Original Article

Tea and lycopene protect against prostate cancer

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Prostate cancer is the most common male cancer in developed countries and is increasing in the developing world. Its long latency and geographical variation suggest the possibility of prevention or postponement of onset by dietary modification. To investigate the possible joint effect of lycopene and green tea on prostate cancer risk, a case-control study was conducted in Hangzhou, China, with 130 prostate cancer patients and 274 hospital controls. Information on tea and dietary intakes, and possible confounders was collected using a structured questionnaire. The risk of prostate cancer for the intake of tea and lycopene and their joint effect were assessed using multivariate logistic regression models. Prostate cancer risk was reduced with increased consumption of green tea. The protective effect of green tea was significant (odds ratio 0.14, 95% CI: 0.06-0.35) for the highest quartile relative to the lowest after adjusting for total vegetables and fruits intakes and other potential confounding factors. Intakes of vegetables and fruits rich in lycopene were also inversely associated with prostate cancer risk (odds ratio 0.18, 95% CI 0.08-0.39). Interaction analysis showed that the protective effect from tea and lycopene consumption was synergistic (*p*<0.01). This study suggests that habitual drinking tea and intakes of vegetables and fruits rich in lycopene could lead to a reduced risk of prostate cancer in Chinese men. Together they have a stronger preventive effect than either component taken separately. This is the first epidemiological study to investigate the joint effect between tea drinking and lycopene intake.

Key Words: green tea, lycopene, prostate cancer, joint effect, China

Introduction

Prostate cancer is the most commonly diagnosed non-skin cancer in men in western countries. In contrast, the incidence in developing countries such as China is considerably lower (age standardized rate, ASR 1.7/100,000). Large difference in incidence has been noted between different racial and ethnic groups with the highest in the USA (ASR 104/100, 000).[1, 2] Studies on immigrants from Asian countries to North America revealed that the incidence of prostate cancer increased in immigrants compared with their native population.[3, 4] The geographic variations in incidence rate and the increased incidence in immigrants suggest a significant role of environmental factors, including nutrition, for developing the disease. The sharp increase incidence of prostate cancer worldwide in recent decade can be partly attributed to the increase in PSA screening. Whilst PSA testing is popular in China, PSA screening is not widespread and prostate cancer is typically diagnosed at an advanced stage. Thus, it is important to put forward strategies for primary prevention.

Recent studies have shown that regular drinking tea and consumption of diet rich in vegetables and fruits are associated with the reduced risk of cancers.[5-8] Green tea may induce apoptosis and inhibit cancer cell growth through their antioxidant properties and by causing cell cycle arrest.[9, 10] Two recent case-control studies evaluated green tea and prostate cancer risk in Asian countries.[6, 11] Both studies received high methodological quality ratings from the US FDA.[12] The Chinese study showed drinking three cups of green tea per day was significantly associated with a reduced risk of prostate cancer (odds ratio 0.27, 95% CI 0.15-0.48).[6] However the Japanese study reported that drinking two to ten cups of green tea per day was not significantly associated with prostate cancer risk (odds ratio 0.67, 95% CI 0.27-1.64).[11] A double-blind, placebo-controlled clinical trial in Italy using 600 mg/d green tea catechins has shown encouraging results.[7]

Red-orange, dark green vegetables and fruits are rich sources of carotenoids, including lycopene, carotene, lutin, zeaxanthin and cryptoxanthin. Lycopene gives the red color to foods including tomatoes, tomato products, watermelon, pink grapefruit, apricots, papaya and pink guavas. In Western countries, over 80% of dietary lycopene comes from the consumption of tomatoes and tomato-based products including tomato sauce/juice/soup, spaghetti sauce, salsa, chili, pasta and pizza sauce.[14, 15] The ability of lycopene to act as an antioxidant and scavenger of free radicals is considered as the most likely mechanism that could account for the hypothesized beneficial effects on human health. Lycopene may quench singlet oxygen, interact with reactive oxygen species and prevent oxidative damage to lipoproteins and DNA.[13] It may increase cell cycle arrest and induction of apoptosis in human prostate cancer cell lines.[16, 17] A well-designed animal study compared the effects of different diets on rats (n=194).[18]

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Rats fed with tomato powder experienced a significant (26%) decrease in prostate cancer specific mortality. The epidemiological study providing the strongest evidence thus far concerning tomatoes and prostate cancer prevention was a cohort study in the USA.[19] This study followed 47,894 men. Raw tomatoes and tomato sauce were the only fruits or vegetables from a 131-item FFQ found to be associated with a reduced risk of prostate cancer with RR=0.74 (95% CI: 0.58-0.93) and RR=0.66 (95% CI: 0.49-0.90), respectively. Our recent case-control study in Chinese men also showed a protective effect of red-orange vegetables and fruits rich in carotenoids against prostate cancer.[20]

