RESEARCH ARTICLE

No Association Between Tea Consumption and Risk of Renal Cell Carcinoma: A Meta-analysis of Epidemiological Studies

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Abstract

Objective: To evaluate the association between tea consumption and the risk of renal cell carcinoma. Methods: We searched PubMed,Web of Science and Scopus between 1970 and November 2012. Two evaluators independently reviewed and selected articles based on predetermined selection criteria. Results: Twelve epidemiological studies (ten case-control studies and two cohort studies) were included in the final analysis. In a meta-analysis of all included studies, when compared with the lowest level of tea consumption, the overall relative risk (RR) of renal cell carcinoma for the highest level of tea consumption was 1.03 (95% confidence interval [CI] 0.89–1.21). In subgroup meta-analyses by study design, there was no significant association between tea consumption and renal cell carcinoma risk in ten case-control studies using adjusted data (RR=1.08, 95% CI 0.84–1.40). Furthermore, there was no significant association in two cohort studies using adjusted data (RR=0.95, 95% CI 0.81–1.12). Conclusion: Our findings do not support the conclusion that tea consumption is related to decreased risk of renal cell carcinoma. Further prospective cohort studies are required.

Keywords: Tea consumption - renal cell carcinoma - meta-analysis - epidemiological studies

Asian Pacific J Cancer Prev, **14 (3)**, 1691-1695

Introduction

Renal cell cancer accounts for 2%–3% of all malignancies in western countries, while it is low in Asia (Cho et al., 2011). Although the etiology of renal cell carcinoma still remains contradictory, both genetic and environmental factors are considered to play important roles.

Well-established risk factors for renal cell carcinoma include smoking (Asal et al., 1988; Mellemgaard et al., 1994; McLaughlin et al., 1995; Yuan et al., 1998; Bulgheroni et al., 2000; Theis et al., 2008), high intake of meat (McLaughlin et al., 1984), beef (Maclure and Willett, 1990) and fatty food (Washio et al., 2005). Additional factors,such as low physical activity,body mass index, hypertension,occupational exposure and medical conditions, are thought to be associated with renal cell carcinoma risk (Dhote et al., 2000; Washio and Mori, 2009).

Tea has been one of the most widely consumed beverages in the world. It has been considered a health-promoting beverage since ancient times. Many studies reported that the beneficial effects of tea are related to their antioxidant effect, protection of DNA from damage and/or methylation, inhibition of proteasome activity in tumour cells, induction of apoptosis in tumour or transformed cells, cell cycle regulation, and inhibition of cell proliferation and tumour-promotion related events (Carlson et al., 2007; Qin et al., 2007; Chen and Dou, 2008; Yang et al., 2009).

Also, in epidemiological studies, such as case-control and cohort studies, the possible relationship between tea consumption and renal cell carcinoma risk has been investigated since the 1970s,and the findings are inconsistent. One case-control study reported that a higher consumption of tea significantly increased the risk of renal cell carcinoma (De Stefani et al., 1998), whereas seven case-control studies showed a non-significant positive association (McLaughlin et al., 1984; Goodman et al., 1986; Talamini et al., 1990; Kreiger et al., 1993; Mellemgaard et al., 1994; Bianchi et al., 2000; Hu et al., 2009), and two case-control studies showed a non-significant negative association between tea consumption and renal cell carcinoma (Montella et al., 2009; Wang et al., 2012). In contrast, one prospective cohort study reported that higher tea consumption could decrease the risk of renal cell carcinoma (Lee et al., 2007), while the other cohrot study showed that there was no significant association (Allen et al., 2011). However, no meta-analysis has been published regarding the relationship between tea consumption and renal cell carcinoma risk.

The purpose of the present study was to estimate the quantitative association between tea consumption and renal cell carcinoma risk by using a meta-analysis of case-

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Table 1. Characteristics of the Included Studies on Tea Consumption and Renal Cell Carcinoma

