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Green tea (Camellia sinensis) for the prevention of cancer (Review)

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Green tea (Camellia sinensis) for the prevention of cancer.
Cochrane Database of Systematic Reviews 2009, Issue 3. Art. No.: CD005004.
DOI: 10.1002/14651858.CD005004.pub2.

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[Intervention Review]

Green tea (Camellia sinensis) for the prevention of cancer

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Editorial group: Cochrane Gynaecological, Neuro-oncology and Orphan Cancer Group.
Publication status and date: Edited (no change to conclusions), published in Issue 9, 2016.

Citation: Boehm K, Borrelli F, Ernst E, Habacher G, Hung SK, Milazzo S, Horneber M. Green tea (Camellia sinensis) for the prevention of cancer. *Cochrane Database of Systematic Reviews* 2009, Issue 3. Art. No.: CD005004. DOI: 10.1002/14651858.CD005004.pub2.

ABSTRACT

Background

Tea is one of the most commonly consumed beverages worldwide. Teas from the plant Camellia sinensis can be grouped into green, black and oolong tea. Cross-culturally tea drinking habits vary. Camellia sinensis contains the active ingredient polyphenol, which has a subgroup known as catechins. Catechins are powerful antioxidants. It has been suggested that green tea polyphenol may inhibit cell proliferation and observational studies have suggested that green tea may have cancer-preventative effects.

Objectives

To critically assess any associations between green tea consumption and the risk of cancer incidence and mortality.

Search methods

We searched eligible studies up to January 2009 in the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, Amed, CancerLit, Psych INFO and Phytobase and reference lists of previous reviews and included studies.

Selection criteria

We included all prospective, controlled interventional studies and observational studies, which either assessed the associations between green tea consumption and risk of cancer incidence or that reported on cancer mortality.

Data collection and analysis

At least two review authors independently applied the study criteria, extracted data and assessed methodological quality of studies. Due to the nature of included studies, which were mainly epidemiological, results were summarised descriptively according to cancer diagnosis.

Main results

Fifty-one studies with more than 1.6 million participants were included. Twenty-seven of them were case-control studies, 23 cohort studies and one randomised controlled trial (RCT).

Twenty-seven studies tried to establish an association between green tea consumption and cancer of the digestive tract, mainly of the upper gastrointestinal tract, five with breast cancer, five with prostate cancer, three with lung cancer, two with ovarian cancer, two with urinary bladder cancer one with oral cancer, three further studies included patients with various cancer diagnoses.

The methodological quality was measured with the Newcastle-Ottawa scale (NOS). The 9 nested case-control studies within prospective cohorts were of high methodological quality, 13 of medium, and 1 of low. One retrospective case-control study was of high methodological quality and 21 of medium and 5 of low.

Results from studies assessing associations between green tea and risk of digestive tract cancer incidence were highly contradictory. There was limited evidence that green tea could reduce the incidence of liver cancer. The evidence for esophageal, gastric, colon, rectum, and pancreatic cancer was conflicting. In prostate cancer, observational studies with higher methodological quality and the only included RCT suggested a decreased risk in men consuming higher quantities green tea or green tea extracts. However, there was limited to moderate evidence that the consumption of green tea reduced the risk of lung cancer, especially in men, and urinary bladder cancer or that it could even increase the risk of the latter. There was moderate to strong evidence that green tea consumption does not decrease the risk of dying from gastric cancer. There was limited moderate to strong evidence for lung, pancreatic and colorectal cancer.

Authors' conclusions

There is insufficient and conflicting evidence to give any firm recommendations regarding green tea consumption for cancer prevention. The results of this review, including its trends of associations, need to be interpreted with caution and their generalisability is questionable, as the majority of included studies were carried out in Asia (n = 47) where the tea drinking culture is pronounced. Desirable green tea intake is 3 to 5 cups per day (up to 1200 ml/day), providing a minimum of 250 mg/day catechins. If not exceeding the daily recommended allowance, those who enjoy a cup of green tea should continue its consumption. Drinking green tea appears to be safe at moderate, regular and habitual use.

PLAIN LANGUAGE SUMMARY

Green tea for the prevention of cancer

Fifty-one studies with more than 1.6 million participants, mainly of observational nature were included in this systematic review. Studies looked for an association between green tea consumption and cancer of the digestive tract, gynecological cancer including breast cancer, urological cancer including prostate cancer, lung cancer and cancer of the oral cavity. The majority of included studies were of medium to high methodological quality. The evidence that the consumption of green tea might reduce the risk of cancer was conflicting. This means, that drinking green tea remains unproven in cancer prevention, but appears to be safe at moderate, regular and habitual use.

BACKGROUND

A United States Department of Agriculture continuing survey of food intakes by individuals indicated that the mean annual consumption of all teas, including green tea in the USA for people older than 2 years was 397 grams and at the 95th percentile 930.3 grams (USDA 1996). In a recent Canadian report green tea was the most commonly used product for self-treating breast cancer survivors (Boon 2007).

Brewed tea from the leaves of the plant Camellia sinensis is the second most common beverage consumed worldwide next to water (Graham 1992; Weisburger 1997) and is particularly popular in Asian countries. Teas from this plant can be grouped into green, black or oolong tea. Approximately 20% of the world's Camellia sinensis consumption is in the form of green tea; the other 80% are consumed in black and oolong tea (Graham 1992). After fermentation from green to black tea about 15% of catechins remain un-

changed. The rest of catechins are converted to theaflavins, which are polyphenol pigments and thearubigins (Blumenthal 2003). Green teas are usually produced as either white, yellow or green tea, the latter being less fermented through a process called wilting. Green tea has a high vitamin and mineral content and 5 cups of green tea will provide 5 to 10% of the daily requirements of riboflavin, niacin, folic acid and pantothenic acid and also about 5% of the daily requirement of magnesium, 25% of potassium and 45% of the requirement for manganese (Shukla 2007). A single cup also provides about 0.1 mg of fluoride. Green tea is available commercially in form of dried tea leaves but also as a powder extract or in tablets.

