Tea consumption and the incidence of cancer: a systematic review and meta-analysis of prospective observational studies

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The aim of this study was to summarize the current evidence on the strength of associations between tea consumption and the incidence of cancer at different sites. We searched PubMed, Embase and the Cochrane Library for relevant articles published before October 2013. Prospective studies that reported effect estimates of cancer incidence, with 95% confidence intervals (CIs), for more than two categories of tea consumption were included. We analysed 87 datasets (57 articles), which included a total of 49 812 incident cases. Overall, high tea consumption had no significant effect on the risk of gastric, rectal, colon, lung, pancreatic, liver, breast, prostate, ovarian, bladder cancers or gliomas. However, high tea consumption was associated with a reduced risk of oral cancer (risk ratio 0.72; 95% CI 0.54–0.95; $P = 0.021$). A dose–response meta-analysis suggested that an increase in tea consumption by one cup per day was associated with a reduced risk of oral cancer (risk ratio 0.89; 95% CI 0.80–0.98; $P = 0.022$), but had little effect on the incidence of other cancers. Subgroup analysis indicated that an increase in the consumption of black tea by one cup per day was associated with an increased risk of breast cancer. Moreover, in western countries, we found that an increase in the consumption of tea by one cup per day was associated with a reduced risk of bladder cancer. Increased tea consumption has no significant effect on the risk of common malignancies. For some cancer types, associations differ according to sex, ethnicity and tea type. ***European Journal of Cancer Prevention* 24:353–362**

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Introduction

Tea is a commonly consumed beverage in many populations. The consumption of tea, in particular black tea and green tea, has been reported to contribute both favourably and adversely to incidences of cancer (Bushman, 1998; Kuroda and Hara, 1999). Black tea is the principal tea beverage in the USA, Europe and western Asia, whereas green tea is more popular in China, Japan and Korea (Food and Agriculture Organization of the United Nations, 1996). The role of tea in cancer prevention is supported by various studies. However, the results of epidemiological studies investigating the effect of tea consumption on the incidence of cancer are inconsistent: some studies report that the consumption of tea is protective, whereas others indicate that it has no effect on cancer incidence or even increases the risk of certain cancers (Bushman, 1998). In 2007, the World Cancer Research Fund (WCRF) used a standardized approach to review the available evidence (World Cancer Research Fund/American Institute for Cancer Research, 2007), and concluded that the cancer-preventive effects of tea and its extracts were controversial. Furthermore, additional unanswered questions remain, such as whether any associations are applicable to less common malignancies, and whether associations differ depending on sex, ethnicity or the type of tea consumed. A comparison of the associations found between studies is challenging because of the heterogeneity in study types, populations and cancer types investigated. Traditional meta-analyses (Seely *et al.*, 2005; Sun *et al.*, 2006a, 2006b; Zhou *et al.*, 2007, 2008; Arts, 2008; Myung *et al.*, 2009; Zhang *et al.*, 2010; Fon Sing *et al.*, 2011; Zheng *et al.*, 2011, 2012; Sasazuki *et al.*, 2012; Wang *et al.*, 2012, 2013; Genkinger *et al.*, 2012; Qin *et al.*, 2012; Wu *et al.*, 2013) have principally focused on the differences in the risk of cancer between high tea consumers, low tea consumers and nonconsumers, or investigated tea consumption with respect to a specific cancer type. However, the tea consumption ranges and category cut-off values differ between studies. Another limitation of previous meta-analyses (Seely *et al.*, 2005; Sun *et al.*, 2006a, 2006b; Zhou *et al.*, 2007, 2008; Arts, 2008; Myung *et al.*, 2009; Fon Sing *et al.*, 2011; Zheng *et al.*, 2011, 2012; Genkinger *et al.*, 2012; Qin *et al.*, 2012;

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Sasazuki *et al.*, 2012; Wang *et al.*, 2013; Wu *et al.*, 2013) is the inclusion of retrospective case–control studies, which are sensitive to confounding factors and bias, especially recall bias. In the present study, we used uniform methods and definitions to perform a systematic review and meta-analysis of previously carried out prospective observational studies. We compared the effect that incremental increases in tea consumption has on the incidence of cancer at different sites and analysed whether these are the same for different sexes, ethnic populations and types of tea.

Methods

Data sources, search strategy and selection criteria

This review was performed and is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Statement issued in 2009 (Moher *et al.*, 2009).

We systematically searched the PubMed, Embase and Cochrane Library electronic databases for studies carried out in humans from the date of database inception to October 2013. There were no language restrictions on the search. We included all studies that investigated associations between tea consumption and the incidence of 12 different types of cancer: gastric cancer, rectal cancer, colon cancer, lung cancer, pancreatic cancer, liver cancer, bladder cancer, glioma and oral cancer for both sexes and breast cancer, prostate cancer and ovarian cancer for the relevant sex. Our core search included the following terms: 'tea' AND ('cancer' OR 'cancers' OR 'carcinoma' OR 'carcinomas' OR 'neoplasm' OR 'neoplasms') AND ('cohort' OR 'cohort studies' OR 'nest case-control' OR 'nest case-control studies'). If a site-specific dataset had been published more than once, we used the most recent publication. We reviewed the reference lists of the identified reports, reviews, meta-analyses and other relevant publications to find additional pertinent studies. The medical subject heading, methods, population, study design, exposure and outcome variables of these articles were used to identify relevant studies.

