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ORIGINAL CONTRIBUTION

Tea consumption and colorectal cancer risk: a meta-analysis of prospective cohort studies

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Abstract

Purpose Data from in vitro and animal studies support the preventive effect of tea (*Camellia sinensis*) against colorectal cancer. Further, many epidemiologic studies evaluated the association between tea consumption and colorectal cancer risk, but the results were inconsistent. We conducted a meta-analysis of prospective cohort studies to systematically assess the association between tea consumption and colorectal cancer risk.

Methods A comprehensive literature review was conducted to identify the related articles by searching PubMed and Embase up to June, 2019. Summary relative risks (RRs) and 95% confidence intervals (CIs) were calculated using a fixed effect model.

Results Twenty cohort articles were included in the present meta-analysis involving 2,068,137 participants and 21,437 cases. The combined RR of colorectal cancer for the highest vs. lowest tea consumption was determined to 0.97 (95% CI 0.94–1.01) with marginal heterogeneity ($I^2 = 24.0\%$, $P = 0.093$) among all studies. This indicated that tea consumption had no significant association with colorectal cancer risk. Stratified analysis showed that no significant differences were found in all subgroups. We further conducted the gender-specific meta-analysis for deriving a more precise estimation. No significant association was observed between tea consumption and colorectal cancer risk in male (combined RR = 0.97; 95% CI 0.90–1.04). However, tea consumption had a marginal significant inverse impact on colorectal cancer risk in female (combined RR = 0.93; 95% CI 0.86–1.00). Further, we found a stronger inverse association between tea consumption and risk of colorectal cancer among the female studies with no adjustment of coffee intake (RR: 0.90; 95% CI 0.82–1.00, $P < 0.05$) compared to the female studies that adjusted for coffee intake (RR = 0.97; 95% CI 0.87–1.09, $P > 0.05$).

Conclusions Our finding indicates that tea consumption has no significant impact on the colorectal cancer risk in both genders combined, but gender-specific meta-analysis shows that tea consumption has a marginal significant inverse impact on colorectal cancer risk in female.

Keywords Tea consumption · *Camellia sinensis* · Colorectal cancer · Prospective cohort studies · Meta-analysis

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Introduction

Colorectal cancer is a major public health concern worldwide [1]. Despite various treatment strategies have been developed and used in clinic, the 5-year overall survival rate of metastatic colorectal cancer is only approximately 10% [2]. The morbidity and mortality rates of colorectal cancer present an upward trend in the world, especially in many medium-to-high human development index countries including China, Russia, and Brazil. It is estimated that over 1.8 million new colorectal cancer cases and 881,000 deaths occurred in 2018. Colorectal cancer has become the third most frequently diagnosed cancer but the second most common cause of cancer death [3]. The pathogenesis of colorectal cancer has not been clearly demonstrated until now. Nevertheless, limited evidence suggests that dietary patterns are important factors to influence the morbidity of colorectal cancer. Dietary intervention has become an important strategy for the colorectal cancer prevention [2].

As a crucial dietary factor, tea, which is originated from the dried leaves of plant *Camellia sinensis*, is gaining increasing attention due to its possible therapeutic effect on various cancers, especially on colorectal cancer [4]. Tea is one of the most widely consumed beverages, second only to water [5, 6]. In vitro and animal studies have shown that tea intake contributes to the prevention of colorectal cancer. This effect is mainly attributed to its main active ingredient, epigallocatechin-3-gallate (EGCG). Numerous studies have showed that EGCG prevents colorectal cancer by various mechanisms, such as antioxidation, growth inhibition, and apoptosis induction [7]. Furthermore, the bioavailability of EGCG in humans is estimated to be only 0.32% after oral administration, and most of EGCG is oxidized and decomposed in large intestine, leading to colorectum as the major target organ of EGCG [8, 9]. Thus, the anti-colorectal cancer effect of tea attracts more attention.

The preventive effect of tea against colorectal cancer is supported by some epidemiological studies [10, 11]. However, the results of epidemiological studies are not always consistent [12, 13]. Furthermore, the association between tea consumption and colorectal cancer risk also remains controversial based on meta-analysis [14–17]. Some meta-analysis showed no significant association between tea consumption and colorectal cancer risk [14–16], while the meta-analysis reported by Chen et al. [17] found an inverse association. This inconsistency may be caused by several factors, such as case–control design related biases and limited sample size. Further, the meta-analysis based on or included case–control studies may be influenced by recall bias and reverse causality, leading to biased results [15, 17]. Additional evidence is necessary to reveal the association between tea consumption and colorectal cancer risk. A prospective cohort study of 0.5 million Chinese adults (a follow-up of 10.1 years) and a prospective cohort study of 31,552 Japanese adults (a follow-up of 8.0 years) were reported recently. Participants recruited in the two prospective cohort studies are about one third of the total number of subjects in the previous meta-analysis [4, 17, 18]. Therefore, we aimed to provide an updated meta-analysis of prospective cohort studies to evaluate the association between tea consumption and colorectal cancer risk.

Materials and methods

Literature search

We conducted a literature search in PubMed and Embase up to June, 2019. The following search terms were used: (1) "colorectal" or "colonic" or "colon" or "rectal" or "large bowel"; (2) "neoplasm" or "cancer" or "carcinoma" or "tumor"; (3) "tea"; (4) "cohort studies" or "prospective studies". These search themes were combined using "and" without restrictions. The articles satisfying the exposure, outcome, and study design criteria were pulled.

Study selection

Studies were selected for meta-analysis if they meet the following criteria: (1) published as an original article; (2) belonged to prospective cohort study; (3) evaluated the association between tea consumption and colorectal cancer risk; (4) provided the quantity of participants or person-years; (5) supplied the relative risk (RR) value with corresponding 95% confidence intervals (CIs) for highest vs. lowest level of tea consumption. Meanwhile, studies were excluded if they satisfy at least one of the following characteristics: (1) review article; (2) case–control study; (3) animal trials; (4) less than one year of follow-up; (5) no quantitative analysis on tea consumption, colorectal cancer risk, RR values or 95% CIs.