In a randomised controlled trial (RCT) green tea has been shown to significantly decrease total cholesterol and low density lipoprotein (LDL) cholesterol in the green tea group after treatment of 150mg green tea catechins a day and 150 mg of other tea polyphenols for 3 months (Maron 2003). A meta-analysis concluded that an increase in tea consumption of three cups (711 ml/day) decreases the risk of myocardial infarction by 11% (Peters 2001). However, the US Food and Drug Administration (FDA) rejected a petition filed by a Japanese company and its US subsidiary, claiming on product labels that green tea has cardiovascular benefits (Schneeman 2006). Based on two phase III clinical trials conducted in Europe, USA, Argentina, Chile, Columbia, Mexico and Peru with more than 1000 patients suffering from genital warts, the FDA approved of a new drug application of a green tea-based ointment Polyphenol ® E (Melville 2007). The FDA further concluded that existing evidence does not support qualified health claims for green tea consumption and a reduced risk of any type of cancer. Desirable green tea intake is 3 to 5 cups per day (up to 1200ml/day), providing a minimum of 250 mg/day catechins.

Pharmacology of Camellia Sinensis

The active ingredients of green tea contain polyphenols i.e. flavanols, which are also known as catechins, which account for 30 to 40% of the extractable solids of dried green tea leaves, alkaloids (such as caffeine and theobromine), carbohydrates, tannins and minerals (such as fluoride and aluminium) (Ahmad 1999). Green tea contains higher amounts of catechins than black tea. Epigallocatechin gallate (EGCG) is a powerful antioxidant believed to be an important determinant in the therapeutic qualities of green tea. EGCG has been suggested to work by suppressing the formation of blood vessels (angiogenesis) and regulating their permeability, thereby cutting off the blood supply to cancerous cells (Demeule 2002; Maiti 2003). In in-vitro and in vivo animal models EGCG have been shown to be potent chemo-preventative agents (Liao 2001). Green tea catechins have also shown to decrease plasma lipid peroxide and malondialdehyde concentrations, increased plasma ascorbide concentrations, decrease non-heme iron absorption and increase the resistance of LDL to oxidation (Williamson 2005). After oral intake concentrations of tea catechins can be detected in blood, urine and faeces and are thus absorbed and spread through the human or animal body (He 1994). Catechins may exert their actions directly at the tissue and at cellular level (He 1994).

It has been recognised that most classes of catechins are sufficiently absorbed to have the potential to exert biological effects as they cross the intestinal barrier and reach concentrations in the blood stream that have been shown to exert effects in-vitro (Liao 2001; Manach 2005; Scalbert 2000).

Possible anti-cancer effects of Camellia Sinensis

Green tea polyphenols inhibit cell proliferation and exert a strong antioxidant activity (Yang 1993; Yang 1997). Polyphenols, specifically EGCG, have been shown to increase the activity of antioxidation in a variety of mouse organs and thus, enhancing the overall chemo-preventative effect of antioxidants in those organs (Khan 1992). Polyphenols, particularly catechins, may enhance gap junctional communication between cells and thus protect cells from tumour development (Sigler 1993). The experimental studies suggest an effect on compounds of green tea extract, which may block the promotion of tumour growth by sealing receptors in the affected cells (Komori 1993). Another possible mechanism indicates that EGCG may facilitate direct binding to certain carcinogens (Hayatsu 1992). It has also been suggested that polyphenols assist the inhibition of tumour genesis in a variety of organs including skin, lung, oral cavity, oesophagus, forestomach, stomach, small intestine, colon, liver, pancreas, ovary and mammary gland (Ahmad 1999; Jankun 1997; Su 2002; Yang 2002; Zhang 2002). Green tea polyphenols have been shown to induce apoptosis in human lymphoid leukaemia cells (Hibasami 1996) and human prostate cancer cells (Kazi 2002). It has been suggested that decaffeinated teas were inactive or less active in inhibiting tumour formation (Wang 1994), therefore, a 3% caffeine content in green tea extract is recommended (Fujiki 2005).

Despite the growing body of research demonstrating the important role of polyphenols as antioxidants with anticarcinogenic properties, a full understanding of the effects of green tea is far from complete. This justifies the need for a systematic review on this topic.

Theories of mechanism of action of polyphenols

There are a number of proposed theories of the preventive activities of EGCG (Fujiki 1999). The first theory suggests an anticarcinogenic effect: anti-promotion, including tumour growth, invasion, metastasis and cell transformation. The second theory proposes a sealing effect in that EGCG inhibits the interaction of tumour promoters, hormones and various growth factors with their receptors. The third theory claims an antimicrobial inhibi-

tion, involving oncogene expression (c-myc, c-H-ras, c-raf), lipid peroxidation, angiogenesis, free radicals, ornithine decarboxylase, urokinase, protein kinase, lipo-oxygenase, cyclo-oxygenase, 5 a-reductase, nitric oxide synthase, telomerase, tumour necrosis factor a gene expression, tumour necrosis factor a release, and interleukin-1 gene expression. Thus, tea polyphenols seem to have many functions and are very different from an enzyme inhibitor, which has a specific function.

Data from epidemiological studies

Numerous epidemiological studies and very few clinical trials have been performed to test whether Camellia sinensis possesses chemopreventive or curative activity on cancer development. Results have been contradictory, as some epidemiological studies comparing tea-drinkers to non tea-drinkers were claiming that drinking tea protects against the development of cancer, whereas others did not support this claim. This may be due to numerous confounding variables, such as diet and population differences that limit the ability of epidemiological studies to detect an effect (Yang 2002). Two studies reported an association between green tea consumption and decreased cancer morbidity. One of these studies involved a total of 18,000 men and reported that people who were drinking either black or green tea were half as likely to develop stomach or oesophageal cancer compared to men who drank no or only little tea, even after demographics were adjusted according to smoking and other dietary factors (Sun 2002). Another study involving 250 skin cancer patients showed that patients consuming 3g of green tea (about 2 cups) per day reduced the size and proliferation of leukoplakia (Hakim 2001).
A study assessing the effect of increased black and green tea consumption on oxidative DNA damage was carried out including 143 heavy smokers (Hakim 2003). Results showed that in the green tea group plasma and urinary catechins levels rose significantly and it has been suggested that regular green tea drinking might protect smokers from oxidative damages and could thus reduce cancer risks.

