# Green tea, black tea and colorectal cancer risk: a meta-analysis of epidemiologic studies 

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Experimental studies have supported tea as a chemopreventive agent for colorectal cancer. No quantitative summary of the epidemiologic evidence on tea and colorectal cancer risk has ever been performed. The current meta-analysis included 25 papers conducted in 11 countries across three continents (North America, Asia and Europe). Summary odds ratios (ORs) for highest versus non/lowest tea consumption levels were calculated based on fixed and random effects models. The meta-regression and stratified methods were used to examine heterogeneity across studies. For green tea, the combined results from eight studies indicated a reduced risk of colorectal cancer with intake [summary $\mathrm{OR}=\mathbf{0 . 8 2}, \mathbf{9 5 \%}$ confidence interval $(\mathrm{CI})=$ $0.69-0.98$ ]. The protective effect is mainly found among the three case-control studies of colon cancer (summary $\mathrm{OR}=\mathbf{0 . 7 4}, \mathbf{9 5 \%} \mathrm{CI}=\mathbf{0 . 6 0 - 0 . 9 3}$ ). Results from studies of rectal cancer irrespective of study design (case-control versus cohort) (summary $\mathrm{OR}=\mathbf{0 . 9 9}, \mathbf{9 5 \%} \mathrm{CI}=0.71-$ 1.37) and cohort studies of colon cancer (summary $\mathrm{OR}=0.99,95 \% \mathrm{CI}=0.79-1.24$ ) were compatible with the null hypothesis. For black tea, the summary OR derived from 20 studies was 0.99 ( $95 \%$ CI $=0.87-1.13$ ). There is wide divergence in results across the 20 individual studies; formal tests for homogeneity across studies revealed statistically significant differences in findings across all studies ( $P<0.001$ ), amongst the 7 cohort studies ( $P=0.002$ ), and amongst the 13 case-control studies ( $P<0.001$ ). Despite the strong evidence from in vitro and non-human in vivo studies in support of green and black tea as potential chemopreventive agents against colorectal cancer, available epidemiologic data are insufficient to conclude that either tea type may protect against colorectal cancer in humans.

## Introduction

The hypothesis of tea as a chemopreventive agent for colorectal cancer development has been extensively studied using in vitro and non-human in vivo experiments. From

[^0]mutagenicity to tumor development, the majority of experimental studies supported this hypothesis. Over the last three decades, a number of epidemiologic studies were conducted to investigate the association between tea consumption and colorectal cancer risk in humans. Recent narrative reviews $(1,2)$ concluded that epidemiologic studies did not provide consistent evidence to support tea as chemopreventive agent for colorectal cancer development. There has never been any quantitative attempt to summarize the results on a possible teacolorectal cancer association. This report presents results of a meta-analysis of all published data on this topic, including testing for homogeneity between studies, and computation of summary odds ratios (ORs) for colorectal cancer in relation to green tea and black tea separately.

## Materials and methods

## Literature search strategy

To search for observational studies of tea consumption in relation to colorectal cancer risk, we conducted a literature search in the following four medical literature databases, MEDLINE, EMBASE, CANCERLIT and BIOSIS PREVIEWS, restricting to English-language papers published from January 1966 to July 2005. For the search on outcome, we identified articles using medical-subject-heading terms 'colorectal neoplasms, colonic neoplasms, or rectal neoplasms', or keywords 'colorectal cancer, colon cancer, rectal cancer, or large bowel cancer.' For the search on exposure, we identified articles using medical-subject-heading terms 'tea, flavonoids, or catechin', or keywords 'green tea, black tea, flavonoid, catechin, thearubigin, or theaflavin.' For the search on study design, we identified articles using medical-subjectheading terms or keywords, 'case-control studies', 'retrospective studies', 'cohort studies', or 'prospective studies.' Articles satisfying the exposure, outcome, and study design criteria were pulled. In addition, all bibliographies of retrieved papers were screened for further relevant publications.

For inclusion in the meta-analysis, the identified articles have to provide information on: (i) the number of colorectal cancer cases and controls studied; and/or (ii) the OR or relative risk (RR) and its corresponding 95\% confidence interval (CI), for highest versus non/lowest level of tea intake. In total, forty papers (3-42) were identified. Three ecological studies $(7,13,33)$ were excluded because they did not satisfy the study design criterion. The report by Tuyns et al. (39) was excluded because tea intake was not examined apart from coffee intake. Five reports $(6,10,24,25,37)$ from two ongoing case-control studies in Italy have been published; only the latest one (37) that analyzed the combined data from these two studies was selected. Zheng et al. $(42)$ and Arts et al. $(3,4)$ reported on the same study (the Iowa Women's Health Study); the report by Zheng et al. (42) was selected because it assessed tea exposure in a similar way as all other studies (cups per day as opposed to total catechins from tea in Arts et al.). The report by Khan et al. (22) and Kinlen et al. (23) were excluded because colorectal cancer mortality instead of incidence was investigated as the outcome of interest. Three studies $(9,31,36)$ were excluded due to insufficient information on numbers of cases and controls, and ORs and their corresponding 95\% CIs. Thus, the meta-analysis on tea and colorectal cancer included 25 papers in total. There were seven papers on green tea $(19-21,28,29,35,41)$ and 20 papers on black tea $(5,8,11,12$, $14-19,21,26,27,30,32,34,37,38,40,42)$, including two papers $(19,21)$ reporting on both green and black tea intake.

[^1]reported on total numbers of cases and controls per category of tea exposure. Thus, for these two studies, we computed crude OR and its corresponding $95 \%$ CI based on the published numbers of cases and controls per category of tea intake.

Statistical computing was performed using the STATA statistical software (College Station, Texas). For cohort studies, the percentages of subjects in the highest and non/lowest consumption levels were calculated either as the proportions of the numbers of subjects in these two categories over the total number of study subjects $(12,14,15,28,34,38,42)$, or as the proportions of person-years in these two categories over the total person-years $(26,35)$. For case-control studies, the proportions (expressed as percentages) of control subjects in the highest and non/lowest consumption categories were stated.
Eight studies $(8,14,19,21,28,35,40,42)$ reported subsite specific (colon and rectum respectively) ORs/RRs (95\% CIs) without comparable figures for colorectal cancer. For these studies, we calculated an overall OR (95\% CI) for colorectal cancer by means of a weighted average of the subsite specific estimates, with the individual weight being the inverse of the respective subgroup variance (43). Zhang et al. (41) reported on four time-period (20 years ago, 10 years ago, 5 years ago, and current) specific OR ( $95 \% \mathrm{CI}$ ) for colorectal cancer by gender. We used the 'weighted average' approach described above on the three earliest time periods ( 20 years ago, 10 years ago, and 5 years ago) to obtain overall gender-specific risk estimates. This 'weighted average' approach was again used to compute an OR $(95 \% \mathrm{CI})$ for colorectal cancer in both sexes combined, based on gender specific estimates in Il'yasova et al. (17) and Zhang et al. (41), and gender/subsite specific estimates in Ji et al. (20). For the latter study, we also derived gender specific and subsite specific estimates of OR ( $95 \%$ CI) from reported figures in the gender/subsite specific cells. Fredrikson et al. (11) reported on ORs and their 90\% CIs. The 95\% CI was recalculated as follow: EXP[LN(OR) $\pm 1.96$ Standard Error]; Standard Error was calculated as [LN(upper 90\% confidence limit) - LN( lower 90\% confidence limit) $] /(2 \times 1.645)$.