The majority of studies so far have focused on individual foods or nutrients. However free-living populations are simultaneously exposed to a variety of food items in one meal. Phytochemicals in whole meals may behave differently to individual compounds given in experimental situations. These complex exposure situations may result in different health outcomes. Thus, investigating the health benefit of different diets and phytochemicals in terms of their joint effects is necessary in order to understand their underlying protective mechanism against cancers. This study aims to assess the possible joint effect of tea and lycopene on prostate cancer risk.

Methods
Subjects
The subjects were men residing in Zhejiang Province for at least 10 years and over 45 years of age. They were recruited during 2001 and 2002 at eight public hospitals in Hangzhou, capital of Zhejiang Province located in southeast China. Potential participants with a history of stroke or Alzheimer's disease were excluded to avoid memory error. Cases were confirmed by histopathological reports of prostate adenocarcinoma. Controls were recruited in the same hospitals during the same period and had no previous diagnosis of malignancies confirmed by physical examination, x-ray, operation or biopsy. Among the 140 cases recruited, 130 (93%) were interviewed and 10 (7%) declined to participate in the study, including one with Alzheimer's disease. Of the 284 eligible controls identified, 274 (96.5%) participated in the study. Two men (3.5%) with Alzheimer's disease and one with a history of stroke were excluded.

Data collection
The interviews were conducted using a structured questionnaire which included a quantitative FFQ component. The interviewer was blind to the final diagnosis when doing the interviews. The study protocol included instructions to follow the printed questionnaire exactly to avoid bias. The reproducibility and validity of the FFQ were assessed by several methods.[21] Information on demographic characteristics, family history of prostate cancer, height, weight and physical activity, and medical history were also collected. A reference recall period (5 years before diagnosis for cases and 5 years before interview for controls) was adopted. Interviews were usually conducted in the presence of next-of-kin to assist in recall. The study was approved by the Human Research Ethics Committee of Curtin University, the Zhejiang hospital

administration and the doctors in charge of the relevant wards. Informed consent was sought prior to interview.

Dietary assessment
The FFQ contained questions on 130 food items including all foods in the usual diet of Zhejiang residents. The habitual frequencies and quantities of foods consumed per meal were recorded.

Tea assessment
Tea drinking questions included both qualitative and quantitative measurements. Participants were first classified as "ever" or "never" (less than once per month) habitual tea drinkers. Information on consumption pattern was then collected from those "ever" tea drinkers. The details of measurement can be obtained from our previous paper.[6]

Physical activity assessment
Information on habitual physical activity was assessed in terms of type, intensity and duration. Daily metabolic equivalent task (MET) scores were calculated by multiplying the reported duration of any activity by the respective intensity score and then summing over all activities.[22]

Statistical analysis
The data analysis was undertaken using the SPSS package (version 11; SPSS Inc., Chicago, IL, USA). Independent-samples t, Mann-Whitney and Chi-square tests were used to compare the demographic characteristics and potential risk factors between cases and controls. Energy and nutrient intakes were calculated using the Chinese nutrient database established by the Institute of Nutrition and Food Health, Chinese Academy of Preventive Medicine.[23] Conversion of lycopene from food items was undertaken using the U.S. Department of Agriculture Database (USDA) because of no available Chinese database.[24] The level of supplementations among the participants were very low, therefore, they were not included in the analysis. Risk of prostate cancer for the intake of tea and lycopene and their joint effect were assessed by odds ratios (ORs) and their 95% confidence intervals (95% CI) using unconditional multivariate logistic regression models. Each fitted regression equation adjusted for age, height, weight, body mass index (BMI), locality, education, income, marital status, family history of prostate cancer, physical activities (MET), intakes of fat and caloric. The quantities of tea and lycopene intakes were classified into quartiles. Adjusted ORs were obtained with the lowest quartile as the reference category. In addition, when assessing green tea consumption, fresh vegetables and fruits were included for adjustment in the model. Meanwhile, when assessing lycopene intakes, green tea intakes were weighted in the model. When assessing their joint effect, a new variable (joint effect of tea and lycopene) was generated according to the match of each pair of established quartiles. For example, if the case was both in the lowest quartile of green tea and lycopene consumptions, he was classified into the lowest quartile of the new variable, and vice versa. If intakes of green tea and lycopene were not in the same category (level) e.g. green tea intake was in the lowest quartile but lycopene intake wasn't, they were