OBJECTIVES

To assess a possible association between green tea consumption and the risk of cancer incidence and mortality. This will be achieved by looking at studies comparing a healthy population with well-matched cancer patients and by looking at studies observing one group of healthy participants over a length of time.

METHODS

Criteria for considering studies for this review

Types of studies

Studies in which green tea was orally consumed in the past and which were carried out by using one of the following designs were included.

- Interventional studies: RCTs.
- Observational studies - Prospective cohort studies and retrospective case-control studies.

Case-series, case reports and other studies without a comparator, editorials, reviews, animal studies and in-vitro studies were excluded from this review.

Types of participants

Both, healthy adults and adults with various forms of cancer were included. No restriction on diagnoses, age groups and settings were applied.

Types of interventions

The consumption of green tea - whether as part of an intervention study or measured in an epidemiological study - was the type of intervention the reviewers were interested in. The assessment variable was the consumption of green tea or green tea extract (only mono preparations for oral consumption in liquid, powder or tablet form). Green tea was defined as non-fermented tea leaves and studies must mention that green tea, non-fermented tea or 'matsu-cha', as it is called in Asia, has been consumed. Any method of quantifying this variable (e.g. direct measurement, questionnaire) was considered. Studies that did not distinguish the type of tea (e.g. black tea versus green tea) or did not report quantitative data of at least two different amounts or frequency of green tea consumption were excluded. Pharmokinetic-type studies were also excluded because they were unlikely to contribute useful data on long-term effects of green tea consumption. Only studies which explicitly or implicitly stated the duration of green tea consumption in their research summary were included.
Should, in the future, any more RCTs of green tea for cancer prevention be published, the Cochrane Gynecological Cancer Collaborative Review Group will be contacted and the review will then be updated accordingly.

Types of outcome measures

Primary outcomes

The primary outcome measures were

- the number of participants developing cancers (incidence),
- the number of participants dying from cancers (mortality).

Results from observational studies had to include an estimate of the relative risk (RR).

Different types of cancer were being analysed in a combined fashion according to the following categories:

- gastro-intestinal cancer (esophageal cancer, gastric cancer, colorectal cancer, pancreatic cancer, and liver cancer),
- uro-genital tract cancer (bladder cancer, ovarian cancer, lower urinary tract, urothelial cancer, prostate cancer)
- breast cancer,
- lung cancer,
- oral cancer, and
- various types of cancer.

Secondary outcomes

Safety data and data on quality of life (QoL).

Search methods for identification of studies

This review has drawn on the search strategy developed for the Cochrane GynCan Group as a whole. Relevant trials were identified in the Specialised Register of Controlled Trials. This register was last searched for trials relevant to this review in January 2009.

Electronic searches

The following electronic databases were searched in January 2009 to retrieve studies for potential inclusion: Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE (via PubMed), EMBASE, Amed, CancerLit, PsychInfo and Phytobase. These databases represent the most often searched databases for carrying out medical systematic reviews. Manufacturers of green tea were contacted and asked to contribute published and unpublished studies.

Search strategy

MeSH terms used to search the databases via the Ovid interface is given in Appendix 1

Searching other resources

References from published studies

References from published studies were checked for further studies. We assumed that some of the articles from Asian countries would not be obtainable via Western medical databases. Thus, all relevant non-English articles were obtained and a Japanese/Chinese Cochrane collaborator acted as a filter for study selection. Publications in languages other than English were translated in-house or by using relevant services.

Unpublished literature

The Cochrane Complementary Medicine Field was contacted and asked to search their register. Manufacturers of green tea (in form of green tea dried extract, green tea powder or green tea supplement) and Internet resources were consulted. Original authors of studies and manufacturers of green tea products were contacted to inquire whether they would be aware of unpublished and ongoing trials. Websites, such as www.clinicaltrials.com and www.scirus.com were searched for ongoing trials.

We wrote to green tea manufacturers for long-term surveillance data on green tea products. The literature included in this review was also used for obtaining data on adverse events.

Data collection and analysis

Selection of studies

To be included, studies had to report on the consumption of green tea, non-fermented tea or 'matsu-cha' as it is called in some parts of Asia. Studies identified by the searchers were checked by two review authors. Articles were only included on initial screen if the review authors could determine from the abstract that the article was a report of either an intervention or epidemiological study. When a title or abstract could not be rejected with certainty, the full text article was obtained for further evaluation.

The full text of all studies of possible relevance was obtained and analysed for independent assessment by two review authors. Reasons for excluding any trials have been stated. The review authors will know the author's name, institution and the source of publication. All disagreements were resolved by discussion between the two review authors. If any data were missing from the trial reports attempts were made to obtain that data by contacting the authors.

Data extraction and management

Data extraction was performed independently by means of pretested data extraction forms. Discrepancies were resolved by discussion. Studies were categorised into RCT, nested case-control studies within prospective cohort studies ('cohort studies' in the following), and retrospective case-control studies ('case-control studies' in the following). Data were grouped according to study design and cancer type. Articles published in languages other than English were translated in-house by native speakers of, for instance, Japanese or Chinese, as some of the articles were written in an Asian language.

Data were entered into Review Manager 5 and double-checked by two review authors. Some authors of included studies were contacted for clarification of study methodology and results.

Assessment of risk of bias and methodological quality

The assessment of risk of bias in interventional studies and of methodological quality of observational studies was independently performed by two review authors.