We examined possible heterogeneity in results across studies using the Q statistic (44). We defined statistical significance as $P<0.10$ rather than the conventional level of 0.05 because of the low power of this test (45). The null hypothesis that the studies are homogeneous would be rejected if $P$ is less than 0.10 . When there is significant heterogeneity among study results, the random effect model was used to calculate summary OR while the fixed effect model was used to calculate summary OR among studies with homogeneous results. The causes of heterogeneity were explored through both meta-regression and stratified analyses. We investigated whether the following factors contributed to the heterogeneity between studies: study design (case-control versus cohort studies), race/ethnicity (Western versus Japanese populations), method of assessing tea intake (in-person interview versus other assessment methods), year of publication of the study report (before 2000, year 2000 or later), adjustment for coffee consumption (yes versus no), and adjustment for other potential dietary confounders (yes versus no).

Results of the meta-analysis may be biased if the probability of a study being published is dependent on its results. In other words, studies with strong positive findings may be more likely to be published. In an attempt to detect publication bias, we first visually explored asymmetry in Begg's funnel plots, that is, plots of effect estimates against their estimated precision (46). In the absence of a publication bias, the funnel plot should be symmetrical with estimates from larger studies in the center, flanked equally on either side by the less precise estimates. The funnel plots would be skewed (i.e. asymmetrical) in the presence of a publication bias. We formally tested the degree of asymmetry in the funnel plot using Egger's un-weighted regression asymmetry test (47). We considered the funnel plot to be asymmetrical if the intercept of Egger's regression line deviated from zero with a $P$ value of less than 0.10 . We should note that this test for asymmetry possesses relatively low power to detect a real publication bias when the total number of studies included in the meta-analysis is small ( 25 or fewer), which is the case in the current review.

## Results

## Green tea

Eight studies (19-21,28,29,35,41) [results from two separate cohort studies were reported in ref. (35)] were included in the meta-analysis on green tea consumption in relation to colorectal cancer risk. There were four cohort studies $(28,29,35)$, two population-based case-control studies (PCCs) $(20,21)$, and two hospital-based case-control studies (HCCs) $(19,41)$ (Table I, Figure 1).

Six of the eight studies were conducted in Japan $(19,21,28,29,35)$ while the remaining two were conducted in China $(20,41)$. There was significant heterogeneity across the studies $(P=0.03)$. The overall results showed a statistically significant, $18 \%$ reduction in risk of colorectal cancer with high green tea consumption (summary OR $=0.82$, $95 \% \mathrm{CI}=0.69-0.98)$. Meta-regression analysis revealed that study design $(P=0.01)$ is a major contributor to the observed heterogeneity, followed by year of publication ( $P=0.07$ ). Among the eight studies, only one assessed green tea intake using in-person interviews (20) and most studies did not adjust for potential dietary confounders ( $20,21,28,29,41$ ). However, method of assessing tea intake (in-person interview versus other methods) and whether adjustment for dietary factors were made were unrelated to study heterogeneity ( $P=0.62$ and 0.94 , respectively).

When we stratified the various studies by design (casecontrol versus cohort), results were consistent within the four cohort studies $(P=0.18)$ and within the four case-control studies ( $P=0.18$ ), but were divergent across the two designs ( $P=0.02$ ) (Table II). The inverse association between green tea intake and colorectal cancer risk was observed only in case-control studies (summary OR $=0.74,95 \% \mathrm{CI}=$ $0.63-0.86$ ). Cohort studies did not support such an association (summary OR $=0.97,95 \% \mathrm{CI}=0.82-1.16$ ). When we stratified the studies by country (China versus Japan), a stronger finding was noted among the two studies conducted in China (summary OR $=0.65,95 \% \mathrm{CI}=0.45-0.93$ ) compared to those conducted in Japan (summary OR $=0.93,95 \% \mathrm{CI}=$ 0.80-1.07) (Table II).

Results among women were highly divergent $(P<0.001)$ while results among men were consistent ( $P=0.97$ ) (Table II). The overall results in women show a non-significant $50 \%$ reduction in colorectal risk with high intake of green tea (summary $\mathrm{OR}=0.52,95 \% \mathrm{CI}=0.25-1.05$ ). No such effect was noted in men (summary $\mathrm{OR}=0.89,95 \% \mathrm{CI}=0.73-1.08$ ) $(P$ for gender difference $=0.16)($ Table II) .

High green tea intake was associated with a moderate reduction in risk for colon cancer (summary $\mathrm{OR}=0.86$, $95 \% \mathrm{CI}=0.73-1.00$ ), mainly based on case-control findings (summary OR $=0.74,95 \% \mathrm{CI}=0.60-0.93$ ). Cohort studies did not support an association between green tea and colon cancer (summary OR $=0.99,95 \% \mathrm{CI}=0.79-1.24$ ). Results in rectal cancer were highly divergent and there was no indication of any association with green tea intake (Table II).

Based on visualization of the Begg's funnel plot (Figure 2), there was some suggestion of publication bias in the reporting of results on green tea intake and colorectal cancer risk. However, formal testing using the Eggers's method did not support the notion of a publication bias (intercept $=-0.007$, $P=0.98$ ).

## Black tea

Twenty studies (5,8,11,12,14-19,21,26,27,30,32,34,37,38, 40,42 ), including seven cohort studies (12,14,15,26,34, 38,42 ), nine population-based case-control studies $(5,8,11,17$, $18,21,30,32,40)$, and four hospital-based case-control studies $(16,19,27,37)$ were included in the meta-analysis on black tea consumption and colorectal cancer risk (Table III, Figure 3). There was statistically significant heterogeneity in results across the 20 studies ( $P<0.001$ ). Results were different among the seven cohort studies $(P=0.002)$. Similarly, the 13 case-control studies yielded varying results ( $P=0.001$ ).