A study was eligible for inclusion if the following criteria were fulfilled: (i) the study had a prospective observational design (prospective cohort or nested prospective case–control study); (ii) the study investigated the association between tea consumption and the risk of cancer incidence; and (iii) if comparisons between high and low tea consumption (with >2 categories) and estimates of the effect [risk ratio (RR), hazard ratio (HR) or odds ratio] with 95% confidence intervals (CIs) were reported. We excluded all case–control studies because various confounding factors could bias the results.

The literature search was performed independently by two authors (Y.-F.Z. and L.Z.) using a standardized approach. Any inconsistencies were resolved by discussions with the first author (Y.-H.Z.) until a consensus was reached. We excluded studies that were not published as full reports, for example conference abstracts and letters to editors. Studies of cancer precursors were also excluded.

Data collection and quality assessment

The following data elements were collected: first author or study group name, publication year, country, study design, assessment of tea consumption, sample size, age at baseline, number of men and women, follow-up duration, effect estimate, comparison categories and the covariates used in the fully adjusted model. We also extracted data on the number of cases per person or per person-year, the effect of different exposure categories and the 95% CIs. For studies that reported several multivariable adjusted RRs, we selected the effect estimate that was adjusted for the maximum number of potential confounders.

The Newcastle–Ottawa Scale (NOS) was used to evaluate methodological quality (Wells *et al.*, 2009; Higgins and Green, 2011). The NOS is a comprehensive tool that has been validated partially for the evaluation of the observational study quality in meta-analyses (Wells *et al.*, 2009). The NOS is based on three subscales: selection (four items), comparability (one item) and outcome (three items). A 'star system' (range 0–9) has been developed for the assessment (Supplementary Table 1). The data extraction and quality assessment were also performed independently by two authors (Y.-F.Z. and H.-W.Z.), and the information obtained was examined and independently verified by an additional author (Y.-H.Z.).

Statistical analysis

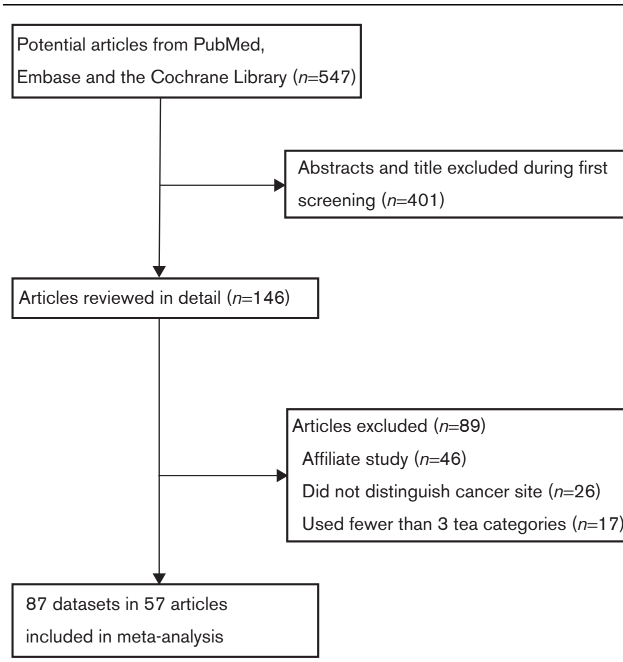
We examined the relationship between tea consumption and the risk of cancer incidence on the basis of the effect estimate (RR or HR) and corresponding 95% CI published in each study. We initially used a random-effects model to calculate summary RRs and 95% CIs for high tea consumption compared with low tea consumption (DerSimonian and Laird, 1986; Ades *et al.*, 2005). Using the generalized least-squares method for trend estimation, we then transformed the category-specific risk estimates into estimates of the RR associated with every additional cup of tea consumed in a day (Orsini *et al.*, 2006). In calculating these estimates, it was assumed that there was a linear relationship between the natural logarithm of the RR and increasing tea consumption. We converted all measures into cups per day and defined one cup as 125 ml of tea. The value assigned to each tea consumption category was the mid-point for closed categories and the median for open categories (assuming a normal distribution for tea consumption). We combined the RRs for each additional cup of tea consumed per day using a random-effect meta-analysis (DerSimonian and Laird, 1986). Finally, we carried out a dose–response random-effects meta-analysis on the basis of the correlated natural log of the RRs or HRs across the tea consumption categories (Greenland and Longnecker, 1992; Orsini *et al.*, 2006). To derive the dose–response curve, we modelled tea consumption using restricted cubic splines with three knots at fixed percentiles of 10, 50 and 90% of the distribution (Orsini *et al.*, 2006). This method requires effect measurements with variance estimates for at least three known categories of exposure.