Interventional studies

The risk of bias in the included RCT was assessed by using the approach of the Cochrane Collaboration (Higgins 2008).The criteria relate to the following domains:

- generation sequence and concealment of allocation,
- blinding of caregivers, participants and outcome assessors,
- incomplete outcomes,
- selective reporting.

Studies, which were assessed as 'adequate' in all main domains, were considered to be of low risk of bias. Studies in which there was no clear judgment concerning the procedures in one or more key domains were considered to be at least of medium risk of bias. Studies with clearly inadequate procedures in one or more of the key domains were considered to be of high risk of bias.

Observational studies

The Newcastle-Ottawa assessment scale (NOS-scale) was used for assessing the methodological quality of epidemiological studies (Wells 2001). This tool contains two forms, one for cohort (Appendix 2) and one for case-control studies (Appendix 3), with which they are being judged on three domains:

- selection of study groups,
- comparability of the groups,
- ascertainment of exposure/outcome of interest.

If all criteria of methodological quality are fulfilled within the domains, points ('stars') are assigned to the respective study. The NOS-scale was adapted for the purpose of this review and a cohort study could receive a maximum of 16 points (nine for the cohort assessment and seven for the assessment of the case-control part) and a case-control study could receive a maximum of nine points. Cohort studies with eight or less points were arbitrarily considered as being of low, with 9 to 12 points of medium and with more than 12 points of high methodological quality. Case-control studies with five or less points were also arbitrarily considered as being of low, 6 to 7 points as of medium and 8 to 9 points as of high methodological quality.

Data analysis

We did not carry out a meta-analysis due to the clinical and methodological heterogeneity of the included studies. The findings of the review are being presented as a descriptive synthesis.
A modified rating system, previously developed by van Tulder was used to make statements about the level of evidence (van Tulder 2003):

- Strong evidence - consistent findings among multiple high quality studies,
- moderate evidence - consistent findings among multiple medium quality studies or one high quality study,
- limited evidence - consistent findings among multiple low quality studies or one medium quality study,
- conflicting evidence - inconsistent findings among studies, and
- no evidence.

RESULTS

Description of studies

A total of 675 hits were retrieved from the literature searches. Thereof 586 clearly did not match our inclusion criteria and were excluded by title and abstract. The main reasons for exclusion were that the paper did not investigate humans or did not deal with cancer. Of the remaining 89 papers, we retrieved the full articles and assessed them according to the inclusion criteria provided in the protocol. Thirty-eight of them did not fulfil the inclusion criteria. The main reasons for exclusion were: no distinction between green and black tea, other endpoints than cancer, amount of frequency of green tea consumption not specified or double publications. Reasons for exclusion of studies are described in Characteristics of excluded studies.
Fifty-one studies were included in this review; 1 RCT, 23 prospective cohort studies and 27 retrospective case-control studies.

Included studies

The 51 studies included a total of 1,236,687 participants (1,149,942 in cohort studies, 86,685 in case-control studies, and 60 in one RCT) from five countries. Thirty-two studies were carried out in Japan, 13 in China, 3 in the USA, two in Singapore, and one in Italy. The studies were published between 1985 and 2008.

Diagnoses

Some authors reported cancer risk by organ systems, others by one or more entities (e.g. breast, esophagus and cardia and gastric).

Cancer of the gastrointestinal tract

Thirty-one observational studies reported data on the risk of cancers of the gastro-intestinal tract. Data on five different types of malignomas were provided:

- Gastric cancer: 6 cohort studies (Fujino 2002; Galanis 1998; Hoshiyama 2002; Koizumi 2003; Sasazuki 2004; Tsubono

2001), 12 case-control studies (Huang 1999; Inoue 1994; Inoue 1998; Ji 1996; Kato 1990b; Kono 1988; Mu 2003; Setiawan 2001; Tajima 1985; Wang 1999; Ye 1998; Yu 1995)

- Esophagus cancer: one cohort studies (Ishikawa 2006), five case-control studies (Gao 1994; Inoue 1998; Mu 2003; Wang 1999; Wang 2002)
- Pancreatic cancer: two cohort studies (Lin 2008; Luo 2007), three case-control studies (Goto 1990; Ji 1997; Mizuno 1992)
- Colorectal cancer: three cohort studies (Sun 2007; Suzuki 2005; Yang 2007), three case-control studies (Inoue 1998; Ji 1997; Kato 1990a)
- Liver cancer: three case-control study (Mu 2003).

Cancer of the urogenital tract

Eight observational studies reported data on the risk of cancers of the urogenital tract. Data on three different types of malignomas were provided:

- Prostate cancer: two cohort studies (Kikuchi 2006; Kurahashi 2007), two case-control studies (Jian 2007; Sonoda 2004)
- Ovarian cancer: two case-control studies (Song 2008; Zhang 2002)
- Urinary bladder cancer: one cohort study (Chyou 1993), one case-control study (Wakai 2004).

One RCT assessed the effects of reported data on the incidence of prostate cancer (Bettuzzi 2006).

Breast cancer

Five observational studies reported data on the risk of breast cancer: two cohort studies (Key 1999; Suzuki 2004), and three case-control studies (Inoue 2008; Wu 2003; Zhang 2007)

Lung cancer

Three observational studies reported data on the risk of lung cancer: one cohort study (Li 2008), and two case-control studies (Bonner 2005; Zhong 2001)

Oral cancer

One cohort study (Ide 2007) reported data on the risk of cancers of oral cancers (cancer of tongue, gum, floor, palate and other parts of the mouth).

Various types of cancer

Three cohort studies investigated whether there was an association between green tea consumption and the risk of developing various forms of cancer (Kuriyama 2006; Nagano 2001; Nakachi 2000).

Outcomes

Of the 23 cohort studies, 18 measured cancer incidence, 4 cancer mortality and one measured both, cancer incidence and mortality. All of the 27 case-control studies assessed any associations between green tea consumption and cancer risk. The only included RCT measured, amongst other outcomes, cancer incidence and QoL.