Table I. Green tea consumption and colorectal cancer risk

| Study | Design | Study period | Population | No. of cases/ No. of noncases | Lowest consumption level | No. of exposure levels | \% in lowest, highest level | Highest consumption level | $\begin{aligned} & \text { RR }(95 \% \mathrm{CI}) \\ & \text { for highest versus } \\ & \text { lowest level } \end{aligned}$ |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| Cohort studies |  |  |  |  |  |  |  |  |  |
| Suzuki 2005 (35) | Cohort | 1984-1992 | Japan | 269/26 042 | <1 cup/day | 4 | 18\%, 43\% | 5+ cups/day | $1.15(0.81-1.64)^{\text {a }}$ |
| Cohort 1 |  |  |  | 158 colon |  |  |  |  | 1.03 (0.65-1.64) |
|  |  |  |  | 111 rectum |  |  |  |  | 1.34 (0.77-2.33) |
| Suzuki 2005 (35) Cohort 2 | Cohort | 1990-1997 | Japan | 247/39 357 | $<1$ cup/day | 4 | 29\%, $26 \%$ | 5+ cups/day | 0.75 (0.53-1.06) ${ }^{\text {a }}$ |
|  |  |  |  | 147 colon |  |  |  |  | 0.93 (0.59-1.46) |
|  |  |  |  | 100 rectum |  |  |  |  | 0.57 (0.34-0.95) |
|  |  | 1984-1997 | Japan | Cohort $1+2$ | <1 cup/day | 4 | 25\%, 33\% | 5+ cups/day | $0.95(0.65-1.40)^{\mathrm{a}}$ |
|  |  |  |  | $304 \text { male }$ |  |  |  |  | $0.86(0.62-1.20)^{\mathrm{a}}$ |
|  |  |  |  | 212 female <br> 596/35 729 |  |  |  |  | 1.07 (0.83-1.39) ${ }^{\text {a }}$ |
| Nagano 2001 (28) | Cohort | 1979-1994 | Japan | 412 colon | 0-1 time/day | 3 | 15\%, 27\% | 5+ times/day | $\begin{aligned} & 1.07(0.83-1.39)^{a} \\ & 1.00(0.76-1.40) \end{aligned}$ |
|  |  |  |  | 184 rectum |  |  |  |  | 1.30 (0.77-2.10) |
| Nakachi 2000 (29) | Cohort | 1986-1997 | Japan | 60/8492 | $\leq 3$ cups/day | 3 | NA | 10+ cups/day | 0.56 (0.22-1.40) |
| Population-based case-control (PCC) studies |  |  |  |  |  |  |  |  |  |
| Ji 1997 (20) | PCC | 1990-1993 | China | 1728/1462 | Non-drinkers | $\begin{aligned} & 3 \text { (female) } \\ & 4 \text { (male) } \end{aligned}$ | $\begin{aligned} & 77 \%, 10 \% \\ & 39 \%, 21 \% \end{aligned}$ | $\begin{aligned} & \geq 3500 \mathrm{~g} \\ & \geq 8500 \mathrm{~g} \end{aligned}$ | 0.76 (0.60-0.95) ${ }^{\text {b }}$ |
|  |  |  |  | 861 female |  |  |  |  | 0.57 (0.40-0.83) ${ }^{\text {a }}$ |
|  |  |  |  | 867 male |  |  |  |  | 0.90 (0.67-1.21) ${ }^{\text {a }}$ |
|  |  |  |  | 885 colon |  |  |  |  | 0.83 (0.61-1.14) ${ }^{\text {c }}$ |
|  |  |  |  | 843 rectum |  |  |  |  | $0.68(0.49-0.95)^{\text {c }}$ |
| Kato 1990 (21) | PCC | 1986-1990 | Japan | 221/578 | < Daily | 2 | NA | Daily | $0.81(0.59-1.11)^{\mathrm{a}}$ |
|  |  |  |  | 132 colon |  |  |  |  | 0.61 (0.41-0.91) |
|  |  |  |  | 91 rectum |  |  |  |  | 1.32 (0.78-2.23) |
| Hospital-based case-control (HCC) studies |  |  |  |  |  |  |  |  |  |
| Zhang 2002 (41) | HCC | 1996-1998 | China | 102/99 | Never | 2 | NA | Ever | $0.52(0.36-0.74)^{\text {c }}$ |
|  |  |  |  | 45/44 female |  |  |  |  | 0.23 (0.13-0.41) |
|  |  |  |  | 57/55 male |  |  |  |  | 0.91 (0.56-1.48) |
| Inoue 1998 (19) | HCC | 1990-1995 | Japan | 628/21 128 | Rarely | 5 | 6\%, 12\% | 7+ cups/day | 0.90 (0.60-1.35) ${ }^{\text {a }}$ |
|  |  |  |  | 362 colon |  |  |  |  | 0.77 (0.47-1.26) |
|  |  |  |  | 266 rectum |  |  |  |  | 1.25 (0.62-2.51) |

${ }^{a}$ Calculation based on colon and rectal specific estimates.
${ }^{\mathrm{b}}$ Calculation based on gender and colon/rectum specific estimates.
${ }^{\mathrm{c}}$ Calculation based on gender-specific estimates.


Fig. 1. Meta-analysis of green tea and colorectal cancer risk.

The summary OR based on all 20 studies was 0.99 (95\% $\mathrm{CI}=0.87-1.13$ ).

Meta-regression analysis revealed that study population (Western versus Japanese) contributed significantly to the overall heterogeneity ( $P=0.002$ ). The summary OR based on three Japanese studies (two were conducted in Japan and one was conducted among Japanese men in Hawaii) $(15,19,21)$ (Summary OR $=1.62,95 \% \mathrm{CI}=1.22-2.14$ ) was significantly higher than the summary OR based on Western populations (5,8,11,12,14,16-18,26,27,30,32,34,37,38,40,42) (summary $\mathrm{OR}=0.93,95 \% \mathrm{CI}=0.82-1.06)$. Study design $(P=0.35)$ and the year of publication of the study report $(P=0.90)$ did not contribute to the observed heterogeneity across study results. Five studies adjusted for coffee intake ( $8,12,19,27,38$ ), and seven studies assessed black tea intake through in-person interviews (15-18,27,32,37). Only six studies failed to adjust for potential dietary confounders in some ways ( $11,15,16,18,21,27$ ). There was no evidence that failure to adjust for coffee intake ( $P=0.63$ ) or dietary confounders ( $P=0.78$ ), or the varying method of assessing tea intake (in person interview versus other methods) $(P=0.17)$ play a role in the heterogeneous findings across studies.

We also examined, using stratified analyses, whether study design (case-control versus cohort), method of assessing black tea intake (in person interview versus other methods), year of

| Category of studies | No. of studies | $\begin{aligned} & \text { Summary OR } \\ & (95 \% \mathrm{CI}) \end{aligned}$ | $P$ for heterogeneity |
| :---: | :---: | :---: | :---: |
| Colorectal cancer |  |  |  |
| All studies | 8 | 0.82 (0.69-0.98) | 0.03 |
| Cohort studies | 4 | 0.97 (0.82-1.16) | 0.18 |
| Case-control studies | 4 | 0.74 (0.63-0.86) | 0.18 |
| Cohort versus case-control studies |  |  | 0.02 |
| China studies | 2 | 0.65 (0.45-0.93) | 0.08 |
| Japan studies | 6 | 0.93 (0.80-1.07) | 0.31 |
| China versus Japan studies |  |  | 0.07 |
| Published before year 2000 | 3 | 0.80 (0.67-0.94) | 0.77 |
| Published on or after year 2000 | 5 | 0.81 (0.59-1.12) | 0.006 |
| Published before versus on or after 2000 |  |  | 0.95 |
| Not adjust for any dietary factor | 5 | 0.76 (0.60-0.98) | 0.03 |
| Adjusted for dietary factors | 3 | 0.92 (0.74-1.13) | 0.24 |
| Not versus adjusted for dietary factor |  |  | 0.25 |
| Women only | 3 | 0.52 (0.25-1.05) | $<0.001$ |
| Men only | 3 | 0.89 (0.73-1.08) | 0.97 |
| Women versus men |  |  | 0.16 |
| Colon cancer |  |  |  |
| All studies | 6 | 0.86 (0.73-1.00) | 0.45 |
| Cohort studies | 3 | 0.99 (0.79-1.24) | 0.95 |
| Case-control studies | 3 | 0.74 (0.60-0.93) | 0.49 |
| Cohort versus case-control studies |  |  | 0.07 |
| Rectal cancer |  |  |  |
| All studies | 6 | 0.99 (0.71-1.37) | 0.03 |
| Cohort studies | 3 | 0.99 (0.57-1.73) | 0.04 |
| Case-control studies | 3 | 0.98 (0.61-1.60) | 0.06 |
| Cohort versus case-control studies |  |  | 0.98 |
| Colon versus rectal cancer |  |  | 0.45 |

publication of the study report (before 2000, year 2000 or later), and adjustment for coffee intake or other dietary factors (yes versus no) played any roles in the immense heterogeneity across studies. We excluded the three Japanese studies from this exercise, given that black tea intake is rare in Japan, thus rendering a meaningful interpretation of study results from these studies quite difficult, if not impossible. Results for the 13 studies that did not adjust for coffee intake were heterogeneous ( $P<0.001$ ) while the four studies that did adjust for coffee intake were relatively homogenous ( $P=0.88$ ). However, summary ORs were similar between studies that did not adjust for coffee intake (summary OR $=0.94$, $95 \%$ $\mathrm{CI}=0.80-1.10$ ) and those that did (summary OR $=0.89,95 \%$ CI $=0.74-1.07$ ) (Table IV). Consistent with results of the meta-regression analysis, year of publication, method of tea assessment, and whether dietary confounders were taken into consideration were unrelated to the heterogeneity across studies (Table IV).