We assessed the heterogeneity between studies using the I^2 statistic to measure the proportion of the total estimated variation that was attributable to study heterogeneity; I^2 values of 25, 50 and 75% were used as cut-off points for low, moderate and high degrees of heterogeneity, respectively (Higgins and Thompson, 2002; Higgins *et al.*, 2003; Deeks *et al.*, 2008). Subgroup analyses were carried out for the incidence of cancer according to sex, ethnic background and tea type. As the number of studies included was small, interaction tests based on the Student *t* distribution rather than on a normal distribution were performed to compare estimate differences for two subsets (e.g. men and women, Asia and USA or Europe, green tea and black tea) (Altman and Bland, 2003). Stratified analyses were carried out in an attempt to identify any additional potential residual confounding factors, such as assessment of exposure, the duration of the follow-up period and adjustments for covariates (including BMI, smoking status and alcohol consumption). We also carried out a sensitivity analysis by removing each individual study from the meta-analysis (Tobias, 1999). Several methods were used to check for potential publication bias. Funnel plots for the incidence of each cancer type were inspected visually. The Eagger (Egger *et al.*, 1997) and Begg (Begg and Mazumdar, 1994) tests were also used to assess publication bias statistically. All reported *P* values are two-sided, and for all of the studies included, *P* values less than 0.05 were considered statistically significant. Statistical analyses were carried out using STATA software (version 12.0; Stata Corporation, College Station, Texas, USA).

Results

Of the 547 citations identified from database searches, 87 datasets from 57 articles (Heilbrun *et al.*, 1986; Kinlen *et al.*, 1988; Shibata *et al.*, 1994; Goldbohm *et al.*, 1996; Zheng *et al.*, 1996; Harnack *et al.*, 1997; Hartman *et al.*, 1998; Key *et al.*, 1999; Michaud *et al.*, 1999, 2001, 2010; Nagano *et al.*, 2001; Terry and Wolk, 2001; Tsubono *et al.*, 2001; Zeegers *et al.*, 2001; Hoshiyama *et al.*, 2002; Su and Arab, 2002; Allen *et al.*, 2004; Suzuki *et al.*, 2004, 2005, 2009; Adebamowo *et al.*, 2005; Michels *et al.*, 2005; Larsson and Wolk, 2005; Hirvonen *et al.*, 2006; Kikuchi *et al.*, 2006; Kuriyama *et al.*, 2006; Ide *et al.*, 2007; Lee *et al.*, 2007; Silvera *et al.*, 2007; Steevens *et al.*, 2007; Sun *et al.*, 2007; Ganmaa *et al.*, 2008; Kurahashi *et al.*, 2008, 2009; Li *et al.*, 2008; Lin *et al.*, 2008; Tworoger *et al.*, 2008; Inoue *et al.*, 2009; Larsson *et al.*, 2009; Ui *et al.*, 2009; Bhoo Pathy *et al.*, 2010; Boggs *et al.*, 2010; Holick *et al.*, 2010; Iwasaki *et al.*, 2010; Ren *et al.*, 2010; Fagherazzi *et al.*, 2011; Ros *et al.*, 2011; Braem *et al.*, 2012; Dubrow *et al.*, 2012; Montague *et al.*, 2012; Shafique *et al.*, 2012; Sinha *et al.*, 2012; Geybels *et al.*, 2013; Hildebrand *et al.*, 2013; Luo *et al.*, 2007) fulfilled the inclusion criteria. The study selection process is shown in Fig. 1. A manual search of the references of the included studies did not yield any new eligible studies. Among the studies included, 20 were from the USA or Canada (Heilbrun *et al.*, 1986; Kinlen *et al.*, 1988; Shibata *et al.*, 1994; Zheng *et al.*, 1996; Harnack *et al.*, 1997; Michaud *et al.*, 1999, 2001; Su and Arab, 2002; Adebamowo *et al.*, 2005; Michels *et al.*, 2005; Silvera *et al.*, 2007; Ganmaa *et al.*, 2008; Tworoger *et al.*, 2008; Boggs *et al.*, 2010; Holick *et al.*, 2010; Ren *et al.*, 2010; Dubrow *et al.*, 2012; Sinha *et al.*, 2012; Hildebrand *et al.*, 2013), 15 were from Europe (Goldbohm *et al.*, 1996; Hartman *et al.*, 1998; Terry and Wolk, 2001; Zeegers *et al.*, 2001; Larsson and Wolk, 2005; Hirvonen *et al.*, 2006; Steevens *et al.*, 2007; Larsson *et al.*, 2009; Bhoo Pathy *et al.*, 2010; Michaud *et al.*, 2010; Fagherazzi *et al.*, 2011; Ros *et al.*, 2011; Braem *et al.*, 2012; Shafique *et al.*, 2012; Geybels *et al.*, 2013) and 22 were from Asia (Key *et al.*, 1999; Nagano *et al.*, 2001; Tsubono *et al.*, 2001; Hoshiyama *et al.*, 2002; Allen *et al.*, 2004; Suzuki *et al.*, 2004, 2005, 2009; Kikuchi *et al.*, 2006; Kuriyama *et al.*, 2006; Ide *et al.*, 2007; Lee *et al.*, 2007; Sun *et al.*, 2007; Kurahashi *et al.*, 2008, 2009; Li *et al.*, 2008; Lin *et al.*, 2008; Inoue *et al.*, 2009; Ui *et al.*, 2009; Iwasaki *et al.*, 2010; Luo *et al.*, 2007; Montague *et al.*, 2012). Table 1 summarizes the characteristics of the studies