Table 1. Characteristics of participants

	Cases (N =130)	Controls (N =274)
Age at interview, mean years (SD)	72.7 (7.1)	71.4 (7.2)
Height, mean cm (SD)	168 (5.3)	169 (5.6)
Weight*, mean kg (SD)	66 (10.3)	65 (9.9)
BMI*, mean kg m^{-2} (SD)	23.4 (3.1)	22.7 (3.1)
Locality of residence, N (%)		
Urban	97 (74.6)	207 (75.5)
Rural	33 (25.4)	67 (24.5)
Education, N (%)		
No formal education	18 (13.8)	29 (10.6)
Primary	37 (28.5)	78 (28.5)
Secondary	44 (33.8)	110 (40.1)
Tertiary	31 (23.8)	57 (20.8)
Personal monthly income in 2000(RMB), N (%)		
≤ 500	24 (18.5)	50 (18.2)
501-1000	55 (42.3)	113 (41.2)
1001-2000	43 (33.1)	99 (36.1)
≥ 2001	8 (6.2)	12 (4.4)
Marital status, n (%)		
Married,	114 (87.7)	245 (89.4)
Widowed, divorced, separated	16 (12.3)	29 (10.6)
Prostate cancer in first-degree relatives*, N (%)		
No	111 (85.4)	241 (88.0)
Yes	3 (2.3)	0 (0.0)
Unclear	16 (12.3)	33 (12.0)
Weekly MET	157 (59.2)	157 (55.4)
Fat, mean g day^{-1}(SD)	60.3 (24.6)	56.2 (20.7)
Calorie, mean kcal day^{-1}(SD)	2386 (809)	2333 (619)
Fresh vegetables and fruits*, mean g day^{-1}(SD)	500 (321)	865 (478)
Drink tea*, N (%)		
No	58 (44.6)	55 (20.1)
Yes	72 (55.4)	219 (79.9)

* $p<0.05$

Table 2. Quartiles of green tea, lycopene and their joint effect on prostate cancer risk

	Cases	Controls	Crude OR	(95.0 % C.I.)	OR†	(95.0% C.I.)
Green tea leaves (g day^{-1})						
(1) 0	58	53	1.00		1.00	
(2) 0.3-2.9	50	110	0.42	(0.25-0.69)	0.45	(0.25-0.82)
(3) 3.0-4.9	13	48	0.25	(0.12-0.51)	0.24	(0.10-0.57)
(4) ≥5	9	63	0.13	(0.06-0.29)	0.13	(0.05-0.32)
Lycopene (μg day^{-1})						
(1) <1609	55	68	1.00		1.00	
(2) 1609-3081	32	69	0.57	(0.33-0.99)	0.47	(0.25-0.86)
(3) 3081-4917	30	69	0.54	(0.31-0.94)	0.40	(0.21-0.77)
(4) >4917	13	68	0.24	(0.12-0.47)	0.17	(0.08-0.39)
Joint effect of tea & lycopene						
(1) Low	24	15	1.00		1.00	
(2) Other combinations ‡	92	192	0.30	(0.15-0.60)	0.28	(0.13-0.59)
(3) Middle	11	31	0.22	(0.09-0.57)	0.21	(0.08-0.57)
(4) High	3	36	0.05	(0.01-0.20)	0.03	(0.01-0.16)

†Variables adjusted for: age at interview, locality (urban, rural), education (none, primary, secondary, tertiary), family income (RMB, ≤500, 501-1000, 1001-2000, ≥2001), marital status (married, widowed/divorced/separated), family history of prostate cancer (yes, no, uncertain), MET, BMI, fat intakes and calories. In addition, when analyzing green tea leaves intakes, total fresh vegetables and fruits were adjusted and when analyzing lycopene intakes, green tea consumption was adjusted. ‡Intakes of green tea and lycopene were not in the same category (level) e.g. green tea intakes in the lowest quartile bur lycopene intakes in the highest quartile

categorized as "other combinations".

Results

Table 1 shows the characteristics of the participants. Demographic characteristics such as age, education, income and marital status were similar in both groups, as well as fat and caloric intakes. Compared with the controls, cases tended to have higher BMI, more prostate cancer patients in the family, drank less tea and ate less fresh vegetables and fruits.

The relationships between green tea drinking, lycopene intakes and prostate cancer risk are presented in Table 2.