We examined the black tea-colorectal cancer association in men and women separately. Results differed between men and women $(P=0.03)$. The overall results in women indicated a statistically significant protective effect of black tea on colorectal cancer risk (summary OR $=0.82,95 \% \mathrm{CI}=$ $0.70-0.95$ ). No such association was seen in men (summary $\mathrm{OR}=1.15,95 \% \mathrm{CI}=0.89-1.50$ ) (Table IV).

Table IV also shows the meta-analysis results on black tea and colorectal cancer risk separately for colon and rectal cancers. The summary ORs were $1.02(95 \% \mathrm{CI}=0.88-1.18)$


Fig. 2. Begg's funnel plot of green tea consumption and colorectal cancer risk.
and 0.91 ( $95 \% \mathrm{CI}=0.73-1.12$ ) for colon cancer and rectal cancer, respectively. There was no evidence that results on colon cancer differed from those on rectal cancer ( $P=0.40$ ).

There was no indication of a publication bias in the reporting of results on black tea and colorectal cancer, either from visualization of the Begg's funnel plot or the Eggers's test of asymmetry (intercept $=0.18, P=0.12$ ) (Figure 4).

## Discussion

This meta-analysis evaluated the association between green tea and black tea consumption and colorectal cancer risk, based on published results from epidemiological studies. We conclude that there is insufficient information from the relatively few number of epidemiologic studies to provide a definitive assessment on the relationship between black or green tea intake and colorectal cancer risk in humans.

The overall summary OR on green tea and colorectal cancer association, based on eight studies conducted in native Chinese $(20,41)$ or Japanese $(19,21,28,29,35)$, indicated a statistically significant $18 \%$ reduction in risk associated with high green tea consumption. However, there was substantial heterogeneity among these eight studies, of which study design is a major source. The reduced risk of colorectal cancer in green tea drinkers was observed in case-control studies only (19-21,41). Furthermore, the protection seemed to be limited to the colon subsite. Given the recognized methodological limitations of the case-control study design, it is premature to conclude at this time that epidemiologic data are in support of green tea as a chemopreventive agent against colorectal cancer in humans. The studies $(20,41)$ conducted in China showed a stronger inverse association between green tea and colorectal cancer than studies conducted in Japan. The relative lack of unexposed subjects in Japan (only a small segment of the population do not consume green tea on a daily basis) could be one reason for the weaker associations in Japanese.
Black tea consumption is rare in Japanese ( $15,19,21$ ), whose main tea beverage is green tea. This gives rise to the concern that a meaningful interpretation of any observed black teacolorectal cancer association in Japanese may not be possible. Indeed, results in Japanese were statistically significantly different from those in western populations ( $P<0.001$ ).