Exposure

All studies either used a self-administered questionnaire in which participants had to declare the frequency and amount of certain food and beverages intake or participated in structured interviews. Amounts of green tea consumption were rated either per day, per week, per month or per year and ranged from 0 cups to 10 cups or more per day. Some studies specified the amount in grams of green tea leaves per year.

Sponsorship

Of the 51 studies, 37 declared sponsorship of studies. In Japan, mainly the Ministry of Health, Labour and Welfare or the Ministry of Education, Science and Culture sponsored grants to support the studies. In China, the Natural Science Foundation sponsored some of the studies. Fourteen of the studies did not declare sponsorship in their publication.

Risk of bias in included studies

Interventional studies

Bettuzzi 2006 had a medium to high risk of selection bias, a low to medium risk of assessment bias and low risk of other biases (Table 1).

Observational studies

The risk of bias assessment of included observational studies was carried out using the Newcastle Ottawa Scale (NOS) for cohort (Appendix 2) and case-control studies (Appendix 3).

Cohort studies

The median score was 12 (out of 16) for the 23 cohort studies with a range of 8 to 15 points (see Table 2).
Nine studies were of high methodological quality and reached 13 or more points (Galanis 1998; Kurahashi 2007; Kuriyama 2006; Li 2008; Lin 2008; Luo 2007; Sasazuki 2004; Sun 2007; Yang 2007). Thirteen studies were of medium methodological quality and reached between 9 and 12 points (Chyou 1993; Fujino 2002; Hoshiyama 2002; Ide 2007; Inoue 2008; Ishikawa 2006; Key 1999; Kikuchi 2006; Koizumi 2003; Nagano 2001; Suzuki 2004;

Suzuki 2005; Tsubono 2001). One study was of low methodological quality and reached 8 points (Nakachi 2000).

Case-control studies

The median score was 7 (out of 9) for the 27 case-control studies with an overall range of 3 to 8 points (see Table 3).

Only one case-controlled study was judged as being of high methodological quality (Jian 2007). Twenty-one studies were of medium methodological quality, ranging from 6 to 7 points (Bonner 2005; Gao 1994; Goto 1990; Huang 1999; Inoue 1994; Inoue 1998; Ji 1997; Kato 1990a; Kato 1990b; Setiawan 2001; Song 2008; Sonoda 2004; Tajima 1985; Wakai 2004; Wang 2007; Wu 2003; Ye 1998; Yu 1995; Zhang 2002; Zhang 2007; Zhong 2001). The remaining five studies were of low methodological quality with three to four points (Ji 1996; Kono 1988; Mizuno 1992; Mu 2003; Wang 1999).

Effects of interventions

The findings are summarised in Table 4 for the RCT, Table 5 for the case-control studies nested within prospective cohorts and in Table 6 the retrospective case-control studies.

Interventional studies

Investigators in the one included RCT administered green tea catechins for the length of one year or placebo to volunteers with high grade prostate intraepithelial neoplasia (Bettuzzi 2006). At the end of the study in one patient of the treatment group, the pre-malignant lesion was progressed into prostate cancer (3%), whereas this was the case in nine patients of the control group (30%), suggesting a 90% chemoprevention efficacy of green tea catechins in men subjected to high risk for developing prostate cancer ($p < 0.01$). At follow-up after three months a statistically significant decrease in the International Prostate Symptom Score (IPSS) was found in the intervention group compared with the control group ($p < 0.05$). No adverse effects of green tea catechins were reported.

These results suggest that green tea catechins might inhibit the progression of pre-malignant lesions into prostate cancer and furthermore, that green tea catechins might positively influence quality of life issues in patients with high grade prostate intraepithelial neoplasia.

Observational studies

Cancer of the gastrointestinal tract

Gastric cancer

There was no data from case-control studies nested within prospective cohort studies that showed significant associations between the consumption of green tea and the risk of gastric cancer (Galanis 1998; Koizumi 2003; Sasazuki 2004; Tsubono 2001). However, the findings from Galanis 1998 suggested a higher risk of gastric cancer in men consuming green tea, whereas those of Sasazuki 2004 suggested a decreased risk in women consuming green tea.

The number of retrospective case-control studies which found no association between the risk of gastric cancer and the consumption of green tea (Huang 1999; Kato 1990b; Inoue 1994; Inoue 1998; Tajima 1985) nearly equals that which reported a positive association (Yu 1995; Ye 1998; Kono 1988; Ji 1996; Mu 2003; Wang 1999).

Kuriyama 2006; Hoshiyama 2002 and Fujino 2002 found that green tea consumption was not related to gastric cancer-specific mortality.

Colorectal cancer

The findings of three case-control studies nested within prospective cohort studies concerning the association between green tea consumption and the risk of cancer of the colon and rectum varied highly: One study reported no association (Suzuki 2005), another study found no association in women but a negative association in male participants, meaning that green tea consumption was associated with an increased risk in men (Sun 2007), and the third study included only women and reported a positive association (Yang 2007).

The results of the retrospective case-control studies also differed considerably: Inoue 1998 found no association between green tea consumption and the risk of cancer of the colon and rectum. Kato 1990a reported a decreased risk for colon cancer but no association with the risk of rectum cancer. Ji 1997 found a decreased risk of both colon and rectum cancer in women consuming green tea but in men only a decreased risk of colon cancer.

Kuriyama 2006 found that green tea consumption was not related to colorectal cancer-specific mortality.

Esophageal cancer

Ishikawa 2006 found in its nested case-control study an increased risk of esophageal cancer in participants consuming higher amounts of green tea. Three out of five retrospective studies found a positive association between the consumption of green tea and the risk of esophageal cancer (Gao 1994; Wang 1999; Wang 2007). In Wang 2007, and Gao 1994, this association was restricted to female participants. In the remaining two case-control studies there was no association between drinking green tea and the risk of esophageal cancer (Inoue 1998; Mu 2003).