Fig. 1



Flow diagram of the literature search and study selection process.

Table 1 Baseline characteristic of the studies included in the systematic review and meta-analysis

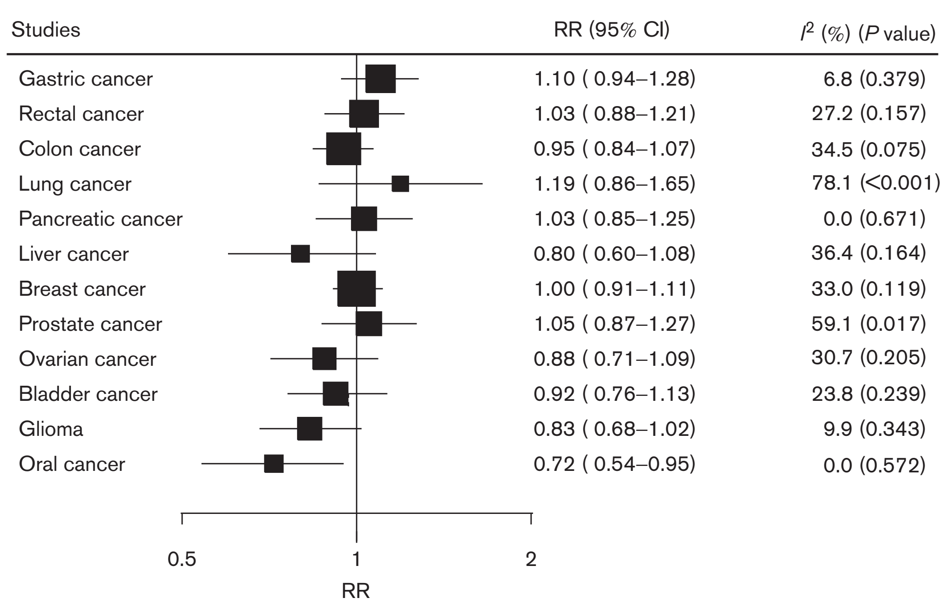
Types of cancer	Number of cohorts	Asia	USA and Europe	Green tea	Black tea	Mixed tea	Men	Women	Number of cases	Total sample size	Duration of follow-up (years)
Gastric cancer	8	5	3	5	1	2	441 388	366 484	2545	807 872	4.3–18.0
Rectal cancer	11	4	7	4	4	4	527 382	561 161	3871	1 154 458	4.3–19.0
Colon cancer	11	4	7	4	3	5	527 382	561 161	9716	1 154 458	4.3–20.0
Lung cancer	5	2	3	2	1	2	106 327	143 460	2532	249 787	4.3–18.0
Pancreatic cancer	9	3	6	3	1	5	169 378	277 773	1166	461 130	8.0–20.0
Liver cancer	4	3	1	3	1	0	48 868	58 081	800	106 949	9.0–19.0
Breast cancer	13	4	9	4	3	6	0	618 150	16741	618 150	4.3–22.0
Prostate cancer	7	4	3	4	4	0	187 017	0	4837	187 017	7.0–37.0
Ovarian cancer	6	0	6	0	1	5	0	619 714	2933	619 714	8.0–24.0
Bladder cancer	7	2	5	2	1	4	189 620	280 830	1792	470 450	7.0–19.0
Glioma	3	0	3	0	0	3	373 877	461 809	1582	1 245 995	8.5–24.0
Oral cancer	3	1	2	1	0	2	737 845	762 371	1297	1 500 216	10.3–26.0

included and Supplementary Table 2 summarizes the studies in greater depth. In total, the analysis included 49 812 incident cases and more than 8 020 078 individuals (3 309 084 men and 4 710 994 women). The follow-up times varied from 4.3 years (for cancer at multiple sites) to 37.0 years (for prostate cancer). The quality of the studies was assessed using the NOS and the details are listed in Supplementary Table 1.