Table III. Black tea consumption and colorectal cancer risk

| Study | Design | Study period | Population | No. cases/ No. noncases | Lowest consumption level | No. of consumption levels | \% in lowest, highest levels | Highest consumption level | RR (95\% CI) for highest versus lowest level |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| Cohort studies |  |  |  |  |  |  |  |  |  |
| Michels 2005 (26) | Cohort | 1980-1998 | USA | 1402/132 455 | Never | 5 | 24\%, 12\% | $2+$ cups/day | 1.01 (0.83-1.22) |
|  |  |  |  | 1146 colon |  |  |  |  | 1.07 (0.86-1.33) ${ }^{\text {a }}$ |
|  |  |  |  | 256 rectum |  |  |  |  | 0.81 (0.51-1.28) ${ }^{\text {a }}$ |
|  |  |  |  | 886 female |  |  |  |  | 0.96 (0.76-1.22) |
|  |  |  |  | 552 male |  |  |  |  | 1.12 (0.78-1.59) |
| Su 2002 (34) | Cohort | 1982-1992 | USA | 250/9970 | Non-users | 3 | $37 \%$, NA | $1.5+$ cups/day | 0.59 (0.35-1.00) |
|  |  |  |  | Colon only |  |  |  |  |  |
|  |  |  |  | 134 female |  |  |  |  | $0.74(0.40-1.39)^{\text {a }}$ |
|  |  |  |  | 116 male |  |  |  |  | 0.30 (0.09-0.98) ${ }^{\text {a }}$ |
| Terry 2001 (38) | Cohort | 1987-1998 | Sweden | 460/61 003 | <1 cup/week | 4 | 32\%, 8\% | $2+$ cups/day | 0.98 (0.64-1.51) |
|  |  |  |  | Female only |  |  |  |  |  |
|  |  |  |  | 291 colon |  |  |  |  | 0.74 (0.42-1.31) |
|  |  |  |  | 159 rectum |  |  |  |  | 1.53 (0.77-3.03) |
| Hartman 1998 (14) | Cohort | 1985-1993 | Finland | 185/26 923 | Non-drinkers | 3 | 64\%, 18\% | 1+ cups/day | $1.55(1.08-2.21)^{\text {b }}$ |
|  |  |  |  | Male only |  |  |  |  |  |
|  |  |  |  | 106 colon |  |  |  |  | 2.09 (1.34-3.26) |
|  |  |  |  | 79 rectum |  |  |  |  | 0.87 (0.47-1.60) |
| Goldbohm 1996 (12) | Ca-Cohort | 1986-1990 | The Netherlands | 564/2929 | Non-drinkers | 6 | 13\%, 16\% | 5+ cups/day | 0.94 (0.66-1.34) |
|  |  |  |  | 347 colon |  |  |  |  | 0.83 (0.53-1.30) ${ }^{\text {a }}$ |
|  |  |  |  | 213 rectum |  |  |  |  | $1.15(0.68-1.95)^{\mathrm{a}}$ |
|  |  |  |  | 236 female |  |  |  |  | $0.70(0.42-1.16)^{\text {b }}$ |
|  |  |  |  | 324 male |  |  |  |  | $1.22(0.78-1.93)^{\text {b }}$ |
| Zheng 1996 (42) | Cohort | 1986-1993 | USA | 474/34 895 | Never/monthly | 4 | 58\%, 9\% | $2+$ cups/day | $0.71(0.48-1.04)^{\text {b }}$ |
|  |  |  |  | Female only |  |  |  |  |  |
|  |  |  |  | 350 colon |  |  |  |  | 0.71 (0.45-1.11) |
|  |  |  |  | 124 rectum |  |  |  |  | 0.70 (0.34-1.46) |
| Helibrun 1986 (15) | Cohort | 1965-1985 | USA Japanese | 76/6882 | Almost never | 5 | 51\%, 2\% | Once/day | 3.87 (1.48-10.1) ${ }^{\text {c }}$ |
|  |  |  | men in Hawaii | Male only |  |  |  |  |  |
|  |  |  |  | Rectum only |  |  |  |  |  |
| Population-based case-control (PCC) studies |  |  |  |  |  |  |  |  |  |
| Ilyasova 2003 (17) | PCC | 1998-1999 | Russia | 663/323 | $<80 \mathrm{~g} /$ month | 3 | 55\%, 18\% | $>160 \mathrm{~g} / \mathrm{month}$ | $0.54(0.36-0.81)^{\mathrm{a}}$ |
|  |  |  |  | Rectum only |  |  |  |  |  |
|  |  |  |  | 320/201 female |  |  |  |  | 0.40 (0.23-0.70) |
|  |  |  |  | $342 / 121$ male |  |  |  |  | 0.77 (0.42-1.43) |
| Ilyasova 2003 (18) | PCC | 1996-2000 | USA | $630 / 1040$ | Non-drinkers | 3 | 23\%, 14\% | $2+$ servings/day | 1.30 (0.90-1.80) |
|  |  |  |  | Colon only |  |  |  |  |  |
| Woolcott 2002 (40) | PCC | 1992-1994 | Canada | 1823/2088 | <1 cup/day | 4 | 52\%, 5\% | 5+ cups/day | 1.14 (0.88-1.47) ${ }^{\text {b }}$ |
|  |  |  |  | 967 colon |  |  |  |  | 1.13 (0.79-1.61) |
|  |  |  |  | 856 rectum |  |  |  |  | $1.15(0.79-1.66)$ |
|  |  |  |  | NA female |  |  |  |  | $0.84(0.56-1.25)^{\text {b }}$ |
|  |  |  |  | NA male |  |  |  |  | $1.38(0.97-1.94)^{\text {b }}$ |
| Cerhan 2001 (8) | PCC | 1986-1989 | USA | 1279/2393 | None | 4 | 54\%, 5\% | >5 cups/day | $0.87(0.61-1.26)^{\text {b }}$ |
|  |  |  |  | 650 colon |  |  |  |  | 0.70 (0.40-1.30) |
|  |  |  |  | 629 rectum |  |  |  |  | 1.00 (0.60-1.50) |
| Slattery 1999 (32) | PCC | 1991-1994 | USA | $1993 / 2410$ | None | 3 | 60\%, 10\% | >1 cup/day | 0.98 (0.79-1.21) |
|  |  |  |  | Colon only |  |  |  |  |  |
| Fredrikson 1995 (11) | PCC | 1980-1983 | Sweden | 329/658 | <2 cups/day | 2 | NA | $2+$ cups/day | 0.61 (0.38-0.97) |
| Baron 1994 (5) | PCC | 1986-1998 | Sweden | 569/512 | None | 3 | 46\%, 22\% | $2+$ cups/day | 0.79 (0.57-1.10) |
|  |  |  |  | 352 colon |  |  |  |  | 0.96 (0.67-1.37) |
|  |  |  |  | 217 rectum |  |  |  |  | 0.56 (0.34-0.90) |
|  | PCC | 1986-1990 | Denmark | 49/362 | 0-3 cups/day | 2 | 86\%, 14\% | 4+ cups/day | 1.50 (0.60-4.10) |
| Kato 1990 (21) | PCC | 1986-1990 | Japan |  | <daily | 2 | NA | Daily | $1.89(0.94-3.79)^{\text {b }}$ |
|  |  |  |  | NA colon |  |  |  |  | 2.50 (1.19-5.26) |
|  |  |  |  | NA rectum |  |  |  |  | 0.27 (0.04-2.03) |
| Hospital-based case-control (HCC) studies |  |  |  |  |  |  |  |  |  |
| Munoz 1998 (27) | HCC | 1993-1997 | Argentina | 190/393 | 0 | 2 | 53\%, 47\% | 1+ cups/day | 0.80 (0.60-1.20) |
| Tavani 1997 (37) | HCC | 1985-1996 | Italy | 3530/7057 | Non-drinkers | 2 | 83\%, 17\% | Drinkers | 1.19 (1.07-1.33) |
|  |  |  |  | 2166 colon |  |  |  |  | 1.21 (1.06-1.37) |
|  |  |  |  | 1364 rectum |  |  |  |  | 1.15 (0.99-1.35) |
| Inoue 1998 (19) | HCC | 1990-1995 | Japan | 628/21 128 | Rarely | 3 | 66\%, $7 \%$ | Daily | $1.42(1.03-1.96)^{\text {b }}$ |
|  |  |  |  | 362 colon |  |  |  |  | 1.59 (1.06-2.37) |
|  |  |  |  | 266 rectum |  |  |  |  | 1.16 (0.67-1.98) |
| Higginson 1966 (16) | HCC | 1959 | USA | 340/1020 | Never/irregular | 4 | 55\%, 2\% | $3+$ cups/day | $0.54(0.18-1.55)^{\text {c }}$ |

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Fig. 3. Meta-analysis of black tea consumption and colorectal cancer risk.


Fig. 4. Begg's funnel plot of black tea consumption and colorectal cancer risk.

Considerable heterogeneity across studies remains even after exclusion of the three Japanese studies $(P<0.001)$. We looked for possible explanations to this substantial study heterogeneity, including variation in study design, method of assessing black tea intake, year of study report publication, and whether adjustment for coffee intake or other potential dietary confounders were performed during statistical analysis. None of these factors were important sources of study heterogeneity.

Our results suggest that the black tea-colorectal cancer association differ between men and women ( $P=0.03$ ). In fact, the summary $O R$ in women indicate a significant
protective effect of black tea $(\mathrm{OR}=0.82,95 \% \mathrm{CI}=0.70-$ 0.95 ) while a moderate, nonsignificant risk enhancement effect was noted in men ( $\mathrm{OR}=1.15,95 \% \mathrm{CI}=0.89-1.50$ ). It is biologically plausible that gender plays a modifying role in the black tea-colorectal cancer association. Findings from the Women's Health Initiative Trial $(48,49)$ corroborated reports of observational studies $(50,51)$ in support of sex hormones having a direct role in protection against colorectal carcinogenesis.

Results from experimental studies using in vitro cell lines and in vivo animal models support the hypothesis of a protective role of both green tea and black tea in the development of