Pancreatic cancer

One nested case-control study found no associations between the risk of pancreatic cancer and the consumption of green tea (Luo 2007). The results of the retrospective case-control studies concerning this association varied: two studies reported a decreased risk of pancreatic cancer (Ji 1997; Goto 1990), whereas Inoue 1998 found no association and Mizuno 1992 reported an increased risk of pancreatic cancer in participants who consumed green tea.
Lin 2008 found that green tea consumption was not related to pancreatic cancer-specific mortality.

Liver cancer

One case-control study also looked at the association between green tea consumption and risk of developing liver cancer (Mu 2003). Green tea consumption was suggested to have a protective effect on liver cancer, especially among alcohol drinkers.

Cancer of the urogenital tract

Bladder cancer

One cohort study (Chyou 1993) investigating Japanese-American men residing in Hawaii reported that green tea consumption did not reduce the risk of bladder cancer. One hospital-based case-control study found that green tea consumption was associated with an increased risk in both, male and female participants (Wakai 2004).

Ovarian cancer

Two case-control studies investigating women with ovarian cancer found an association between increased green tea consumption and decreased risk of ovarian cancer (Song 2008; Zhang 2002).

Prostate cancer

Of two cohort studies investigating the risk of prostate cancer, one found no association between green tea consumption and prostate cancer risk (Kikuchi 2006) whereas the other found a positive association (Kurahashi 2007).
Similarly, of two case-control studies, one study found a decreased risk of prostate cancer (Jian 2007) and the other study reported that drinking 2 to 10 cups of green tea per day had no significant association with risk of prostate cancer (Sonoda 2004).

Breast cancer

None of the three cohort studies investigating the association between green tea consumption and the risk of breast cancer in women found such an association (Inoue 2008; Key 1999; Suzuki 2004).
However, both of the case-control studies found a positive association between increased green tea consumption and decreased risk of breast cancer risk. One case-control study carried out in the US including Chinese, Japanese and Filipino women indicated that there was an association between green tea consumption and the risk of breast cancer (Wu 2003) and another case-control study also found a positive association (Zhang 2007).

Lung cancer

A recent cohort study found no association between the risk of lung cancer and increased green tea consumption in both, male and female participants (Li 2008). Two case-control studies also investigated a possible association. One hospital and population-based case-control study with female participants found a decreased risk of lung cancer (Zhong 2001), whereas Bonner 2005 found no association for both gender.
Kuriyama 2006 found that green tea consumption was not related to lung cancer-specific mortality.

Oral cancer

One cohort study found no association between increased green tea consumption and decreased risk of oral cancer in men but a positive association but did find an association in in women (Ide 2007).

Various cancers

One cohort study reported that green tea consumption was found to be virtually unrelated to incidence of various types of cancer in both, male and female participants (Nagano 2001). Another cohort study found no association in men but did find an association in women (Nakachi 2000).

DISCUSSION

The aims of this review were to examine the possible association between green tea consumption and the risk of cancer incidence and mortality. The review includes data from 50 observational studies and one RCT.

Generally, there was a lack of consistency in the results of the observational studies assessing the effect of green tea on the incidence of cancer. This was especially the case for cancer of the digestive tract. With the exception of liver cancer, for which there was limited evidence of a preventive effect of green tea consumption, for all other entities - esophageal, gastric, colon, rectum, and pancreatic cancer - the evidence was conflicting. Conflicting evidence was also found with regard to the incidence of prostate and breast cancer. However, in prostate cancer, observational studies

with higher methodological quality and the only included RCT suggested a decreased risk in men consuming higher amounts of green tea or green tea extracts whereas in breast cancer, all nested case-control studies within prospective cohorts suggested no influence of green tea consumption on the risk of breast cancer. Limited evidence was found in regard to the consumption of green tea and a decrease of the incidence of ovarian cancer and oral cancer in women. In contrast, there was limited to moderate evidence that the consumption of green tea did not have any preventative effects on lung cancer, especially in men, and urinary bladder cancer or that it could even increase the risk of the latter.

There is moderate to strong evidence that the consumption of green tea does not decrease the risk of dying from gastric cancer and limited to moderate evidence that this is also the case for lung cancer, pancreatic cancer, and colorectal cancer.

Other systematic reviews

Borrelli 2004 only included studies investigating the association between green tea consumption and gastrointestinal cancer. The authors decided to include precancerous conditions such as adenomatous polyps, atrophic gastritis e.t.c. in their review. The conclusion reads that green tea seems to be protective for these precancerous conditions but that there is no clear evidence that green tea could prevent gastric and other intestinal cancer.

Sun 2006 investigated the effect of green and black tea consumption on colorectal cancer and carried out a meta-analysis. This meta-analysis contained eight studies also included in this review and found that there was a 18% reduction in risk of colorectal cancer with high green tea consumption. However, the authors found an increased risk of cancer morbidity with increased green tea consumption in case-control but not in cohort studies. There was some suggestion for a publication bias. Additionally, six studies were of Japanese origin, the other two of Chinese.

Finally, Seely 2005 published a systematic review and meta-analysis of the association between green tea and breast cancer, in which seven studies were included. They concluded that the consumption of at least five cups of green tea per day leads to a decrease in the risk of developing breast cancer, albeit this effect was statistically not significant. The reviewers also suggested that green tea consumption may prevent from recurrence in early stages of the disease.

Limitations

This review holds certain limitations. First of all, the methodological quality of included observational studies varied; specifically that of cohort studies and case-control studies. Thus, there was no reliable evidence from cohort and weak evidence from case-control studies to confirm the suggestion of an association between green tea consumption and a decreased risk of cancer.