First author (year)	Country	Follow up period	Ethnicity	No. of cases,n	No. of controls or size of corhort,n	Range of tea consumption	Variables of adjustment	Tea assessment
Case-controlstudies(n=10)								
McLaughlin(1984)	USA	1979-1980	Caucasian	495	697	≥3 cups/d vs none	Age, cigarette smoking, and relative weight	Interview
Goodman(1986)	USA	1977-1983	Caucasian,	267	267	>2 cups of tea/d vs none	Quetelet index, ecaffeinated coffee use, pack-years and chewing tobacco use	Interview
Talamini(1990)	Italy	1986-1989	Caucasian	240	665	≥1 cups/d vs none	Age, sex, education, area of residence, and BMI	Interview
Kreiger(1993)	Canada	1986-1987	Caucasian	518	1369	≥5 cups/d vs <1 cup/d	Age, active cigarette smoking status, and combined Quetelet index	Questionnaire
Mellemgaar d (1994)	Denmark	1989-1992	Caucasian	368	396	>2 cups/d vs none	Age, socioeconomic status, BMI, and cigarette pack-years	Questionnaire
Stefani(1998)	Uruguay	1988-1995	Caucasian	121	243	Ever vs never	Age,sex, reskdence,urban-ruralstatus,education,tobacco smoking,BMI,red meat and vegetable intakes.	Questionnaire
Bianchi(2000)	USA	1986-1989	Caucasian	406	2434	>2.6 cups/d vs none	Age, education, smoking status, pack-years of smoking, family history of kidney cancer, hypertension, BMI, and dietary factors (intake of fruits, vegetables, meat, fat, coffee)	Questionnaire
Montella(2009)	Italy	1992-2004	Caucasian	767	1552	≥1 cups/d vs none	Sex, age, education,smoking, alcohol consumption, BMI, and physical activity	Questionnaire
Hu(2009)	Canada	1994-1997	Caucasian	1138	5039	>2.5 cups/d vs none	Age,province,education,BMI,sex,smoking,alcohol,consumption of meat, total consumption of vegetables and fruit, and total energy intake	Questionnaire
Wang(2012)	China	2007-2009	Asian	250	299	≥500ml/d vs <500ml/d	Sex,age,smoking status,alcohol consumption,BMI,hypertension,diabetes,urolithisasis,polymorphism	Interview
Cohort studies(n=2)								
Lee(2007)	USA	1980-2003	Caucasian	1478	774952	≥1/d vs nondrinker	Age, hypertension, BMI, smoking, parity and age at first birth, fruit and vegetable consumption, alcohol intake and total energy intake	Questionnaire
Allen(2011)	UK	1996-2001	Caucasian	588	779369	≥12 drinks/d vs 1-7 drinks/d	Socioeconomic status, BMI, smoking	Questionnaire

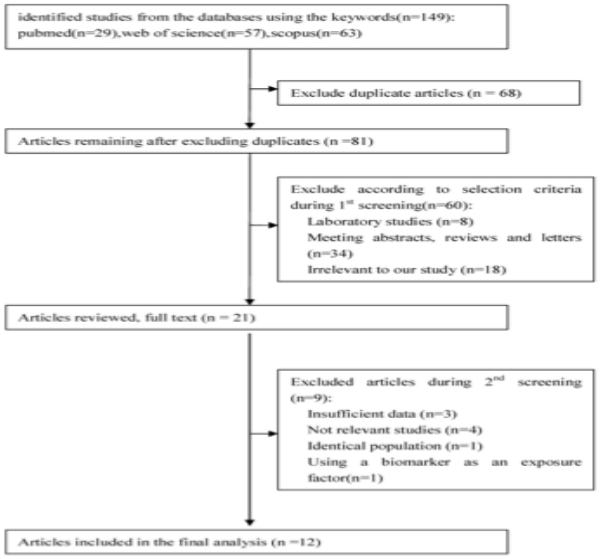

Figure 1. Process of Study Selection

control and cohort studies.We also performed subgroup meta-analyses based on the type of study design (case-control or cohort study), the geographical region of the studies (Europe, the USA/Canada or others) and type of exposure assessment (interview or questionnaire).

Materials and Methods

Literature research

We searched PubMed,Web of Science and Scopus between 1970 and December 2012 using common keywords regarding tea consumption and renal cell carcinoma risk in case-control and cohort studies. For the literature search, we selected 'tea' for the exposure factor and'renal cell carcinoma', 'renal cell cancer' for the outcome factors.

We included case-control and cohort studies reporting an association between tea consumption and renal cell carcinoma risk (no randomized controlled trials have been reported). We selected articles written in English and excluded those studies with no data available.

Figure 1 is a flow diagram of the procedure used to identify the relevant studies. A total of 12 articles were finally included in the meta-analysis (McLaughlin et al., 1984; Goodman et al., 1986; Talamini et al., 1990; Kreiger et al., 1993; Mellemgaard et al., 1994; De Stefani et al., 1998; Bianchi et al., 2000; Lee et al., 2007; Hu et al., 2009; Montella et al., 2009; Allen et al., 2011;Wang et al., 2012).

Data extraction

All searches were conducted independently by two evaluators, each of whom is a co-author of the present study.Disagreements between evaluators about selected studies were resolved by discussion. In instances in which data were insufficient or missing,we attempted to contact the authors of the articles to request the relevant data. Of the articles searched from the databases, those that did not meet selection criteria were excluded.