| Category of studies | No. of studies | $\begin{aligned} & \text { Summary OR } \\ & (95 \% \text { CI) } \end{aligned}$ | $P$ for heterogeneity |
| :---: | :---: | :---: | :---: |
| Colorectal cancer |  |  |  |
| All studies | 20 | 0.99 (0.87-1.13) | <0.001 |
| Western population | 17 | 0.93 (0.82-1.06) | $<0.001$ |
| Japanese | 3 | 1.62 (1.22-2.14) | 0.14 |
| Western versus Japanese |  |  | <0.001 |
| Cohort studies | 7 | 1.02 (0.78-1.34) | 0.002 |
| Case-control studies | 13 | 0.98 (0.84-1.15) | <0.001 |
| Cohort versus case-control studies |  |  | 0.80 |
| Studies based on Western populations |  |  |  |
| Cohort studies | 6 | 0.95 (0.76-1.19) | 0.03 |
| Case-control studies | 11 | 0.92 (0.78-1.09) | 0.001 |
| Cohort versus case-control studies |  |  | 0.82 |
| Adjusted for coffee intake | 4 | 0.89 (0.74-1.07) | 0.88 |
| Not adjusted for coffee intake | 13 | 0.94 (0.80-1.10) | <0.001 |
| Adjusted versus not adjusted for coffee intake |  |  | 0.66 |
| In-person interview | 6 | 0.93 (0.73-1.18) | 0.001 |
| Not in-person interview | 11 | 0.93 (0.79-1.09) | 0.02 |
| In-person versus not in-person interview |  |  | 1.00 |
| Adjusted for dietary factors | 13 | 0.95 (0.83-1.10) | 0.001 |
| Not adjusted for any dietary factor | 4 | 0.84 (0.57-1.23) | 0.04 |
| Adjusted versus not adjusted for any dietary factors |  |  | 0.56 |
| Published before year 2000 | 10 | 0.94 (0.78-1.13) | 0.002 |
| Published on or after year 2000 | 7 | 0.92 (0.75-1.13) | 0.01 |
| Published before versus on or after year 2000 |  |  | 0.88 |
| Women only | 7 | 0.82 (0.70-0.95) | 0.13 |
| Men only | 6 | 1.15 (0.89-1.50) | 0.08 |
| Women versus men |  |  | 0.03 |
| Colon cancer |  |  |  |
| All studies | 12 | 1.02 (0.88-1.18) | 0.004 |
| Cohort studies | 6 | 0.93 (0.67-1.30) | 0.002 |
| Case-control studies | 6 | 1.13 (1.02-1.24) | 0.24 |
| Cohort vesus case-control studies |  |  | 0.27 |
| Rectal cancer |  |  |  |
| All studies | 10 | 0.91 (0.73-1.12) | 0.01 |
| Cohort studies | 5 | 0.96 (0.74-1.24) | 0.47 |
| Case-control studies | 5 | 0.86 (0.62-1.19) | 0.001 |
| Cohort versus case-control studies |  |  | 0.60 |
| Colon versus rectal cancer |  |  | 0.40 |

colorectal cancer. Both green tea and black tea and their respective polyphenols demonstrated inhibition effects against heterocyclic aromatic amines ( PhIP and IQ) induced mutagenicity (52-54). Heterocyclic aromatic amines have been linked to increased risk of human colorectal cancer (55). Using different colon cancer cell lines, both catechins and theaflavins demonstrated inhibitory effects against cancer cell proliferation but not against normal cell growth (5659). Both green and black tea have been shown to inhibit PhIP-DNA adduct formation in the colon of rats $(60,61)$. A protective effect of both green and black tea against the development of pre-cancerous lesions in rat colon also has been shown (62-65). In vivo animal studies have demonstrated that both green and black tea extracts or specific tea polyphenols inhibited the development of carcinogen-induced colorectal tumor in rodents (66-69).

We found six reports on tea consumption and risk of colorectal adenomas (21,30,70-73). Four reported on intake of black tea only, one on intake of green tea only, while one reported on both green tea and black tea intake. Baron et al. (70) reported a non-significant positive association between black tea consumption and colorectal adenoma recurrence following excision of the primary polyps. Cope et al. (71) mentioned that black tea consumption was unrelated to colorectal adenomatous polyps development but did not provide estimates of ORs. When we pooled the remaining three reports $(21,30,72)$ on black tea intake and risk of colorectal polyps, the summary OR was 0.99 ( $95 \% \mathrm{CI}=$ $0.70-1.39, P$ for heterogeneity $=0.19$ ). The two case-control studies on green tea intake and colorectal adenoma were conducted in Japan and their summary OR was 0.67 ( $95 \%$ $\mathrm{CI}=0.56-0.81, P$ for heterogeneity $=0.92$ ). Therefore, the tea-colorectal adenoma results are in general agreement with those on tea-colorectal cancer as summarized in this meta analysis. There is no evidence of black tea exerting any beneficial effect on colon health. Green tea may have beneficial effects on colon carcinogenesis, although the sparseness and other methodologic limitations of the data preclude any firm conclusions at this time.

In summary, despite strong evidence from in vitro and nonhuman in vivo studies supporting a chemopreventive effect of either green tea or black tea on colorectal carcinogenesis, there is insufficient information from epidemiologic studies to conclude that either tea type can be linked to the prevention of colorectal cancer in humans. To our knowledge, there are no intervention trial data on this topic. Small-scale intervention trials employing intermediate endpoint biomarkers may help to elucidate the biological activities and mechanistic pathways behind the possibly anti-carcinogenic effects of green/black tea in humans.

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## References

1. Arab,L. and Il'yasova,D. (2003) The epidemiology of tea consumption and colorectal cancer incidence. J. Nutr., 133, 3310S-3318S.
2. Tavani,A. and La Vecchia,C. (2004) Coffee, decaffeinated coffee, tea and cancer of the colon and rectum: a review of epidemiological studies, 19902003. Cancer Causes Control, 15, 743-757.
3. Arts,I.C., Jacobs,D.R. Jr, Gross,M., Harnack,L.J. and Folsom,A.R. (2002) Dietary catechins and cancer incidence among postmenopausal women: the Iowa Women's Health Study (United States). Cancer Causes Control, 13, 373-382.
4. Arts,I.C., Jacobs,D.R.Jr and Folsom,A.R. (2002) Dietary catechins and cancer incidence: the Iowa Women's Health Study. IARC Sci. Publ., 156, 353-355.
5. Baron,J.A., Gerhardsson de Verdier,M. and Ekbom,A. (1994) Coffee, tea, tobacco, and cancer of the large bowel. Cancer Epidemiol. Biomarkers Prev., 3, 565-570.
6. Bidoli,E., Franceschi,S., Talamini,R., Barra,S. and La Vecchia,C. (1992) Food consumption and cancer of the colon and rectum in north-eastern Italy. Int. J. Cancer, 50, 223-229.
7. Blot,W.J., McLaughlin,J.K. and Chow,W.H. (1997) Cancer rates among drinkers of black tea. Crit. Rev. Food Sci. Nutr., 37, 739-760.
8. Cerhan,J.R., Putnam,S.D., Bianchi,G.D., Parker,A.S., Lynch,C.F. and Cantor,K.P. (2001) Tea consumption and risk of cancer of the colon and rectum. Nutr. Cancer, 41, 33-40.
9. Dales,L., Friedman,G., Ury,H., Grossman,S. and Williams,S. (1979) A case-control study of relationships of diet and other traits to colorectal cancer in American Blacks. Am. J. Epidemiol., 109, 132-144.
10. Franceschi,S., Favero,A., La Vecchia,C., Negri,E., Conti,E., Montella,M., Giacosa,A., Nanni,O. and Decarli,A. (1997) Food groups and risk of colorectal cancer in Italy. Int. J. Cancer, 72, 56-61.