Data extraction and quality assessment

The search, data extraction, and quality assessment were completed independently by two reviewers (M.Z. and D.L.). Any discrepancies between the two reviewers were resolved by consultation with the third reviewer (F.Z.). Data were collected using a standardized extraction form. The following information was collected: (1) first author's last name, (2) population of country, (3) case/participants, (4) follow-up period, (5) tea consumption (highest vs. lowest), (6) exposure level, (7) tea type, (8) gender, (9) cancer site, (10) adjusted RRs and corresponding 95% CIs for extreme categories of

exposure, (11) adjustment confounding variables. Study quality was evaluated according to the Newcastle–Ottawa quality assessment scale [19]. Eight domains were evaluated in each included study as follows: representativeness of the exposed cohort; selection of the non-exposed cohort; ascertainment of exposure; interest of the outcome at start of study; comparability of cohorts on the basis of the design or analysis; assessment of outcome; follow-up duration; adequacy of follow up of cohorts. A possible score between 0 and 9 was acquired by each study. Score >7 and ≤ 5 were defined as high quality and low quality, respectively.

Statistical analysis

Data were analyzed by Stata version 12.0 (State Corporation, College Station, TX, USA). The combined RR was calculated by pooling RRs for highest vs. lowest categories of tea consumption from each study. Heterogeneity of effect size across the studies was examined using the Cochran's Q test and I^2 statistics. I^2 statistic from 0 to 30% was defined as no or marginal heterogeneity, 30–75% as mild heterogeneity, and over 75% as notable heterogeneity [20]. The random effect model was used only when there existed significant heterogeneity; otherwise, the fixed effect model was used for further analysis [21]. The causes of heterogeneity were further explored through stratified and meta-regression analysis. The potential confounders included geographic region, tea type, cancer site, quality score, and adjustment for age, smoking, and coffee. Sensitivity analysis was performed to test the robustness of main results. Publication bias was visually evaluated for any asymmetry of the funnel plots. The funnel plots were further checked with Egger's regression asymmetry test and Begg's adjusted rank correlation test, and the statistical significant was set to $P<0.05$ [22].

Results

Search results, study characteristics, and quality assessment

Detailed process of the relevant study selection was shown in Fig. 1. A total of 208 articles were initially screened from PubMed and Embase. 156 of 208 articles were excluded because they were obviously irrelevant to the current meta-analysis by a careful review of the title and abstract. Then we screened the remaining 52 full-text articles. 32 of 52 articles were excluded because of no available data on tea consumption, colorectal cancer risk, RR values or 95% CIs. Finally, 20 articles involving 2,068,137 participants and 21,437 cases of colorectal cancer were recruited for meta-analysis [4, 10–13, 18, 23–36]. The characteristics of the 20 studies were summarized in Table 1. Four studies were conducted in Europe (332,300 participants and 3778 cases), five in North America (731,273 participants and 10,015 cases), and eleven in Asia (1,004,564 participants and 7644 cases). As shown in Table 1, the quality scores of all studies ranged from 3 to 8. Nine studies were considered to have medium or low quality, and eleven studies had high quality.