Figure 2 shows the results of RR meta-analyses according to high versus low tea consumption. Separate meta-analyses for the type of cancer are provided in Supplementary Figs 1–12. The summary RR indicated that high tea consumption was associated with a reduced risk of oral cancer (RR 0.72; 95% CI 0.54–0.95). Furthermore, compared with low tea consumption, high tea consumption was not associated with gastric cancer (RR 1.10; 95% CI 0.94–1.28), rectal cancer (RR 1.03; 95% CI 0.88–1.21), colon cancer (RR 0.95; 95% CI 0.84–1.07), lung cancer (RR 1.19; 95% CI 0.86–1.65), pancreatic cancer (RR 1.03; 95% CI 0.85–1.25), liver cancer (RR 0.80; 95% CI 0.60–1.08), breast cancer (RR 1.00; 95% CI 0.91–1.11), prostate cancer (RR 1.05; 95% CI 0.87–1.27), ovarian cancer (RR 0.88; 95% CI 0.71–1.09), bladder cancer (RR 0.92; 95% CI 0.76–1.13) or glioma (RR 0.83; 95% CI 0.68–1.02). Interstudy heterogeneity was high for lung and prostate cancers, and moderate or low for all other cancers.

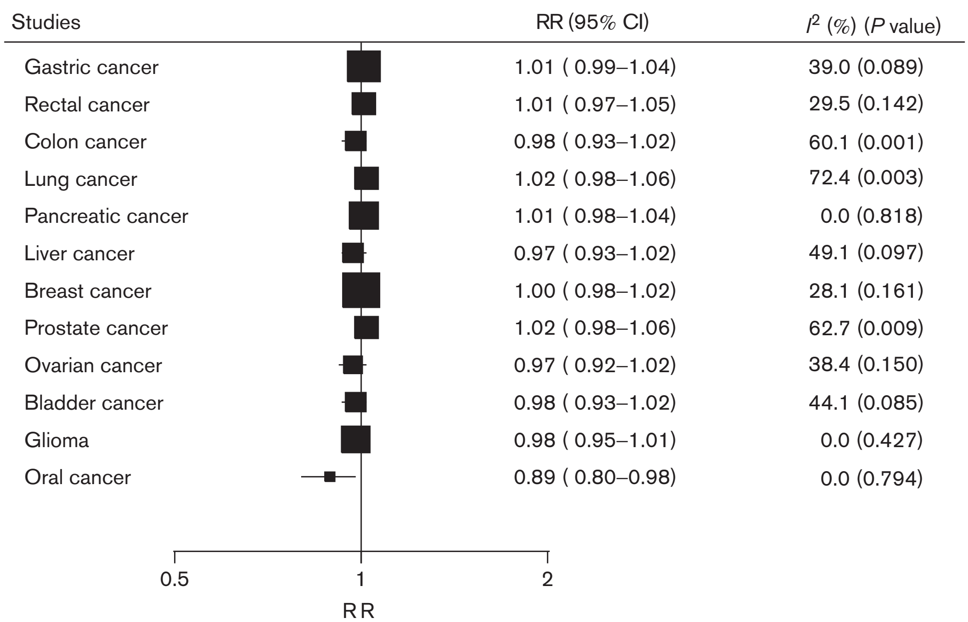
All the studies included were eligible for trend estimation. A dose–response analysis indicated that an additional one cup of tea each day was not associated with a decreased risk of gastric cancer (RR 1.01; 95% CI 0.99–1.04), rectal cancer (RR 1.01; 95% CI 0.97–1.05),

Fig. 2



Summary risk estimates by cancer sites for high versus low tea consumption. CI, confidence interval; RR, risk ratio.

Fig. 3



Summary risk estimates by cancer sites for one cup per day increment in tea consumption. CI, confidence interval; RR, risk ratio.

colon cancer (RR 0.98; 95% CI 0.93–1.02), lung cancer (RR 1.02; 95% CI 0.98–1.06), pancreatic cancer (RR 1.01; 95% CI 0.98–1.04), liver cancer (RR 0.97; 95% CI 0.93–1.02), breast cancer (RR 1.00; 95% CI 0.98–1.02), prostate cancer (RR 1.02; 95% CI 0.98–1.06), ovarian cancer (RR 0.97; 95% CI 0.92–1.02), bladder cancer (RR 0.98; 95% CI 0.93–1.02) or glioma (RR 0.98; 95% CI 0.95–1.01). Furthermore, increased tea consumption was associated with reduced risk of oral cancer (RR 0.89; 95% CI 0.80–0.98; Fig. 3). The heterogeneity between studies was high for colon, lung and prostate cancers, and moderate or low for other types of cancer (Supplementary Figs 13–24).

To assess the association between tea consumption and the incidence of different types of cancer, all of the studies were included in a restricted cubic splines analysis. As shown in Supplementary Figs 25–36, on the basis of the *P* value for nonlinearity, we found no evidence of a nonlinear relationship between tea consumption and the incidence of cancer.