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11.Fredrikson,M., Hardell,L., Bengtsson,N. and Axelson,O. (1995) Colon cancer and dietary habits-a case-control study. Int. J. Oncol., 7, 133-141.
12. Goldbohm,R.A., Hertog,M.G., Brants,H.A., van Poppel,G. and van den Brandt,P.A. (1996) Consumption of black tea and cancer risk: a prospective cohort study. J. Natl Cancer Inst., 88, 93-100.
13.Hara,N., Sakata,K., Nagai,M., Fujita,Y., Hashimoto,T. and Yanagawa,H. (1984) Statistical analyses on the pattern of food consumption and digestive-tract cancers in Japan. Nutr. Cancer, 6, 220-228.
14.Hartman,T.J., Tangrea,J.A., Pietinen,P., Malila,N., Virtanen,M., Taylor,P.R. and Albanes,D. (1998) Tea and coffee consumption and risk of colon and rectal cancer in middle-aged Finnish men. Nutr. Cancer, 31, 41-48.
15.Heilbrun,L.K., Nomura,A. and Stemmermann,G.N. (1986) Black tea consumption and cancer risk: a prospective study. Br. J. Cancer, 54, 677-683.
16. Higginson,J. (1966) Etiological factors in gastrointestinal cancer in man. J. Natl Cancer Inst., 37, 527-545.
17. Dora,I., Arab,L., Martinchik,A., Sdvizhkov,A., Urbanovich,L. and Weisgerber,U. (2003) Black tea consumption and risk of rectal cancer in Moscow population. Ann. Epidemiol., 13, 405-411.
18. Il'yasova,D., Martin,C. and Sandler,R.S. (2003) Tea intake and risk of colon cancer in African-Americans and whites: North Carolina colon cancer study. Cancer Causes Control, 14, 767-772.
19. Inoue,M., Tajima,K., Hirose,K., Hamajima,N., Takezaki,T., Kuroishi,T. and Tominaga,S. (1998) Tea and coffee consumption and the risk of digestive tract cancers: data from a comparative case-referent study in Japan. Cancer Causes Control, 9, 209-216.
20. Ji,B.T., Chow,W.H., Hsing,A.W., McLaughlin,J.K., Dai,Q., Gao,Y.T., Blot,W.J. and Fraumeni,J.F.Jr (1997) Green tea consumption and the risk of pancreatic and colorectal cancers. Int. J. Cancer, 70, 255-258.
21. Kato,I., Tominaga,S., Matsuura,A., Yoshii,Y., Shirai,M. and Kobayashi,S. (1990) A comparative case-control study of colorectal cancer and adenoma. Jpn. J. Cancer Res., 81, 1101-1108.
22. Khan,M.M., Goto,R., Kobayashi,K., Suzumura,S., Nagata,Y., Sonoda,T., Sakauchi,F., Washio,M. and Mori,M. (2004) Dietary habits and cancer mortality among middle aged and older Japanese living in hokkaido, Japan by cancer site and sex. Asian Pac. J. Cancer Prev., 5, 58-65.
23. Kinlen,L.J., Willows,A.N., Goldblatt,P. and Yudkin,J. (1988) Tea consumption and cancer. Br. J. Cancer, 58, 397-401.
24.La Vecchia,C., Negri,E., Decarli,A., D'Avanzo,B., Gallotti,L., Gentile,A. and Franceschi,S. (1988) A case-control study of diet and colo-rectal cancer in northern Italy. Int. J. Cancer, 41, 492-498.
25.La Vecchia,C., Negri,E., Franceschi,S., D’Avanzo,B. and Boyle,P. (1992) Tea consumption and cancer risk. Nutr. Cancer, 17, 27-31.
26. Michels,K.B., Willett,W.C., Fuchs,C. and Giovannucci,E. (2005) Coffee, tea, and coffeine consumption and incidence of colon and rectal cancer. J. Natl Cancer Inst., 97, 282-292.
27. Munoz,S.E., Navarro,A., Lantieri,M.J., Fabro,M.E., Peyrano,M.G., Ferraroni,M., Decarli,A., La Vecchia,C. and Eynard,A.R. (1998) Alcohol, methylxanthine-containing beverages, and colorectal cancer in Cordoba, Argentina. Eur. J. Cancer Prev., 7, 207-213.
28. Nagano,J., Kono,S., Preston,D.L. and Mabuchi,K. (2001) A prospective study of green tea consumption and cancer incidence, Hiroshima and Nagasaki (Japan). Cancer Causes Control, 12, 501-508.
29. Nakachi,K., Matsuyama,S., Miyake,S., Suganuma,M. and Imai,K. (2000) Preventive effects of drinking green tea on cancer and cardiovascular disease: epidemiological evidence for multiple targeting prevention. Biofactors, 13, 49-54.
30. Olsen,J. and Kronborg,O. (1993) Coffee, tobacco and alcohol as risk factors for cancer and adenoma of the large intestine. Int. J. Epidemiol., 22, 398-402.
31.Phillips,R.L. and Snowdon,D.A. (1985) Dietary relationships with fatal colorectal cancer among Seventh-Day Adventists. J. Natl Cancer Inst., 74, 307-317.
32. Slattery,M.L., Caan,B.J., Anderson,K.E. and Potter,J.D. (1999) Intake of fluids and methylxanthine-containing beverages: association with colon cancer. Int. J. Cancer, 81, 199-204.
33. Stocks,P. (1970) Cancer mortality in relation to national consumption of cigarettes, solid fuel, tea and coffee. Br. J. Cancer, 24, 215-225.
34. Su,L.J. and Arab,L. (2002) Tea consumption and the reduced risk of colon cancer-results from a national prospective cohort study. Public Health Nutr., 5, 419-425.
35. Suzuki,Y., Tsubono,Y., Nakaya,N., Koizumi,Y., Suzuki,Y., Shibuya,D. and Tsuji,I. (2005) Green tea and the risk of colorectal cancer: pooled analysis of two prospective studies in Japan. J. Epidemiol., 15, 118-124.
36. Tajima,K. and Tominaga,S. (1985) Dietary habits and gastro-intestinal cancers: a comparative case-control study of stomach and large intestinal cancers in Nagoya, Japan. Jpn. J. Cancer Res., 76, 705-716.
37. Tavani,A., Pregnolato,A., La Vecchia,C., Negri,E., Talamini,R. and Franceschi,S. (1997) Coffee and tea intake and risk of cancers of the colon and rectum: a study of 3530 cases and 7057 controls. Int. J. Cancer, 73, 193-197.
38. Terry,P. and Wolk,A. (2001) Tea consumption and the risk of colorectal cancer in Sweden. Nutr. Cancer, 39, 176-179.
39. Tuyns,A., Kaaks,R. and Haelterman,M. (1988) Colorectal cancer and the consumption of foods: a case-control study in Belgium. Nutr. Cancer, 11, 189-204.
40. Woolcott,C.G., King,W.D. and Marrett,L.D. (2002) Coffee and tea consumption and cancers of the bladder, colon and rectum. Eur. J. Cancer Prev., 11, 137-145.
41.Zhang,B., Li,X., Nakama,H., Zhang,X., Wei,N. and Zhang,L. (2002) A case-control study on risk of changing food consumption for colorectal cancer. Cancer Invest., 20, 458-463.
42.Zheng,W., Doyle,T.J., Kushi,L.H., Sellers,T.A., Hong,C.P. and Folsom,A.R. (1996) Tea consumption and cancer incidence in a prospective cohort study of postmenopausal women. Am. J. Epidemiol., 144, 175-182.
43. Petitti,D.B. (2000) Meta-Analysis, Decision Analysis, and CostEffectiveness Analysis. (Second Edition edn). Oxford University Press, New York.
44. DerSimonian,R. and Laird,N. (1986) Meta-analysis in clinical trials. Control. Clin. Trials, 7, 177-188.
45. Hedges,L.V. and Pigott,T.D. (2001) The power of statistical tests in metaanalysis. Psychol. Methods, 6, 203-217.
46.Light,R.J. and Pillemer,D.B. (1984) Summing Up: The Science of Reviewing Research. Harvard University Press, London.