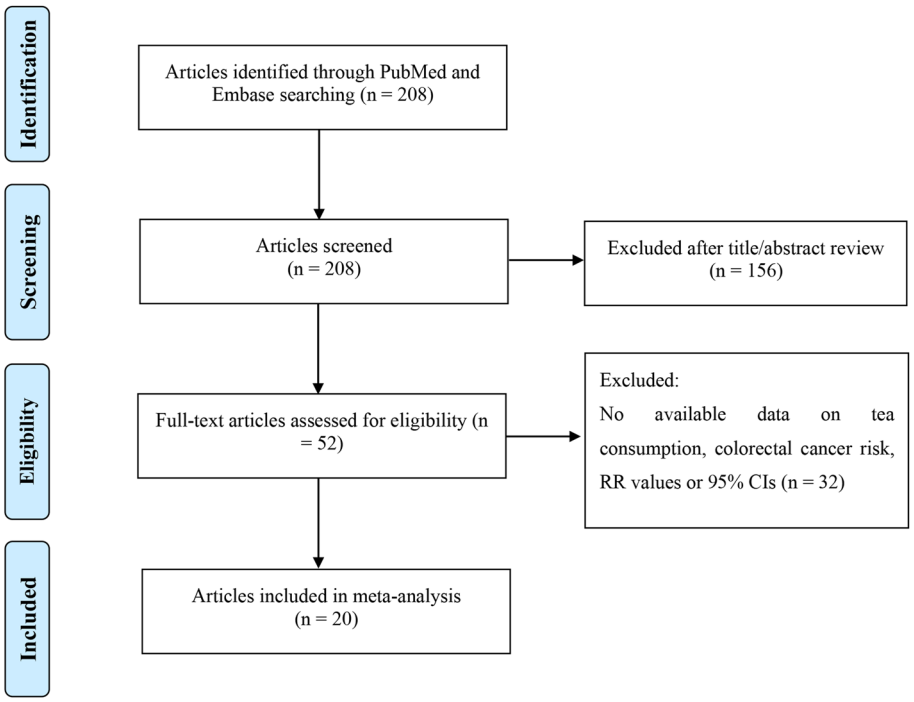

Fig. 1 Flow diagram of included studies

Table 1 Characteristics of included studies

Study [References]	Population of country	Case/participants	Follow-up (year)	Tea consumption (highest vs. lowest)	Exposure level	Tea type	Gender	Cancer site	Adjusted RR (95% CI)	Adjustment factors	Study quality
Goldbohm et al. [23]	Netherlands	650/120,825	4.3	≥5 cups/day vs. non tea drinkers	6	Black tea	Both	Colorectum	0.94 (0.66–1.34)	Family history, body mass index, gallbladder surgery, and intake of fiber, folate, alcohol, and coffee	6
							Male	Colon	1.01 (0.53–1.91)		
								Rectum	1.49 (0.78–2.85)		
							Female	Colon	0.69 (0.37–1.29)		
								Rectum	0.71 (0.29–1.72)		
Zheng et al. [24]	America	474/35,369	8.0	≥2 cups/day vs. non tea drinkers	4	Tea (unclear)	Female	Colon	0.71 (0.45–1.11)	Age, education, smoking status, physical activity, fruit and vegetable intake, waist/hip ratio, and family history	4
								Rectum	0.70 (0.34–1.46)		
Hartman et al. [25]	Finland	185/29,133	8.0	≥1 cup/day vs. non tea drinkers	3	Tea (unclear)	Male	Colon	2.09 (1.34–3.26)	Age, intervention group, calcium, occupational physical activity, and BMI	6
								Rectum	0.87 (0.47–1.60)	Age, intervention group, calcium, occupational physical activity, and serum cholesterol	
Terry et al. [26]	Sweden	460/61,463	9.6	≥2 cups/day vs. < 1 cup/week	4	Tea (unclear)	Female	Colorectum	0.98 (0.64–1.51)	Age, body mass index, education level, quartiles of total calories, red meat, coffee, alcohol, energy-adjusted total fat, fruit fiber, vegetable fiber, cereal fiber, calcium, vitamin C, folic acid, and vitamin D	8
								Colon	0.74 (0.42–1.31)		
								Rectum	1.53 (0.77–3.03)		
Nagano et al. [27]	Japan	625/38,540	13.0	> 5 cups/day vs. 0–1 cup/day	3	Green tea	Both	Colon	1.00 (0.76–1.40)	City, age, gender, radiation exposure, smoking status, alcohol drinking, body-mass index, education level, and calendar time	6
								Rectum	1.30 (0.77–2.10)		
Su et al. Cohort-1 [11]	America	267/14,407	20.0	> 1.5 cups/day vs. non tea drinkers	3	Tea (unclear)	Both	Colon	0.85 (0.56–1.30)	Age, race, education, BMI, aspirin use, intakes of calories, fat, fiber and calcium, and alcohol use	8
							Male	Colon	0.53 (0.26–1.11)		
							Female	Colon	1.19 (0.70–2.03)		
Su et al. Cohort-2 [11]	America	250/10,220	10.0	> 1.5 cups/day vs. non tea drinkers	3	Tea (unclear)	Both	Colon	0.59 (0.35–1.00)		
							Male	Colon	0.30 (0.09–0.98)		
							Female	Colon	0.74 (0.40–1.39)		
Michels et al. [28]	America	1438/133,893	2 million person-years	≥2 cups/day vs. non tea drinkers	5	Tea (unclear)	Both	Colorectum	1.01 (0.83–1.22)	Age, family history, history of sigmoidoscopy, height, body mass index, smoking, physical activity, aspirin use, vitamin supplement intake, alcohol, red meat, total caloric intake, and among women in addition for menopausal status, post-menopausal, hormone use	6
								Colon	1.07 (0.86–1.33)		
							Male	Colorectum	1.12 (0.78–1.59)		
								Colon	1.05 (0.69–1.59)		
								Rectum	1.34 (0.67–2.68)		
							Female	Colorectum	0.96 (0.76–1.22)		
								Colon	1.08 (0.83–1.39)		
								Rectum	0.54 (0.29–0.99)		

Table 1 (continued)

Study [References]	Population of country	Case/participants	Follow-up (year)	Tea consumption (highest vs. lowest)	Exposure level	Tea type	Gender	Cancer site	Adjusted RR (95% CI)	Adjustment factors	Study quality
Suzuki et al. Cohort-1 [29]	Japan	269/31,345	7.0 to 9.0	> 5 cups/day vs. < 1 cup/day	4	Green tea	Both	Colon	1.03 (0.65–1.64)	Sex, age, family history, cigarette smoking, alcohol consumption, body mass index, consumption of black tea and coffee, consumption of meat, green-yellow vegetables, other vegetables, and fruits	8
							Both	Rectum	1.34 (0.77–2.33)		
Suzuki et al. Cohort-2 [29]	Japan	247/47,605		> 5 cups/day vs. < 1 cup/day	4	Green tea	Both	Colon	0.93 (0.59–1.46)	Sex, age, family history, cigarette smoking, alcohol consumption, body mass index, consumption of black tea and coffee, consumption of beef, pork, ham, chicken, liver, spinach, carrot or pumpkin, tomato, orange, other fruits, and juice	
							Both	Rectum	0.57 (0.34–0.95)		
Suzuki et al. Cohort 1 + 2 [29]				> 5 cups/day vs. < 1 cup/day	4	Green tea	Both	Colon	0.97 (0.70–1.35)	Sex, age, family history, cigarette smoking, alcohol consumption, body mass index, consumption of black tea and coffee, consumption of meat, vegetables, orange, other fruits, and juice	
							Both	Rectum	0.85 (0.58–1.23)		
							Male	Colon	1.12 (0.72–1.74)		
							Male	Rectum	0.62 (0.38–1.02)		
							Female	Colon	0.79 (0.49–1.29)		
							Female	Rectum	1.30 (0.70–2.42)		
Oba et al. [30]	Japan	213/30,221	8.0	> 1 cup/day vs. never to < 1 cup/month	3	Green tea	Male	Colon	0.75 (0.49–1.16)	Age, height, BMI, cigarette smoking, alcohol intake, physical activity, black tea intake and green tea/coffee intake	8
							Female	Colon	1.08 (0.67–1.76)		
Sun et al. [31]	Singapore	845/61,320	8.9	Daily vs. non tea drinkers	5	Green tea	Both	Colorectum	1.18 (0.97–1.45)	Sex, age, year of interview, dialect group, education, family history, history of diabetes, cigarette smoking, alcohol drinking, coffee drinking, physical activity, body mass index, total energy, total fat, dietary fiber, calcium, and vitamin C	8
							Male	Colorectum	1.36 (1.06–1.74)		
							Female	Colorectum	0.91 (0.63–1.32)		
						Black tea	Both	Colorectum	0.92 (0.73–1.16)		
							Male	Colorectum	0.87 (0.66–1.15)		
							Female	Colorectum	1.03 (0.67–1.57)		
						Tea (unclear)	Both	Colorectum	1.07 (0.89–1.29)		
							Male	Colorectum	1.18 (0.93–1.50)		
							Female	Colorectum	0.92 (0.67–1.25)		
Yang et al. [32]	China	246/69,710	6.0	≥ 5 g/day vs. non tea drinkers	3	Green tea	Female	Colorectum	0.56 (0.32–0.98)	Age, education, household income, cigarette smoking, alcohol drinking, physical activity, body mass index, menopausal status, nonsteroidal anti-inflammatory drug use, vitamin, prior histories, family history, and intakes of total energy, vegetables, fruits, and red meat	7
Lee et al. [33]	Japan	1163/96,162	10.0	> 5 cups/day vs. almost never	5	Green tea	Male	Colorectum	0.96 (0.71–1.29)	BMI, smoking status, alcohol drinking, family history, physical activity, and intake of green vegetables, beef, pork, coffee, Chinese tea and black tea	6
								Colon	0.92 (0.63–1.33)		
								Rectum	1.04 (0.63–1.72)		
							Female	Colorectum	1.02 (0.70–1.47)		
								Colon	1.10 (0.70–1.73)		
								Rectum	0.85 (0.45–1.61)		
Suzuki et al. [34]	Japan	43 (death)/12,251	6.0	≥ 7 cups/day vs. < 1 cup/day	4	Green tea	Both	Colorectum	0.95 (0.84–1.08)	Smoking status, alcohol consumption, body mass index, and physical activity	3