Secondly, review authors can only make limited statements regarding associations between green tea intake and cancer incidence or cancer mortality based on the included studies, as the majority of included studies was carried out in Asia, where green tea drinking is more of a culturally-based tradition than in other parts of the world. The majority of studies was carried out in Japan (n = 32), followed by China (n = 13), the USA (n = 3), Singapore (n = 2) and Italy (n = 1). Apart from one case-control study (Bonner 2005) all other epidemiological studies carried out in China suggested a positive association. Eleven of all 20 cohort studies carried out in Japan found no association between green tea consumption and risk of cancer incidence for neither male nor female participants and three found no association investigating women only. Only two of the 20 Japanese cohort studies found a positive association for male participants (Kurahashi 2007) and a trend of a positive association for female participants (Sasazuki 2004). Two of the three studies carried out in the USA detected a positive associations between increased green tea consumption and a decreased risk of cancer incidence for women (Song 2008; Wu 2003) and one showed a negative association for men and none for women (Galanis 1998).

Apart from a possible location bias, which was not further investigated in this review, observational studies are affected by a great number of confounding variables and this may explain their controversial results.

Sample size

Sample sizes should be large in epidemiological studies in order to reduce random error, which can effect measurement in an inconsistent manner. Sample sizes in our included epidemiological studies ranged from 213 (Goto 1990) to 488,989 participants (Key 1999) with a median of 11,907 for cohort studies and 1043 for case-control studies. However, the majority of studies (n = 36) included less than 10,000 participants and n = 11 studies less than 1000 participants.

Many studies have too small a sample size for their findings to be conclusive. In a paper on the empirical evaluation of the Chinese literature in genetic epidemiology researchers reported a literature bias showing that Chinese studies were, on average, smaller in sample size that non-Chinese studies and, in general, reported a stronger gene-disease association and more frequently statistically significant results (Pan 2005).

Inferences from observational studies

It must be noted that the inferences that can be drawn from case-control and cohort studies are no more than of suggestive or moderately firm nature (Clark 2003). However, these types of studies are often used to answer questions regarding the prevention of a disease, prognosis and the aetiology or harm of an intervention.

Therapeutic effect and bias

In our view, the possibility of measuring the therapeutic effect of green tea based on isolated case-control or cohort studies is not very likely as other confounding variables come into place. Even if studies are age and gender-matched and statistically control for certain lifestyle factors, such as, for instance, smoking or family history of cancer; study results are likely to be affected by different types of bias (selection bias, publication bias).

Choice of control group

The choice of control group is also very important when discussing epidemiological studies. Random sampling should always be part of the planning of an epidemiological study. Studies included in this review are mainly hospital- or population-controlled. Hospital controls are often convenient and can be low-cost, and patients might be more motivated to participate in a study at the hospital (Grimes 2005). However, the background rate of exposure might not be equal to the sample under investigation and admission rate at hospitals might also bias the representativeness of a hospital control group (Sackett 1979). Additionally, there is the argument that hospital controls may resemble cases more than population controls and possible differences in weight, smoking patterns and burden of illness can bias the results of a study with hospital controls (Olson 1994). Population controls, on the other hand, have an advantage in that they are recruited by random sampling and should thus be representative. However, participants of a population control group could be less motivated to participate in research or there is the possibility that a substantial number of control participants cannot be reached (Wacholder 2007).

Variation in risks

Many factors may contribute to the variation in the RR estimates across the included studies, such as the genetic make-up of the population under investigation (albeit mostly of Asian cultures), the type of patients included, the selection of controls and the methodological quality of the study design. All these factors could lead to an over- or under-estimation of the true risks.

Furthermore, other confounding variables influencing the heterogeneity in green tea research are quality of product, quantity of consumption, duration of drinking, diet and the general environment.

Safety

Green tea (Camellia sinensis) is currently attracting the media and the public with news of its cancer-protective effects and green tea extracts are offered widely across many countries. Therefore some safety issues should be raised and discussed.

Different green tea drinking cultures have been observed cross-culturally between continents as well as between two countries on the same continent, such as, for instance, Japan and China. Green tea is often consumed in Asian cultures and has not been associated with any significant adverse effects (Nemecz 2000). However, since it is widely consumed the researchers dedicate one abstract to the safety of Camellia sinensis. When used orally in moderate amounts studies have shown that green tea is likely to be safe (Inoue 1998; Ji 1996; Kono 1988; Mitscher 1997; Nemecz 2000; Tajima 1985; Yu 1991; Zhang 2002). Green tea extract containing 7% caffeine has been used safely for six months (Pisters 2001) when used topically and appropriately (Ahn 2003; Katiyar 2000). However, green tea consumption is possibly unsafe when used orally, long-term and in high doses. Doses greater than 250 to 300 mg per day have been associated with tachyarrhythmia and sleep disturbances (IOM 2001). This is due to the caffeine contained in the standard green tea products but would not apply for decaffeinated green tea.

Orally, green tea can cause nausea, vomiting, abdominal bloating and pain, dyspepsia, flatulence and diarrhoea. It can also affect the central nervous system and cause adverse reactions such as dizziness, insomnia, fatigue, agitation, tremors, restlessness and confusion. These types of adverse events have been observed with higher doses of green tea (5 to 6 litres per day) (Jatoi 2003; Pisters 2001). One case report exists of a female otherwise healthy patient who had been taking six capsules of Green Lite Polyphenon per day used for weight loss (Gloro 2005). Her hepatic biopsy result was reported as "toxic hepatitis" and a liver transplant was performed. The World Health Organisation (WHO) database of adverse events in Uppsala was searched for case reports. Forty-nine case reports were found, of which 40 occurred with Camellia sinensis as an additional ingredient to other weight loss products: Tealine Arkomedika and Exolise Arkopharmaka. These products are advertised as weight loss products. Adverse events reported for these two products, which mainly stem from France and Spain, included hepatitis (n = 12), jaundice (n = 6), vomiting (n = 4), supraventricular tachycardia (n = 2), pulmonary hypertension (n = 1) and atrial fibrillation (n = 1). An end-of-the-year report from Arkopharma in 2002 stated that the sales of Exilose and Tealine had experienced a steep fall.