47.Egger,M., Davey Smith,G., Schneider,M. and Minder,C. (1997) Bias in meta-analysis detected by a simple, graphical test. Br. Med. J., 315, 629-634.
48. Anderson,G.L., Limacher,M., Assaf,A.R. et al. (2004) Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. JAMA, 291, 1701-1712.
49. Chlebowski,R.T., Wactawski-Wende,J., Ritenbaugh,C. et al. (2004) Estrogen plus progestin and colorectal cancer in postmenopausal women. N. Engl. J. Med., 350, 991-1004.
50. Hebert-Croteau,N. (1998) A meta-analysis of hormone replacement therapy and colon cancer in women. Cancer Epidemiol. Biomarkers Prev., 7, 653-659.
51. Grodstein,F., Newcomb,P. and Stampfer,M. (1999) An incentive to start hormone replacement: the effect of postmenopausal hormone replacement therapy on the risk of colorectal cancer. Am. J. Med., 106, 574-782.
52. Apostolides,Z., Balentine,D.A., Harbowy,M.E. and Weisburger,J.H. (1996) Inhibition of 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP) mutagenicity by black and green tea extracts and polyphenols. Mutat. Res., 359, 159-163.
53. Weisburger,J.H., Hara,Y., Dolan,L., Luo,F.Q., Pittman,B. and Zang,E. (1996) Tea polyphenols as inhibitors of mutagenicity of major classes of carcinogens. Mutat. Res., 371, 57-63.
54. Hernaez,J.F., Xu,M. and Dashwood,R.H. (1998) Antimutagenic activity of tea towards 2-hydroxyamino-3-methylimidazo[4,5-f]quinoline: effect of tea concentration and brew time on electrophile scavenging. Mutat. Res., 402, 299-306.
55.Butler,L.M., Sinha,R., Millikan,R.C., Martin,C.F., Newman,B., Gammon,M.D., Ammerman,A.S. and Sandler,R.S. (2003) Heterocyclic amines, meat intake, and association with colon cancer in a populationbased study. Am. J. Epidemiol., 157, 434-445.
56. Chen,Z.P., Schell,J.B., Ho,C.T. and Chen,K.Y. (1998) Green tea epigallocatechin gallate shows a pronounced growth inhibitory effect on cancerous cells but not on their normal counterparts. Cancer Lett., 129, 173-179.
57.Lu,J., Ho,C.T., Ghai,G. and Chen,K.Y. (2000) Differential effects of theaflavin monogallates on cell growth, apoptosis, and Cox-2 gene expression in cancerous versus normal cells. Cancer Res., 60, 6465-6471.
58. Uesato,S., Kitagawa,Y., Kamishimoto,M., Kumagai,A., Hori,H. and Nagasawa,H. (2001) Inhibition of green tea catechins against the growth of cancerous human colon and hepatic epithelial cells. Cancer Lett., 170, 41-44.
59. Tan, X., Hu,D., Li,S., Han,Y., Zhang,Y. and Zhou,D. (2000) Differences of four catechins in cell cycle arrest and induction of apoptosis in LoVo cells. Cancer Lett., 158, 1-6.
60.Huber,W.W., McDaniel,L.P., Kaderlik,K.R., Teitel,C.H., Lang,N.P. and Kadlubar,F.F. (1997) Chemoprotection against the formation of colon DNA adducts from the food-borne carcinogen 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP) in the rat. Mutat. Res., 376, 115-122.
61. Schut,H.A. and Yao,R. (2000) Tea as a potential chemopreventive agent in PhIP carcinogenesis: effects of green tea and black tea on PhIP-DNA adduct formation in female F-344 rats. Nutr. Cancer, 36, 52-58.
62. Jia, X. and Han,C. (2001) Effects of green tea on colonic aberrant crypt foci and proliferative indexes in rats. Nutr. Cancer, 39, 239-243.
63. Metz,N., Lobstein,A., Schneider,Y., Gosse,F., Schleiffer,R., Anton,R. and Raul,F. (2000) Suppression of azoxymethane-induced preneoplastic lesions and inhibition of cyclooxygenase-2 activity in the colonic mucosa of rats drinking a crude green tea extract. Nutr. Cancer, 38, 60-64.
64. Weisburger,J.H., Rivenson,A., Garr,K. and Aliaga,C. (1997) Tea, or tea and milk, inhibit mammary gland and colon carcinogenesis in rats. Cancer Lett., 114, 323-327.
65.Xu,M., Bailey,A.C., Hernaez,J.F., Taoka,C.R., Schut,H.A. and Dashwood,R.H. (1996) Protection by green tea, black tea, and indole-3carbinol against 2-amino-3-methylimidazo[4,5-f]quinoline-induced DNA adducts and colonic aberrant crypts in the F344 rat. Carcinogenesis, 17, 1429-1434.
66. Caderni,G., De Filippo,C., Luceri,C., Salvadori,M., Giannini,A., Biggeri,A., Remy,S., Cheynier,V. and Dolara,P. (2000) Effects of black tea, green tea and wine extracts on intestinal carcinogenesis induced by azoxymethane in F344 rats. Carcinogenesis, 21, 1965-1969.
67. Yamane,T., Nakatani,H., Kikuoka,N., Matsumoto,H., Iwata,Y., Kitao,Y., Oya,K. and Takahashi,T. (1996) Inhibitory effects and toxicity
of green tea polyphenols for gastrointestinal carcinogenesis. Cancer, 77, 1662-1667.
68. Narisawa,T. and Fukaura,Y. (1993) A very low dose of green tea polyphenols in drinking water prevents $N$-methyl- $N$-nitrosourea-induced colon carcinogenesis in F344 rats. Jpn. J. Cancer Res., 84, 1007-1009.
69. Jung,Y.D., Kim,M.S., Shin,B.A., Chay,K.O., Ahn,B.W., Liu,W., Bucana,C.D., Gallick,G.E. and Ellis,L.M. (2001) EGCG, a major component of green tea, inhibits tumour growth by inhibiting VEGF induction in human colon carcinoma cells. Br. J. Cancer, 84, 844-850.
70. Baron,J.A., Greenberg,E.R., Haile,R., Mandel,J., Sandler,R.S. and Mott,L. (1997) Coffee and tea and the risk of recurrent colorectal adenomas. Cancer Epidemiol. Biomarkers Prev., 6, 7-10.
71. Cope,G.F., Wyatt,J.I., Pinder,I.F., Lee,P.N., Heatley,R.V. and Kelleher,J. (1991) Alcohol consumption in patients with colorectal adenomatous polyps. Gut, 32, 70-72.
72. Ilyasova,D., Hodgson,M.E., Martin,C., Galanko,J. and Sandler,R.S. (2003) Tea consumption, apoptosis, and colorectal adenomas. Eur. J. Cancer Prev., 12, 439-443.
73. Kono,S., Shinchi,K., Ikeda,N., Yanai,F. and Imanishi,K. (1991) Physical activity, dietary habits and adenomatous polyps of the sigmoid colon: a study of self-defense officials in Japan.[comment]. J. Clin. Epidemiol., 44, 1255-1261.

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[^0]:    Abbreviations: CI, confidence interval; HCC, hospital-based case-control study; OR, odds ratio; PCC, population-based case-control study; RR, relative risk.

[^1]:    Meta-analysis
    Study-specific ORs/RRs and corresponding 95\% CIs for highest versus non/ lowest tea consumption levels were extracted. Heilbrun et al. (15) provided numbers of cases and controls and RR estimates in their report, but not the $95 \%$ CIs corresponding to the RR estimates. Similarly, Higginson et al. (16) only

[^2]:    ${ }^{a}$ Calculation based on gender specific estimates.
    ${ }^{\mathrm{b}}$ Calculation based on colon and rectum estimates.
    ${ }^{\text {c }}$ Crude OR and $95 \%$ CI was calculated based on number of cases and controls.