Table 1 (continued)

Study [References]	Population of country	Case/participants	Follow-up (year)	Tea consumption (highest vs. lowest)	Exposure level	Tea type	Gender	Cancer site	Adjusted RR (95% CI)	Adjustment factors	Study quality
Simons et al. [35]	Netherlands	2483/120,852	13.3	> 3 cups/day vs. ≤ 1 cup/day	4	Tea (unclear)	Male	Colorectum	0.92 (0.75–1.13)	Age, family history, physical activity, smoking status, educational level, body mass index, ethanol intake, meat intake, processed meat intake, folate intake, vitamin B6 intake, fiber intake, and fluid intake from other fluids	7
								Rectum	0.85 (0.63–1.16)		
							Female	Colorectum	0.92 (0.74–1.14)	Age, family history, physical activity, smoking status, educational level, body mass index, ethanol intake, meat intake, processed meat intake, folate intake, vitamin B6 intake, fiber intake, and fluid intake from other fluids	
								Rectum	1.00 (0.66–1.51)		
Yang et al. [10]	China	243/60,567	5.0	≥ 250 g/month vs. non tea drinkers	2	Green tea	Male	Colorectum	0.77 (0.59–1.01)	Age, education, cigarette smoking, alcohol consumption, regular exercise, body mass index, history of diabetes, family history and intakes of vegetables, fruits and red meat	6
								Colon	0.69 (0.48–0.98)		
								Rectum	0.89 (0.59–1.34)		
Nechutas et al. [36]	China	711/69,310	11.0	≥ 150 g/month vs. non tea drinkers	4	Tea (unclear)	Female	Colorectum	0.86 (0.63,1.18)	Age, marital status, education, occupation, BMI, exercise, fruit and vegetable intake, meat intake, diabetes, and family history	8
								Colon	0.85 (0.56,1.27)		
								Rectum	0.89 (0.55,1.43)		
Sinha et al. [13]	America	6905/489,706	10.5	≥ 1 cup/day vs. non tea drinkers	5	Tea (unclear)	Both	Colorectum	0.97 (0.90–1.05)	Age, sex, race, education, smoking status, time since quitting for former smokers, smoking dose, ever smoke a pipe or cigar, diabetes, colorectal screening, family history, regular nonsteroidal, anti-inflammatory drug use, marital status, BMI, frequency of vigorous physical activity, calories, fruit and vegetables, red meat, dietary calcium intake, alcohol, and menopausal hormone therapy in women	8
								Colon	0.99 (0.91–1.08)		
								Rectum	0.92 (0.80–1.07)		
Dominianni, et al. [12]	America	681/47,678	11.4	≥ 2 cups/day vs. non tea drinkers	4	Tea (unclear)	Both	Colorectum	0.77 (0.55–1.09)	Age, gender, race, family history, education, body mass index, physical activity, smoking status, NSAID intake, history of diabetes, number of colorectal examinations up to 3 years before the start of study, hormone use, fruit intake, vegetable intake, meat intake, alcohol intake and study center	7
								Rectum	0.70 (0.33–1.46)		
Wada et al. [18]	Japan	772/31,552	8.0	≥ 4 times/day vs. < once/day	4	Green tea	Male	Colorectum	0.92 (0.65–1.30)	Age, height, body mass index, smoking status, physical activity score, education years, history of aspirin use, alcohol consumption, total energy intake, the intakes of total fiber, red meats, processed meats, and calcium, the frequency of coffee consumption	7
								Colon	0.78 (0.49–1.22)		
								Rectum	1.21 (0.70–2.09)		
				≥ 4 times/day vs. < once/day	4	Green tea	Female	Colorectum	1.03 (0.72–1.49)	Age, height, body mass index, smoking status, physical activity score, education years, history of aspirin use, alcohol consumption, total energy intake, the intakes of total fiber, red meats, processed meats, and calcium, the frequency of coffee consumption and menopausal status	
								Colon	1.08 (0.70–1.67)		
								Rectum	0.97 (0.50–1.88)		

