21 (0.80 – 1.84)
-	The above + SCC risk factors [*]	0.54 (0.33 – 0.89)	1.06 (0.37 – 1.15)

[*] History of treated actinic keratosis, tanning ability after prolonged sun exposure and number of current freckles on the arms.

The independent and combined effects of citrus peel and hot black tea consumption are shown in Table 3. Among those who did not consume citrus peel, 38.8% (38/98) of the cases compared to 44.3% (39/88) of controls consumed hot black tea (p = 0.44). Whereas among those who did report citrus peel use, 59.0% (23/39) of cases

Table 3: Independent and interactive effects of hot black tea consumption and citrus peel use on the risk of skin SCC

Intake Citrus peel factors	Hot black tea	Cases No.	Controls No	Crude	OR (95% confidence Interval) Adjusted for age & gender	Adjusted for age, gender & SCC risk
no	no	60	49	1	1	1
no	yes	38	39	0.80 (0.44 – 1.42)	0.75 (0.41 – 1.37)	0.60 (0.30 – 1.23)
yes	no	16	27	0.48 (0.23 – 0.99)	0.45 (0.22 – 0.97)	0.30 (0.13 – 0.72)
yes	yes	23	38	0.49 (0.26 – 0.94)	0.47 (0.24 – 0.92)	0.22 (0.10 – 0.51)
P for trend				0.013	0.012	0.000

compared to 58.5% (38/65) of controls consumed hot black tea (p = 0.96). On average, 21% of the subjects reported consumption of both citrus peel and hot tea (16.8% in cases vs 24.8% controls).

Compared with those who did not consume hot black tea or citrus peel, the adjusted ORs associated with sole consumption of hot black tea or citrus peel were 0.60 (95% CI = 0.30 – 1.23) and 0.30 (95% CI = 0.13 – 0.72), respectively. Subjects who reported consumption of both hot black tea and citrus peel had a significant marked decrease in risk of skin SCC. (OR= 0.22; 95% CI = 0.10 – 0.51).

Similarly, the independent and combined effects of citrus peel and iced black tea consumption are shown in Table 4. Among those who did not consume citrus peel, 56.5% (78/138) of the cases compared to 55.9% (62/111) of controls consumed iced black tea (p = 0.92). Whereas among those who did report citrus peel use, 74.6% (47/63) of cases compared to 62.5% (45/72) of controls consumed iced black tea (p = 0.13). On average, 24% of the subjects reported consumption of both citrus peel and iced tea (20.4% in cases vs 24.6% controls).

Compared with those who did not consume iced black tea or citrus peel, the adjusted ORs associated with sole consumption of iced black tea and citrus peel were 0.91 (95% CI = 0.46 – 1.45] and 0.32 (95% CI = 0.14 – 0.75), respectively. Subjects who reported consumption of both iced black tea and citrus peel had lower risk of skin SCC (OR= 0.58; 95% CI = 0.30 – 1.12).

Table 4: Independent and interactive effects of iced black tea consumption and citrus peel use on the risk of skin SCC

Intake Citrus Peel	Iced black tea	Cases No.	Controls No.	Crude	OR (95% confidence Interval) Adjusted for age & gender	Adjusted for age, gender & SCC risk factors
no	no	60	49	1	1	1
no	yes	78	62	1.02 (0.62 – 1.69)	1.00 (0.60 – 1.67)	0.91 (0.46 – 1.45)
yes	no	16	27	0.48 (0.23 – 0.99)	0.47 (0.22 – 0.99)	0.32 (0.14 – 0.75)
yes	yes	47	45	0.85 (0.49 – 1.49)	0.84 (0.48 – 1.50)	0.58 (0.30 – 1.12)
P for trend				0.29	0.30	0.04

Discussion

Arizona has one of the highest risks of skin SCC worldwide and tea beverages, as well as, citrus products are commonly consumed by Arizonans. This older Arizona population offered a unique opportunity to study potential associations between consumption of tea and/or citrus peel and risk of skin SCC. In this population, two-thirds of all subjects reported black tea consumption in the previous year compared to about one third reporting citrus peel use. Our data showed that persons without

skin cancer significantly consumed more citrus peel and hot black tea than did cases of skin SCC. We have previously demonstrated that among Arizonans [29], black tea beverages were prepared and consumed in various ways and that iced tea beverages were more likely to be prepared diluted.