Sensitivity analyses indicated that exclusion of any individual study did not significantly alter the results (data not shown). We stratified studies into groups according to sex, ethnic background and the tea type for different types of cancer to examine the sources of study heterogeneity. Results from the subgroup analyses of the RRs for a one cup per day increase in tea consumption for different cancer sites are listed in Table 2. We found that a one cup per day increase in the consumption of black tea was associated with an increased risk of breast cancer (RR 1.04; 95% CI 1.01–1.08). In western countries, we found that an increase of one cup of tea per day was associated with a reduced risk of bladder cancer (RR 0.95; 95% CI 0.91–0.98). Subgroup analyses on the basis of additional potential residual confounding factors were also carried out and are listed in Supplementary Table 3. Furthermore, subgroup analyses of the RRs for high versus low tea consumption for different types of cancer were also carried out, and the results are listed in Supplementary Table 4. Overall, we noted that high tea consumption was associated with an increased risk of gastric cancer in men. Moreover, high black tea consumption was also associated with an increased risk of breast cancer. When we repeated the analyses using a fixed-effects model instead of a random-effects model, the results were generally consistent (data not shown). Except for the incidence of breast cancer between consumers of green tea and black tea ($P = 0.033$; Table 2), there were no significant differences between subgroups in the effect of tea consumption on cancer incidence.

Although the Egger (Egger *et al.*, 1997) and Begg (Begg and Mazumdar, 1994) test results showed no evidence of publication bias for different types of cancer (Supplementary Figs 37–48), a review of the funnel plots did not rule out the potential of publication bias for different types of cancer (Supplementary Figs 37–48).

Discussion

Our large standardized meta-analysis indicates that increased tea consumption is associated with a reduction

Table 2 Subgroup analysis of risk ratios per one cup per day increase in tea consumption for different cancer sites

Cancer sites	Group	Number of cohorts	RR (95% CI)	Heterogeneity (%)	*P* value for heterogeneity	*P* value for interaction test
Gastric cancer	Sex					
	Men	4	1.04 (0.99–1.09)	64.1	0.039	0.097
	Women	3	0.98 (0.93–1.03)	0.0	0.742	
	Both	4	0.99 (0.96–1.03)	0.0	0.748	
	Country					
	Asia	8	1.00 (0.98–1.02)	0.0	0.439	0.467
	USA or Europe	3	1.03 (0.96–1.12)	50.8	0.131	
	Type of tea					
	Green tea	8	1.00 (0.98–1.02)	0.0	0.439	0.656
	Black tea	1	0.98 (0.90–1.07)	–	–	
	Mixed	2	1.08 (1.03–1.13)	0.0	0.497	
Rectal cancer	Sex					
	Men	6	1.07 (0.98–1.17)	33.3	0.186	0.119
	Women	4	0.98 (0.92–1.05)	0.8	0.388	
	Both	4	0.99 (0.93–1.04)	33.8	0.209	
	Country					
	Asia	6	1.01 (0.98–1.05)	0.0	0.864	1.000
	USA or Europe	8	1.01 (0.91–1.11)	57.5	0.021	
	Type of tea					
	Green tea	5	1.01 (0.98–1.05)	0.0	0.759	0.216
	Black tea	5	1.10 (0.97–1.26)	51.2	0.084	
	Mixed	4	0.93 (0.86–1.01)	0.0	0.537	
Colon cancer	Sex					
	Men	7	0.91 (0.78–1.06)	79.7	< 0.001	0.369
	Women	6	0.98 (0.93–1.03)	12.9	0.332	
	Both	4	1.00 (0.95–1.04)	30.7	0.228	
	Country					
	Asia	6	0.98 (0.95–1.02)	14.9	0.319	0.813
	USA or Europe	11	0.97 (0.90–1.05)	70.7	< 0.001	
	Type of tea					
	Green tea	5	0.98 (0.95–1.02)	14.9	0.319	0.596
	Black tea	4	0.96 (0.90–1.03)	0.0	0.903	
	Mixed	8	0.97 (0.86–1.09)	78.7	<0.001	
Pancreatic cancer	Sex					
	Men	5	1.02 (0.98–1.06)	0.0	0.972	1.000
	Women	4	1.02 (0.98–1.08)	0.0	0.975	
	Both	2	0.85 (0.59–1.22)	67.5	0.079	
	Country					
	Asia	5	1.01 (0.98–1.04)	0.0	0.798	0.797
	USA or Europe	6	1.02 (0.95–1.09)	0.0	0.511	
	Type of tea					
	Green tea	5	1.01 (0.98–1.04)	0.0	0.798	0.983
	Black tea	1	1.00 (0.41–2.43)	–	–	
	Mixed	5	1.00 (0.90–1.11)	6.3	0.371	
Breast cancer	Sex					
	Women	13	1.00 (0.98–1.02)	28.1	0.161	–
	Country					
	Asia	4	0.99 (0.96–1.02)	0.0	0.724	0.615
	USA or Europe	9	1.00 (0.98–1.03)	46.6	0.059	
	Type of tea					
	Green tea	4	0.99 (0.96–1.02)	0.0	0.724	0.033
	Black tea	3	1.04 (1.01–1.08)	0.0	0.372	
	Mixed	6	0.99 (0.97–1.01)	5.8	0.379	
Prostate cancer	Sex					
	Men	8	1.02 (0.98–1.06)	62.7	0.009	–
	Country					
	Asia	5	1.02 (0.96–1.07)	45.9	0.117	0.841
	USA or Europe	3	1.01 (0.93–1.09)	82.1	0.004	
	Type of tea					
	Green tea	4	1.01 (0.97–1.05)	19.1	0.295	0.834
	Black tea	4	1.02 (0.94–1.11)	79.5	0.002	
Bladder cancer	Sex					
	Men	3	0.95 (0.90–1.01)	0.0	0.486	0.903
	Women	2	0.97 (0.70–1.35)	78.3	0.032	
	Both	3	0.97 (0.93–1.01)	0.0	0.479	
	Country					
	Asia	3	1.02 (0.95–1.11)	63.9	0.063	0.106
	USA or Europe	5	0.95 (0.91–0.98)	0.0	0.632	
	Type of tea					
	Green tea	3	1.02 (0.95–1.11)	63.9	0.063	0.408
	Black tea	1	0.73 (0.33–1.60)	–	–	
	Mixed	4	0.95 (0.91–0.99)	0.0	0.541	