Table 1 (continued)

Study [References]	Population of country	Case/participants	Follow-up (year)	Tea consumption (highest vs. lowest)	Exposure level	Tea type	Gender	Cancer site	Adjusted RR (95% CI)	Adjustment factors	Study quality
Li et al. [4]	China	2267/455,981	10.1	> 4.0 g/day vs. < less than weekly	5	Tea (unclear)	Both	Colorectum	1.19 (1.01–1.40)	Education, occupation, marital status, household income, physical activity, intakes of red meat, fresh fruits and vegetables, body mass index, waist-hip ratio, family history of cancer, and prevalent diabetes	5

Tea consumption and colorectal cancer risk

As shown in Fig. 2, the multivariable-adjusted RRs from twenty studies were extracted. A fixed effect model was used for the calculation of the combined RR due to the marginal heterogeneity ($I^2 = 24.0\%$, $P = 0.093$). The combined RR was determined to 0.97 (95% CI 0.94–1.01) by comparing highest vs. lowest tea consumption levels against colorectal cancer. This indicated that tea consumption had no statistically significant association with colorectal cancer risk.

Subsequently, we stratified the studies by geographic region, tea type, cancer site, quality score, and adjustment for age, smoking, and coffee (Table 2). No statistically significant differences were found in these subgroups. The one-out sensitivity analysis demonstrated that the RRs and CIs values were 0.97–0.99 and 0.93–1.03, respectively. This indicated that the main result was robustness. Besides, the factors including geographic region, tea type, cancer site, quality score, and adjustment for age, smoking, and coffee, were taken into consideration for meta-regression analysis. As shown in Table 3, the *P* values ranged from 0.566 to 0.903, which indicated that none of them were the potential source of heterogeneity.

Gender-specific meta-analysis for the association between tea consumption and colorectal cancer risk

Thirteen studies were used for the meta-analysis on the association between tea consumption and colorectal cancer risk in female [11, 18, 24, 26, 28–33, 35–37]. The fixed effect model was used for calculating the combined RR due to the homogeneity ($I^2 = 0$, $P = 0.918$). As shown in Fig. 3a, the combined RR was determined to 0.93 (95% CI 0.86–1.00) by comparing highest vs. lowest tea consumption levels against colorectal cancer in female. Thus, there was a marginal significant inverse association between tea consumption and colorectal cancer risk in female. Further, we found a stronger inverse association between tea consumption and risk of colorectal cancer among studies with no adjustment of coffee intake (RR: 0.90; 95% CI 0.82–1.00, $P < 0.05$) compared to studies that adjusted for coffee intake (RR: 0.97; 95% CI 0.87–1.09, $P > 0.05$). Nevertheless, no statistically significant differences were found in other subgroups, including geographic region, tea type, cancer site, quality score, and adjustment for age and smoking (Table 2).

Besides, eleven studies were used for the meta-analysis on the association between tea consumption and colorectal cancer risk in male [10, 11, 25, 28–31, 33, 35–37]. As shown in Fig. 3b, the combined RR was determined to 0.97 (95% CI 0.90–1.04) with mild heterogeneity ($I^2 = 45.0\%$, $P = 0.007$), indicating that no significant association was observed between tea consumption and colorectal cancer risk in male. Stratified analysis showed that no statistically significant differences

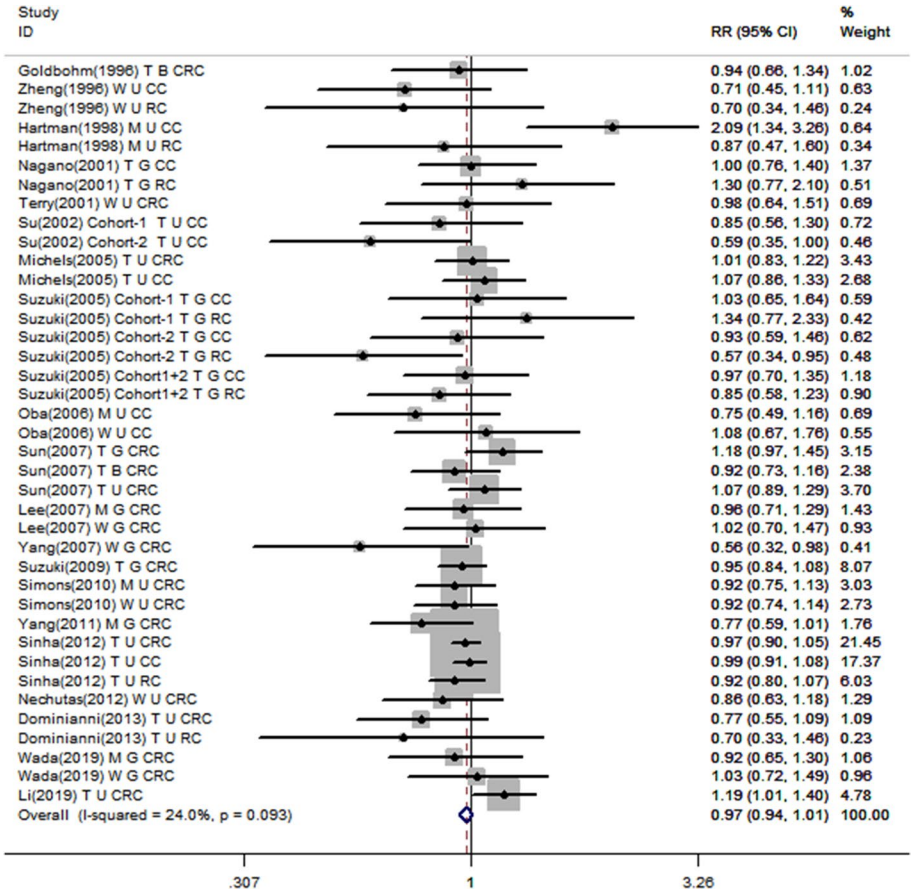

Fig. 2 Forest plot of tea consumption and colorectal cancer risk in both genders combined. *T* total group, *M* male, *F* female, *B* black tea, *G* green tea, *U* unclear tea, *CC* colon cancer, *RC* rectal cancer, *CRC* colorectal cancer