Laboratory investigations support the capability of citrus peel or its major constituents, d-limonene, and also the ability of tea extract or its constituents, tea polyphenols to reduce not only the incidence and tumor size of chemically-induced tumors at several sites [4,8,9,17,18,20,22] but also the growth of various tumor cells in culture [11,33]. Both d-limonene, representative of citrus peel, and tea polyphenols, representative of black tea, are known to impact antiproliferative effects, including apoptosis, on neoplastic cells [4,34–37]. Dietary d-limonene has been shown to be effective in the chemoprevention and chemotherapy of cancer. As a result, its cancer chemotherapeutic activities are under evaluation in Phase I human clinical trials [38,39]. Moreover, much research has been focused on the potential use of flavonoids (in citrus and tea) as inhibitors of neoplastic transformation [40] and as free radical scavengers to prevent oxidative skin damage [41,42]

Oxidative damage is one of the many mechanisms leading to skin cancer and other chronic diseases. Black tea is a good source of antioxidants and addition of lemon to tea increases its antioxidant potential [43]. Our data indicates that among older Arizonans, citrus peel use and hot black tea intake were each independently associated with reduced risk of skin SCC. However, among these study subjects, citrus peel use was associated with a more than 70% reduced risk for skin SCC, whereas hot black tea consumption alone conferred 40% reduced risk for skin SCC. Moreover, the present study suggested that a dietary pattern that includes the consumption of both hot black tea and citrus peel markedly decreased the risk of skin SCC (ORs = 0.22 – 0.58). Even though iced black tea consumption alone was not associated with reduced risk of skin SCC (OR = 0.91), consumption of both iced black tea and citrus peel was associated with lower risk of skin SCC (OR = 0.58). Among Arizonans, citrus peel was reported to be frequently consumed along with iced tea beverages at meals.

Some limitations and strengths of the study deserve consideration. In case-control studies, the possibilities for recall and interviewer bias are a major concern. Differential recall of tea and citrus consumption between cases and controls can lead to biased estimates of effect. Furthermore, since there was a lag between diagnosis of the skin cancer and interview (average of 4 months), there is potential for cases to have altered their behavior and to then report their recently changed behaviors. Several steps were taken to reduce potential bias. Standard questionnaires were administered to all subjects by a trained interviewer who was not aware of the case-control status of the subjects at the time of the tea and citrus questionnaire administration. There is some evidence, however, that skin cancer cases did recently alter their behavior for risk factors they thought were related to skin cancer. For instance, they reported similar recent (past year) exposure to the sun to the controls. The interview did not record information on sun exposure experiences in the more distant past; however, given that skin SCC is related to other measures of high UV exposure (i.e. history of actinic keratosis, history of sunburns), then the lack of a finding for a differential sun exposure history for cases and controls argues for a change in behavior since the diagnosis of the skin cancer.

However, while it appears that the cases did modify some of their behaviors, there is no evidence that they recently altered their consumption of tea or citrus products. Also, since there have been no prior studies of skin cancer occurrence and tea or citrus consumption, it is unlikely that this population would have considered tea or citrus peel consumption, or lack of consumption, to be related to their risk of skin cancer. Public perception of tea and citrus consumption has been that there would be no difference in the potential effect of tea or citrus based on different products.

This study controlled for important confounding factors, including history of physician-diagnosed actinic keratosis, tanning ability, and number of current freckles on the arms. Consumption of citrus peel along with black tea appeared to be generally protective. Significant independent inverse associations between citrus peel use and skin SCC were observed. Moreover, a synergistic and/or additive effect(s) on skin SCC risk was observed when both citrus peel and black tea were consumed. While this study was only of moderate sample size, particularly when exploring relationships within subgroups of different consumption patterns, we were able to observe a significant protective effect for citrus peel and hot black tea consumption in relation to skin SCC.

Competing interests

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