CI, confidence interval; RR, risk ratio.

in the risk of oral cancer, but has no significant effect on the risk of other common cancers. Our findings add to the results of previous reviews, and show the association between increased tea consumption and the risk of less common malignancies. Furthermore, our findings provide evidence that the association between tea consumption and breast cancer might differ for green tea and black tea. For most other types of cancer, the magnitude of the association between increased tea consumption and the risk of cancer was similar for both sexes, populations of different ethnic backgrounds and the type of tea consumed. These findings need to be confirmed in future studies.

Our current study assessed the methodological quality of the studies included using the NOS system (Wells *et al.*, 2009) and also evaluated the effect of tea consumption on the incidence of cancer at different sites in specific populations using subgroup analyses. We showed that the studies included used different methods to determine the type of tea consumed and that this was a source of significant heterogeneity in the correlation with the risk of cancer. This is a possible reason why our findings are inconsistent with those of earlier reports, which indicate that black tea is associated with reduced risk of breast cancer (Fon Sing *et al.*, 2011). Furthermore, the effect of ethnicity is underestimated. Black tea is more popular in western countries, and the results of our study indicate that this preference might have impacted the association found between bladder cancer and high tea consumption in western countries.

The negative correlation found between tea consumption and oral cancer might be explained by several biological mechanisms. Some of the constituents of tea, such as epigallocathechin-3-gallate and other polyphenols, could selectively induce apoptosis in oral carcinoma cells and subsequently inhibit cancer growth and invasion (Komori *et al.*, 1993; Stoner and Mukhta, 1995; Hsu *et al.*, 2002; Lee *et al.*, 2004; Schwartz *et al.*, 2005). In addition, several studies have also shown that green tea is useful for the prevention of dental caries and periodontal disease. Overall, these findings indicate that the risk of oral cancer could be reduced by increased tea consumption. However, further basic research is required to provide more evidence and identify the specific mechanisms underlying this effect in humans.

Increased tea consumption might play an important role in the risk of some cancers. The specificity of these associations suggests that these are not just because of confounding factors or bias, and that there is a possible causal relationship between increased tea consumption and the risk of developing some types of cancer. Some important confounding factors might not have been quantified or quantified with sufficient precision in these studies. Previous meta-analyses (Zheng *et al.*, 2012) have also reported inconsistent findings for pooled crude data and pooled adjusted data. For some types of cancer, smoking appears to be a major confounding factor for an association between increased tea consumption and the risk of cancer. This is exemplified in the case of lung cancer; however, we could not determine the effect of tea consumption on the risk of lung cancer because very few studies on this cancer subset were included in our study.

Several meta-analyses (Seely *et al.*, 2005; Sun *et al.*, 2006a, 2006b; World Cancer Research Fund/American Institute for Cancer Research, 2007; Zhou *et al.*, 2007, 2008; Arts, 2008; Myung *et al.*, 2009; Zhang *et al.*, 2010; Fon Sing *et al.*, 2011; Zheng *et al.*, 2011, 2012; Genkinger *et al.*, 2012; Qin *et al.*, 2012; Sasazuki *et al.*, 2012; Wang *et al.*, 2012; Wu *et al.*, 2013) have previously quantified the association between tea consumption and the risk of cancer at specific sites. Some studies have quantified these associations stratified by sex (Seely *et al.*, 2005; Sun *et al.*, 2006a, 2006b; World Cancer Research Fund/American Institute for Cancer Research, 2007; Zhou *et al.*, 2007, 2008; Arts, 2008; Myung *et al.*, 2009; Zhang *et al.*, 2010; Fon Sing *et al.*, 2011; Zheng *et al.*, 2011; Genkinger *et al.*, 2012; Qin *et al.*, 2012; Wang *et al.*, 2012; Wu *et al.*, 2013) or tea type (green tea or black tea) (Seely *et al.*, 2005; Sun *et al.*, 2006a, 2006b; World Cancer Research Fund/American Institute for Cancer Research, 2007; Zhou *et al.*, 2007, 2008; Arts, 2008; Myung *et al.*, 2009; Zhang *et al.*, 2010; Fon Sing *et al.*, 2011; Genkinger *et al.*, 2012; Zheng *et al.*, 2012; Qin *et al.*, 2012; Wu *et al.*, 2013), whereas other studies (Zheng *et al.*, 2011, 2012; Wang *et al.*, 2012) have not provided stratified data. Furthermore, there has been no uniformity in the inclusion criteria of earlier meta-analyses, and several have included both conventional case–control studies and cohort studies. In this study, we used uniform methods and definitions to carry out a dose–response meta-analysis of prospective observational studies to determine the association between tea consumption and the incidence of different types of cancer. In this stratified factor analysis, the probability of differences in cancers at several sites was raised (>6 datasets were included).