were found by geographic region, tea type, cancer site, quality score, and adjustment for age, smoking, and coffee (Table 2). When we omitted one study in each turn, the RRs and CIs values were 0.97–1.02 and 0.89–1.10, respectively, indicating the main result was robustness. Meta-regression analysis showed that geographic region, quality score, and adjustment for age and coffee may be the causes of heterogeneity (Table 2). However, the stratified analysis in male suggested that the four factors were not heterogeneous sources.

Publication bias

The funnel plot was visually symmetrical, indicating no publication bias. This result was further confirmed by Begg's rank correlation test and Egger's tests on whole groups (Begg's test $P=0.116$; Egger's test $P=0.181$), female (Begg's test $P=0.254$; Egger's test $P=0.170$), and male (Begg's test $P=0.895$; Egger's test $P=0.517$) (Fig. 4).

Discussion

Strong evidences from animal and cell experiments have demonstrated that tea could inhibit the formation and proliferation of colorectal cancer [38]. Some epidemiological studies have also sought to reveal the association between tea consumption and colorectal cancer risk in the last few decades, but there was no consensus. Recently, Chen et al. [17] reported a meta-analysis on the association between tea consumption and colorectal cancer risk, which enrolled both cohort studies and case–control studies. Their results showed that the summary odds ratio (OR) of colorectal cancer for the highest vs. lowest tea consumption was 0.93 (95% CI 0.87–1.00) among all studies, which indicated that tea consumption had an inverse impact on colorectal cancer risk. Stratified analysis showed that tea, especially green tea (OR = 0.87, 95% CI 0.76–0.98), had a protective effect for female (OR = 0.86, 95% CI 0.78–0.94) and rectal

Table 2 Stratified analysis of tea consumption and colorectal cancer risk

Group	Number of studies	Adjusted RR (95% CI)	*P* value	Heterogeneity	
				I^2	*P* value
Both genders combined					
Geographic region					
Europe	4	0.99 (0.87–1.11)	0.81	58.50%	0.03
North America	5	0.96 (0.92–1.01)	0.11	4.40%	0.4
Asia	11	0.99 (0.93–1.05)	0.73	21.80%	0.18
Tea type					
Tea (unclear)	12	0.98 (0.94–1.02)	0.34	36.80%	0.05
Green tea	8	0.96 (0.89–1.04)	0.3	16.00%	0.27
Black tea	2	0.93 (0.76–1.12)	0.44	0.00%	0.92
Cancer site					
Colorectum	14	0.98 (0.93–1.02)	0.14	13.30%	0.29
Colon	8	0.99 (0.92–1.06)	0.74	43.60%	0.05
Rectum	6	0.91 (0.81–1.02)	0.11	14.10%	0.32
Quality score					
Low score (3–4)	7	0.92 (0.82–1.04)	0.19	2.60%	0.36
Medium score (5–6)	2	1.06 (0.97–1.15)	0.19	46.40%	0.05
High score (7–8)	11	0.98 (0.94–1.03)	0.05	0.90%	0.45
Adjustment for age					
Yes	16	0.97 (0.93–1.00)	0.08	24.50%	0.1
No	4	1.02 (0.93–1.11)	0.67	20.30%	0.29
Adjustment for smoking					
Yes	16	0.97 (0.94–1.01)	0.16	5.90%	0.37
No	4	0.97 (0.81–1.15)	0.7	68.70%	0.01
Adjustment for coffee					
Yes	7	0.99 (0.92–1.08)	0.89	0.00%	0.72
No	13	0.97 (0.93–1.00)	0.12	43.60%	0.02
Female					
Geographic region					
Europe	3	0.92 (0.79–1.08)	0.32	0.00%	0.67
North America	3	0.99 (0.78–1.24)	0.3	21.80%	0.26
Asia	7	0.954 (0.84–1.05)	0.25	21.80%	0.95
Tea type					
Tea (unclear)	8	0.93 (0.85–1.02)	0.1	0.00%	0.79
Green tea	5	0.96 (0.83–1.11)	0.55	0.00%	0.72
Black tea	2	0.88 (0.63–1.22)	0.43	0.00%	0.51
Cancer site					
Colorectum	8	0.93 (0.84–1.03)	0.16	0.00%	0.89
Colon	10	0.94 (0.83–1.08)	0.38	0.00%	0.68
Rectum	9	0.92 (0.76–1.12)	0.41	0.00%	0.5
Quality score					
Low score (3–4)	1	0.77 (0.48–1.04)	0.08	0.00%	0.97
Medium score (5–6)	3	0.96 (0.84–1.10)	0.53	0.00%	0.51
High score (7–8)	9	0.94 (0.85–1.03)	0.16	0.00%	0.93
Adjustment for age					
Yes	11	0.93 (0.86–1.01)	0.08	0.00%	0.85
No	2	0.94 (0.74–1.19)	0.08	0.00%	0.72
Adjustment for smoking					
Yes	10	0.94 (0.86–1.02)	0.13	0.00%	0.84
No	3	0.92 (0.78–1.08)	0.29	0.00%	0.73

Table 2 (continued)