Table 3. Interactions of tea and lycopene on prostate cancer using binary variables

	Lycopene intakes	Cases (%)	Controls (%)	Adjusted OR (95%CI)	p
Green tea drinking					
Low	Low	74 (56.9)	88 (32.1)	1.00	
Low	High	34 (26.2)	75 (27.4)	0.44 (0.25-0.78)	0.005
High	Low	13 (10.0)	49 (17.9)	0.26 (0.13-0.54)	0.000
High	High	9 (6.9)	62 (27.6)	0.11 (0.05-0.26)	0.000
Interaction				0.20 (0.09-0.44)	0.000

[†]Variables adjusted for: age at interview, locality, education, family income, marital status, family history of prostate cancer, MET, BMI, fat intakes and calories.

After adjusting for age, family history of prostate cancer and other demographic characteristics, BMI, MET, fat, caloric and fresh vegetables and fruits intakes, the OR was 0.13 (95% CI 0.05-0.32) for men who consumed at least 5 g green tea leaves daily compared with non-tea drinkers. Similarly, men who consumed over 4917μg of lycopene daily had adjusted OR 0.17 (95% CI 0.08-0.39) compared with the lowest quartile (<1608.6μg day^{-1}) of intake.

The possible joint effects and interactions of tea and lycopene on prostate cancer risk are presented in Table 2 and Table 3. Compared with the independent effects of tea and lycopene on the cancer risk, the joint effect was 0.03 (95% CI 0.007-0.164) in high dose combination group relative to low dose combination group. The adjusted OR was 0.11 (95%CI 0.05-0.26) for high dose of both green tea and lycopene intakes relative to low dose of tea and lycopene intakes.

Discussion

Many risk factors such as age, race, and family history cannot be controlled. However, research on risk of prostate cancer suggests that some environmental and lifestyle factors might be modified to achieve better outcome in terms of decreasing the risk of the cancer.[5, 6, 14, 25] In this study, we observed the synergistic protective effect of green tea and lycopene against prostate cancer.

In recent years, there are increasing number of epidemiological studies on "functional food" and their correlations with cancers. Phytochemicals in plants are often considered as the major bioactive compounds with human health benefits linked to their antioxidant activities. Unfermented green tea leaves contain up to 30 percent dry weight of tea polyphenols.[24] Lycopene is the most abundant carotenoid in tomatoes, tomato products and watermelon. While both green tea and lycopene have been shown to prevent prostate cancer, we have found no published studies examined their joint effects on prostate cancer. As prostate cancer is a multifactor disease and food is consumed in meals, studies of the interactions of protective factors may provide useful information on prevention. The joint effects and the high consumption of tea and fresh vegetables and fruits in Asian countries may partially explain the different clinical incidence of prostate cancer between countries. To the best of our knowledge, this is the first report that investigated the possible joint effect of green tea and lycopene consumption on prostate cancer risk in Chinese people, a population with low risk of the cancer.

Nevertheless, attempt to investigate the joint effect of dietary factors on the risk of prostate cancer via a case-control study is vulnerable to selection and information bias. However, effort has been made to minimize the selection bias by recruiting participants from eight major public hospitals including four provincial hospitals and four city hospitals in Hangzhou. The low refusal rate of participation in both case and control groups may also indirectly demonstrate our effort in minimizing selection bias. Because of the latency of the cancer, the reference recall period was set at five years before diagnosis for cancer cases and five years before interview for controls. Therefore, the food and tea consumptions could represent habitual intakes before the onset of the disease. More detailed information on tea and food consumption was collected in our study than other studies such as a recent cohort study from Japan, in which, only one question related to tea consumption and 36 on food items.[26] In addition, the relationship of tea, lycopene, and prostate cancer risk was not established at the time of interview, so that information bias could be assumed to be minimum. Furthermore, people with Alzheimer' disease or recent stroke were excluded to avoid memory error. For participants who neither shopped for food nor cooked meals, 97% of interviews were conducted in the presence of participants' next of kin to confirm the usual quantities and frequencies of habitual food and beverage consumption. Standard containers were shown to the participants to help in recall. To avoid inter-interviewer bias, a single interviewer conducted all interviews following the same protocol. In addition, the risk of prostate cancer was assessed using adjusted OR and accounted for possible confounders. In the logistic regression analysis, three sets of models were used separately to exam potential joint effects.

In summary, diets rich in lycopene and green tea are inversely related to the prostate caner risk, together, they offer stronger preventive effect. This preliminary study may provide an example for nutritional cancer epidemiological studies for assessing the joint effect of foods and nutrients on cancer risks. Further laboratory study is needed to understand the molecular mechanism and biochemistry of the joint effect between phytochemicals.

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