Subgroup group analyses indicated that the benefit of tea drinking was mainly the prevention of bladder cancer in western countries, and the harmful effect of tea drinking was an increased incidence of breast cancer for black tea consumers. The possible reasons for this could be that drinking more fluids is associated with a decreased risk of bladder cancer. The urogenous contact hypothesis suggests that the development of bladder cancer is associated with prolonged exposure to carcinogens in urine, and high tea consumption may reduce this exposure by diluting the urine and reducing the contact time by increasing the frequency of urination (Jones and Ross, 1999; Michaud *et al.*, 1999). Furthermore, the positive association between black tea consumption and breast cancer could be a consequence of black tea consumption being associated with increased plasma oestrone levels (Wu *et al.*, 2005).

In reviewing previous meta-analyses of the association between tea consumption and cancer, it is notable that most of the epidemiological evidence for the protective effect of tea comes from retrospective case–control studies. In traditional case–control studies, because information that reflects past exposure is collected subsequent to cancer diagnosis, recall bias is inevitable and cannot be ignored. This bias may partly explain the differences in the findings of prospective observational studies and retrospective case–control studies. Furthermore, the cut-off values for tea consumption categories differ between studies. Given the limitations of traditional case–control studies, the conclusion that high tea consumption is protective against the risk of cancer is not convincing.

The WCRF review (Wang *et al.*, 2013) also examined the association between tea consumption and several different types of cancer. However, in contrast with the WCRF review, we stratified the risk estimates according to sex, ethnic background and tea type. We also calculated risk estimates for several additional types of cancer. Moreover, despite attempts to standardize the methodological processes across different centres, the selection of studies for the WCRF review was inconsistent. Our combined risk estimates were generally more conservative than those from previous reviews, and we only found weak evidence for an association between increased tea consumption and the incidence of most common cancers.

Compared with previous meta-analyses, our meta-analysis has some obvious strengths. First, only prospective observational studies were included in our study, which eliminates selection bias and recall bias. Second, the large sample size allowed us to quantitatively assess the association between tea consumption and the risk of cancer at different sites, and thus our findings are potentially more robust than those of any individual study. Third, the dose–response analysis in our study included a wide range of tea consumption, which allowed for an accurate assessment of the relationship between the amount of tea consumed and the risk of cancer at different sites. Fourth, we assessed the association between tea consumption and the incidence of the most common cancers and less common cancers, and thus, we have presented a comprehensive profile of the anti-tumour effects of tea consumption.

However, our study has some limitations. First, we could not exclude the possibility of residual confounding factors from different diets. Second, relatively few studies include data on lung cancer, liver cancer, ovarian cancer, glioma and oral cancer, which limited our assessment of the relationship between the amount of tea consumed and incidence of these five types of cancer in some specific subsets of individuals. Third, the methods of assessing tea consumption differed across the studies included. Fourth, the level of tea consumption is generally assessed as the number of cups consumed per day or per week, but cup size may vary considerably in different studies. Finally, the adjusted models are different across the studies included, and these factors might play an important role in the development of cancers.

Despite the limitations, our findings have important public health implications. The prevention of cancer at different sites continues to be an important public health issue for researchers, especially in terms of how lifestyle can be altered to reduce the incidence of different types of cancer. Evidence from previous experimental and observational studies has suggested that the consumption of tea can have either a protective or a harmful effect depending on the specific type of cancer, although the results of these studies have been inconclusive. Systematic reviews and meta-analyses are therefore the most powerful assessment tool to clarify these inconsistent associations. Our present study provides evidence that tea consumption is associated with a reduced risk of oral cancer, and our subgroup analyses suggest that black tea consumption is associated with an increased risk of breast cancer. Furthermore, our meta-analysis indicates that high levels of tea consumption are associated with increased risk of gastric cancer in men. Finally, tea consumption was found to be associated with a reduced risk of bladder cancer in western countries. These protective and harmful effects of tea consumption need further investigation in large prospective studies.

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All authors contributed towards the planning, execution and interpretation of the submitted manuscript and read and approved the final manuscript.

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Conflicts of interest

There are no conflicts of interest.

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