Group	Number of studies	Adjusted RR (95% CI)	*P* value	Heterogeneity	
				I^2	*P* value
Adjustment for coffee					
Yes	7	0.97 (0.87–1.09)	0.53	0.00%	0.97
No	6	0.90 (0.82–1.00)	0.04	0.00%	0.53
Male					
Geographic region					
Europe	3	1.01 (0.88–1.17)	0.86	64.10%	0.02
North America	2	0.99 (0.78–1.24)	0.9	49.70%	0.09
Asia	6	0.95 (0.87–1.04)	0.26	39.20%	0.06
Tea type					
Tea (unclear)	6	1.01 (0.90–1.13)	0.88	58.30%	0.01
Green tea	5	0.94 (0.84–1.04)	0.22	39.80%	0.08
Black tea	2	0.95 (0.75–1.21)	0.7	12.00%	0.32
Cancer site					
Colorectum	6	1.00 (0.91–1.10)	0.97	48.80%	0.06
Colon	9	0.92 (0.79–1.07)	0.29	62.20%	0.01
Rectum	8	0.92 (0.78–1.10)	0.29	0.00%	0.45
Quality score					
Medium score (5–6)	6	0.96 (0.88–1.06)	0.45	49.80%	0.02
High score (7–8)	5	0.98 (0.87–1.09)	0.66	44.30%	0.04
Adjustment for age					
Yes	9	0.96 (0.90–1.04)	0.98	54.10%	0
No	2	1.00 (0.83–1.22)	0.34	0.00%	0.78
Adjustment for smoking					
Yes	9	0.96 (0.89–1.03)	0.28	23.50%	0.16
No	2	1.14 (0.83–1.55)	0.43	82.30%	0
Adjustment for coffee					
Yes	6	1.01 (0.92–1.12)	0.74	42.50%	0.18
No	5	0.92 (0.82–1.02)	0.1	57.50%	0.01

Table 3 Meta-regression analysis

Variable	Coefficient	Standard error	Tau (τ)	*P* value	95% CI	
Both genders combined						
Geographic region	− 0.0148554	0.0563059	0.26	0.794	− 0.1296920	0.0999812
Tea type	− 0.0105844	0.0652244	− 0.16	0.872	− 0.1436104	0.1224417
Cancer site	− 0.0090268	0.0447767	− 0.20	0.842	− 0.1003494	0.0822958
Quality score	− 0.0150403	0.0704813	− 0.21	0.832	− 0.1587879	0.1287074
Adjustment for age	− 0.0587914	0.1143232	− 0.51	0.611	− 0.2919552	0.1743723
Adjustment for smoking	− 0.0140577	0.1141373	− 0.12	0.903	− 0.2468423	0.2187269
Adjustment for coffee	0.0448890	0.0774650	0.58	0.566	− 0.1131019	0.2028799
Male						
Geographic region	− 0.4011830	0.1135544	− 3.53	0.002	− 0.6397519	− 0.1626140
Tea type	0.1199810	0.0882567	1.36	0.191	− 0.0654394	0.3054015
Cancer site	− 0.0869423	0.0593382	− 1.47	0.160	− 0.2116071	0.0377226
Quality score	− 0.6047182	0.1837258	− 3.29	0.004	− 0.9907118	− 0.2187246
Adjustment for age	0.7428939	0.2559340	2.90	0.009	0.2051965	1.2805910
Adjustment for smoking	0.0609983	0.2030763	0.30	0.767	− 0.3656491	0.4876457
Adjustment for coffee	0.8619959	0.2258530	3.82	0.001	0.3874963	1.3364950

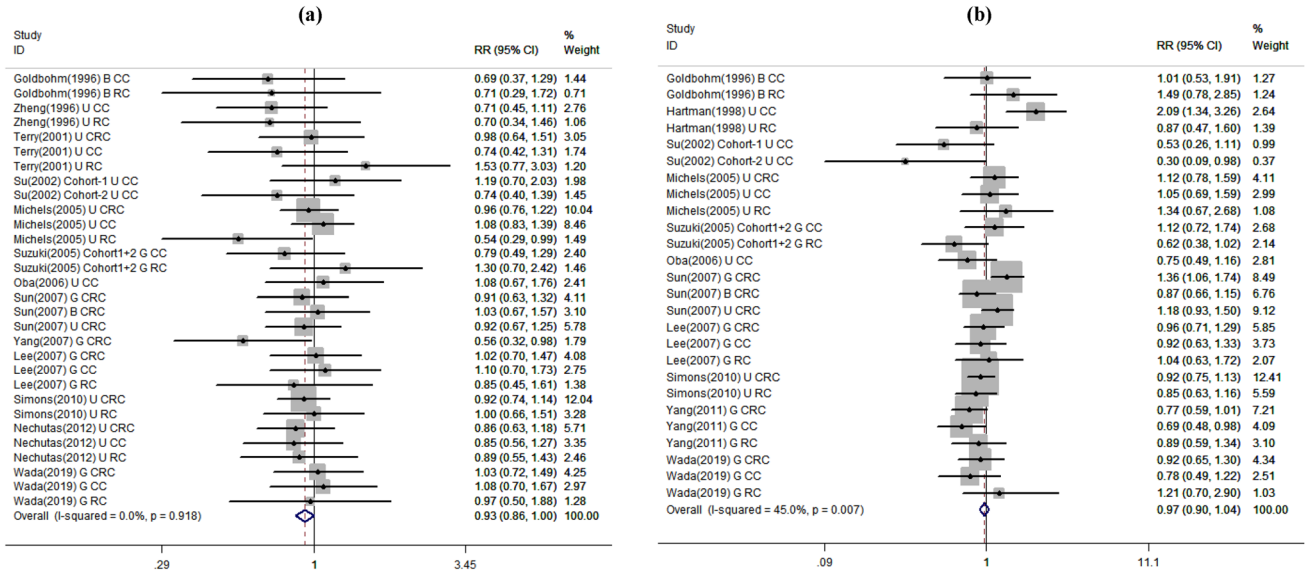

Fig. 3 Forest plot of tea consumption and colorectal cancer risk in female (**a**) and male (**b**). *B* black tea, *G* green tea, *U* unclear tea, *CC* colon cancer, *RC* rectal cancer, *CRC* colorectal cancer

cancer patients (OR = 0.91, 95% CI 0.85–0.99). Nevertheless, all ORs and 95% CIs were close to 1, suggesting that tea consumption was just a slightly prevention strategy for colorectal cancer. Further, they recruited case–control studies for meta-analysis, which might be influenced by recall bias and reverse causality [16].