The following data were extracted from the studies included in the final analysis: study name (first author and year of publication), country and study design, study period (years), number of cases and controls, adjusted odds ratio (OR) or relative risk (RR) with 95% CI, level of tea consumption, adjustment factors and exposure assessment. Considering that renal cell carcinoma is a rare disease, the OR was assumed to be approximately the same as RR, and the RR was used as the study outcome. We used adjusted ORs or RRs with 95% CIs for meta-analysis,whenever possible.We also performed subgroup meta-analyses by the type of study design (case-control or cohort study), the geographical region of the studies (Europe, the USA/Canada or others) and type of exposure assessment (interview or questionnaire).

Statistical analysis

To determine whether to use the fixed- or random-effects model, we measured statistical heterogeneity between and within groups using the Q statistic, $P<0.05$ was considered statistically significant. We used fixed-effects methods if the result of the Q test was not significant. Otherwise, we calculated pooled estimates and confidence intervals assuming a random-effects model. While publication bias was not expected, we assessed this possibility using Begg's funnel plots and Egger's bias test. To validate the credibility of outcomes in this meta-analysis, sensitivity analysis was performed by sequential omission of individual studies. Analyses were conducted in Stata version 11.0 (Stata Corporation). All *P* values are two tailed.

Results

The present study included twelve epidemiological studies (ten case-control (McLaughlin et al., 1984; Goodman et al., 1986; Talamini et al., 1990; Kreiger et al., 1993; Mellemgaard et al., 1994; De Stefani et al., 1998; Bianchi et al., 2000; Hu et al., 2009; Montella et al., 2009; Wang et al., 2012) and two cohort studies (Lee

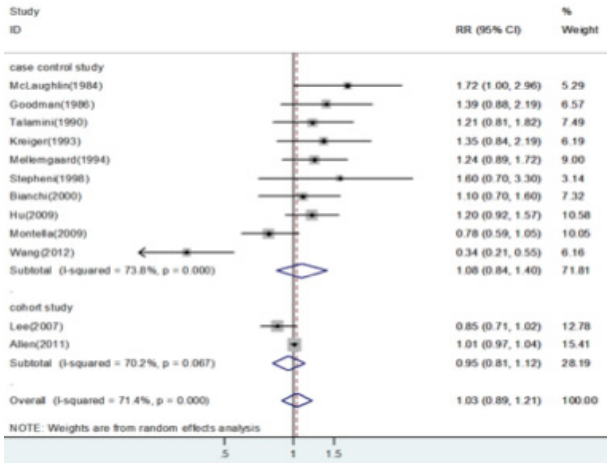

Figure 2. Forest Plot Showing Risk Estimates from Case-control and Cohort Studies Estimating the Association Between Tea Consumption and Risk for Renal Cell Carcinoma

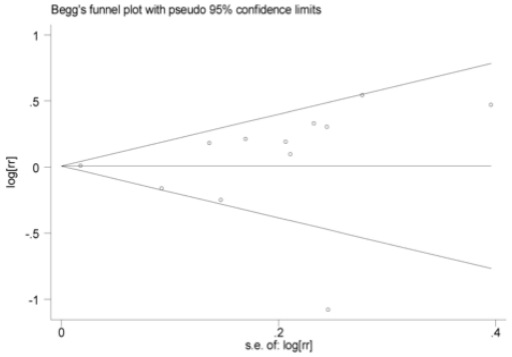

Figure 3. Begg's Funnel Plot of Tea Consumption and Renal Cell Carcinoma, with Pseudo-95% CI

et al., 2007; Allen et al., 2011)) published between 1984 and 2012.The general characteristics of the twelve studies included in the final analysis are presented in Table 1. Of the ten case-control studies, five were conducted in the USA/Canada (McLaughlin et al., 1984; Goodman et al., 1986; Kreiger et al., 1993; Bianchi et al., 2000; Hu et al., 2009), and the remaining five were conducted in Denmark (Mellemgaard et al., 1994), Italy (Montella et al., 2009), Uruguay (De Stefani et al., 1998), and China (Wang et al., 2012). Of the two cohort studies, one was conducted in UK (Allen et al., 2011), and the other one was conducted in the USA (Lee et al., 2007).

Figure 2 shows the association between tea consumption and renal cell carcinoma risk by using a meta-analysis of all 12 studies. Compared with the lowest consumption of tea, the pooled RR of the highest tea consumption and renal cell carcinoma risk was 1.03 (95% CI 0.89–1.19) in a random-effects model. There was no indication of publication bias from the Begg funnel plot (Figure 3) .

Figure 2 also shows the results from the subgroup meta-analysis by type of study design. In case-control studies, there was no significant relationship between tea consumption and renal cell carcinoma risk (RR=1.08, 95%CI 0.84–1.40),whereas there was no significant association in two cohort studies using adjusted data (RR=0.95, 95% CI 0.81–1.12) either.