In the present study, we provided a meta-analysis based on prospective cohort studies to evaluate the association between tea consumption and colorectal cancer risk. Participants recruited in our meta-analysis was up to about 2 million, outpacing the previous meta-analysis by more than about 0.5 million [17]. Thus, our meta-analysis could offer more precise and credible risk estimate than the previous meta-analysis. We found that highest vs. lowest level of tea consumption was not associated with a decreased risk of colorectal, colon, or rectal cancer. It is also worth noting that the differences of morbidity and pathogenesis of colorectal cancer exist between men and women, which may lead to potential differences of tea consumption on the prevention of colorectal cancer [1–3]. So, we further conducted the gender-specific meta-analysis for deriving a more precise estimation. No significant association was observed between tea consumption and colorectal cancer risk in male. However, tea consumption had a marginal significant inverse impact on colorectal cancer risk in female.

Several limitations should be taken into consideration for our study. First, some studies included in our meta-analysis had certain weakness in experimental design, such as non-stratification of tea type and caner site. Additionally, although some important confounding factors including gender, age, and smoking were included in the most of studies, some other potentially important variables, such as coffee, alcohol, and fruits, were ignored in some studies. Besides, colorectal cancer is an extremely complicated and heterogeneous disease, which is well-known for remarkable global variations in etiology and morbidity [1–3]. Heterogeneity could not be fully eliminated in the present meta-analysis. The results obtained in the present study should be considered cautiously due to the existence of confounding factors. Second, measurement error in dietary assessment is an inherent problem [39]. The methods for measuring tea consumption in the included studies were different, which may result in the deviation of risk estimate values and confounding factors. In fact, we detected marginal to moderate heterogeneity among all studies. Third, the sample size of Asians in the present meta-analysis was relatively large due to the popularity of tea in Asia, especially in China and Japan, resulting in the potential selection bias [4, 18]. The results should be cautiously extrapolated to the populations in other countries.

Conclusions

Our finding suggests that tea consumption has no significant impact on the colorectal cancer risk in both genders combined, but gender-specific meta-analysis indicates that tea consumption has a marginal significant inverse impact on colorectal cancer risk in female. Large prospective cohort studies are warranted to reach a more definitive conclusion

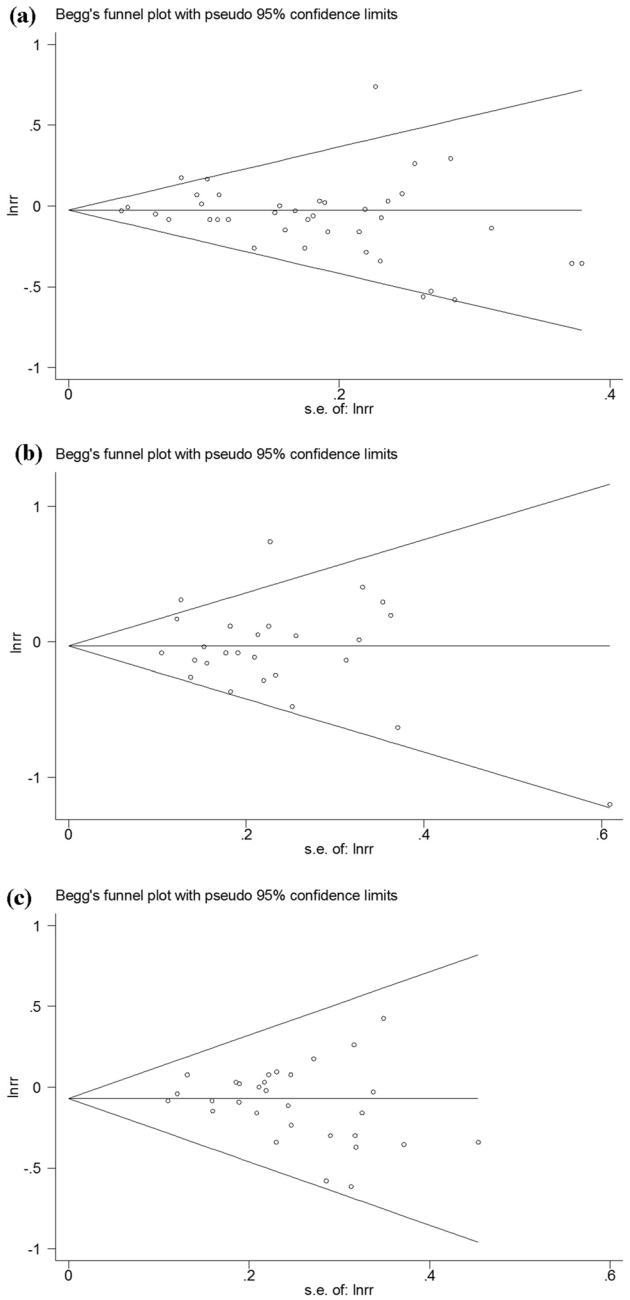

Fig. 4 Begg's funnel plot. **a** Both genders combined; **b** male; **c** female

on the association between tea consumption and colorectal cancer risk.

Author contributions All authors have made substantial contributions to the conception and design of the study. MZ, DL, and FZ conducted the search and data extraction. JO, PH, BG, JT, FS, JL, XZ, YL, HL, SC, JH, JL, KW, and JW collected the data. MZ and ZL analyzed the data and wrote the manuscript.

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Compliance with ethical standards

Conflicts of interest The authors declare no conflict of interest.

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