The results of subgroup analyzes by geographical region (the USA/Canada, Europe, Uruguay and China) and tea dringking assessment (interview and questionnaire) are shown in Table 2. The RR estimates from subgroup analysis varied little, showing tea consumption was not associated with the likelihood of renal cell carcinoma when separately analyzed by geographical regions or tea assessment.

Table 2. Summary of Pooled Ralative Risk (RRs)for Renal Cell Carcinoma by Study Design, Geographical Region, and Tea Assessment

Subgroup	Number of studies	Pooled RR (95% CI)	Q-test for heterogeneity *P*-value (I^2 score)	Egger test *P*-value	Begg test *P*-value
All studies	12	1.03(0.89–1.21)	0.000(71.4%)	0.703	0.373
Study design					
Case control	10	1.08(0.84-1.40)	0.000(73.8%)	0.713	0.325
Cohort	2	0.95(0.81-1.12)	0.067(70.2%)	-	-
Geographical region					
Europe	4	1.01(0.87-1.18)	0.154(42.9%)	0.909	0.497
US/Canada	6	1.05(0.92-1.19)	0.036(58.1%)	0.162	0.091
Uruguay	1	1.6(0.7-3.3)	-	-	-
China	1	0.34(0.21-0.55)	-	-	-
Tea assessment					
Interview	4	0.99(0.50-1.98)	0.000(88.5%)	0.968	0.497
Questionnaire	8	1.02(0.91-1.14)	0.085(44.1%)	0.602	0.322

Discussion

This is the first meta-analysis evaluating the relationship between tea comsuption and renal cell carcinoma.There has been considerable interest in the possible impact of tea consumption on renal cell carcinoma risk. In this meta-analysis of epidemiological studies of the association between tea and risk of renal cell carcinoma including ten case-control and two cohorts studies,we found that tea consumption was not associated with reduced risk of renal cell carcinoma.

Many studies conducted on cell-culture systems and animal models as well as human epidemiological studies show that tea could afford protection against a variety of cancer types (Qin et al., 2007; Thakur et al., 2012; Zhong et al., 2012; He et al., 2013; Henning et al., 2013). Several laboratory studies have tried to investigate the link between tea and renal cell carcinoma (Yoshioka et al., 1999; Gu et al., 2009). Most of tea research on renal cell carcinoma to date has focused on the effect and mechanism of green tea It is generally agreed that many of the chemoprevention effects of green tea are mediated by polyphenols. The major catechins in green tea are epigallocatechin-3-gallate (EGCG), epicatechin-3-gallate,epigallocatechin, and epicatechin. EGCG accounts for 50% to 80% of catechin in green tea.

Gu et al. (2009) found that EGCG inhibits growth and induces apoptosis in renal cell carcinoma through TFPI-2 overexpression. The nonsignificant findings regarding the effects of tea consumption on renal cell carcinoma in our meta-analyses contradict the results of previous experimental studies on this topic using in vitro renal cell carcinoma cell lines and in vivo animal models. The difference between the results from experimental studies and our meta-analyses is likely to be due to the lower quantities of human tea consumption compared to the doses used in experimental studies and the fact that

bioavailability is an important factor for consideration.

As a meta-analysis of previously published observational studies, our study has several limitations that need to be taken into account when considering its contributions. First, as a meta-analysis of published studies in English, we are exposed to publication bias, although the present results seem to suggest that there was no evidence of publication bias. Second, our meta-analysis is likely affected by some misclassification of tea consumption. Tea exposure is mostly assessed regarding the number of cups of tea consumed daily or weekly. However,cup size may vary considerably. Third, there are two major types of tea, black tea and green tea, which may have different effects on the prevention of cancer. However, most studies involved in our analysis provided general data on tea consumption other than detailed information on specific type of tea, which may result in inaccurate estimates. Fourth, it is known that in Asia, people consume large amounts of tea and this is an ideal population to study their action in health. However, only one study from China was included in this meta-analysis. Fifth, both cohort and case-control studies were included in the analysis, the difference in study design may probably bring bias in the results. Furthermore, because most studies were case-control ones, the meta-analysis could not cover the selection and recall bias from them.

In summary, our meta-analysis indicates that there is no association between tea consumption and renal cell carcinoma. The present findings should be evaluated from further additional prospective cohort studies.

Acknowledgements

This study was supported by grants from National Key Clinical Specialty Construction Project of China, Health sector scientific research special project (Grant No.201002010), Combination of traditional Chinese and Western medicine key disciplines of Zhejiang Province (Grant No. 2012-XK-A23), Key medical disciplines of Zhejiang province and Zhejiang Provincial Natural Science Foundation of China (Grant No. Z2090356; Grant No. LY12H05006).

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