The Department of Health and Human Services issued a statement saying that "the relevance of these findings to Polyphenon E, in any, is not clear". However, the Committee of Medicine Security of Human Use has reviewed the data of security of the pharmaceutical specialties with green tea extract as a result of the notification of four cases in Spain and nine in France of hepatitis adverse reactions related to Exolise. As a result, Exolise is no longer marketed in at least two European countries (France & Spain). Only nine of the WHO reports were from the sole consumption of Camellia sinensis. These come from Spain (n = 5), Brazil (n = 3) and Canada (n = 1). In these cases, green tea was mainly consumed for weight loss. Adverse events reported from sole consumption of green tea included hepatitis (n = 2), nervousness (n = 2), insomnia (n = 2), hypertension (n = 2), jaundice (n = 1) and euphoria (n =

1). In a small pilot study with 102 healthy volunteers who were asked to consume 10 Japanese sized cups of green tea daily (about 2.5 g green tea extract) 50% of volunteers experienced very mild temporary disorders, such as abdominal bloating, heartburn, and insomnia due to the caffeine in green tea extract (Fujiki 2002).

AUTHORS' CONCLUSIONS

Implications for practice

As so often when researchers of systematic review are faced only with data from observational studies, the assessment of their methodological quality varies greatly.

There should be no expectation that drinking green tea regularly will reduce the risk of GI, uro-genital tract, breast, lung, prostate and liver cancer. However, those people who enjoy a cup of green tea as a beverage can continue to drink it if recommended daily dosages are not exceeded. The consumption of green tea appears to be safe at moderate, regular, and habitual use and can be seen as a healthy addition to the human diet.

Implications for research

The body of literature is generally contradictory due to the type of research studies assessing cancer-preventative effects of green tea. This systematic review showed that evidence for green tea preventing cancer incidence is sparse and highly conflicting. RCTs are almost non-existent in this topic area. The available epidemiological studies were of medium to high methodological quality. The researchers are not in a position to draw any valid conclusions about the associations of green tea consumption in cancer incidence and mortality. Future research should follow the example of the RCT and design clinical trials assessing green tea (in capsule and/or liquid form) as a preventative option for cancer occurrence. Furthermore, multi-center trials with random allocation of patients in which patients, clinicians and examiners are both blinded, involving patients at high cancer risk of the same cancer type are recommended.

Outcomes of RCTs should preferably be measured over a longer period to assess whether apparent preventative effects of interventions are maintained over time. However, should RCTs not be managable due to various reasons (e.g. expenses) a large, well-designed prospective cohort study with adequate green tea consumption levels is highly recommended by the reviewers. Therefore, in order to make an informed recommendation for a possible association between the consumption of green tea and a reduced cancer mortality more cohort studies and large RCTs are needed.

Evidence-based-medicine has changed preventative practice and has produced a lasting need of more RCTs as well as systematic reviews and meta-analyses. We need to aim at creating high level evidence in this much talked about but little researched topic area. Funding and infrastructure for clinical trials remain major challenges for the future.

ACKNOWLEDGEMENTS

We would like to thank all members of the Cochrane Gynaecological Cancer Review Group for their valuable support. Furthermore, we would like to thank Dr. Hitoshi Yamashita for his valuable help in acting as a translator.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Bettuzzi 2006

Methods	2-arm, double blind, placebo controlled, parallel, RT in Italy
Participants	60 men with high-grade prostate intraepithelial neoplasia (30 in each arm)
Interventions	Three green tea catechins capsules, 200 mg each (total 600 mg/d)
Outcomes	Prostate cancer incidence, total serum PSA, changes in LUTS as assessed by IPSS and QoL scores, medical events and side-effects
Cancer type & time of follow-up	Prostate cancer, treatment for 1 year
Sponsor	Grant support in part by PRIN 2004 (Miur, Italy), Dr. Rizzi supported by Genprofiler Srl (Bolzano, Italy)
Notes	At end of study n = 1 tumor was detected in treatment group (incidence ~ 3%) and n = 9 in control group (incidence ~ 30%) -> suggests a 90% chemoprevention efficacy of GTCs in men subjected to high risk for developing prostate cancer (highly significant P < .01) GTCs treatment did not significantly affect PSA values throughout the study but mean value of total PSA was always lower in treatment group and a trend toward a more stable total PSA value was evident in this group Small but significant decrease in IPSS score in GTC group for 3 months (P <0.05) Non-significant decrease in QoL scores in 35% of men in GTC group (P = 0.08) No adverse effects were reported.

Bonner 2005

Methods	Case-control study, population-based in China
Participants	122 cases, 122 controls
Interventions	N/A
Outcomes	Association of green tea consumption with cancer risk Matched for age, gender, residence, type of heating and cooking fuel Adjusted for pack-years of smoking
Cancer type & time of follow-up	Lung cancer
Sponsor	Not declared
Notes	Smoky coal < 130 tons Non-drinkers OR = 1.00 2 to 3 times/week OR = 1.91 (95% CI, 0.51 to 7.13)

Bonner 2005 (*Continued*)

	≥ 1 times/day OR = 0.96 (95% CI, 0.25 to 3.74) p = 0.65 Smoky coal ≥ 130 tons Non-drinkers OR = 1.00 2 to 3 times/week OR = 0.50 (95% CI, 0.17 to 1.47) ≥ 1 times/day OR = 0.73 (95% CI, 0.25 to 2.16) p = 0.61

Chyou 1993

Methods	Case-control study within a cohort study of Japanese population living in Hawaii, USA
Participants	7,995 cohort participants (men) 96 cases, sub-cohort control
Interventions	N/A
Outcomes	Incidence Adjusted for age and 'relevant co-variates' (no further description) Matching variables not described
Cancer type & time of follow-up	Urinary bladder cancer (22 years follow-up)
Sponsor	Grant provided by National Cancer Institute, Bethesda MD, USA
Notes	RR (95% CI) green tea consumption "almost never" = 1.00 RR (95% CI) green tea consumption "ever" = 1.34 (0.79 to 2.27) No p-values provided

Fujino 2002

Methods	Case-control study within a cohort study in Japan
Participants	44,930 cohort participants 379 cases, sub-cohort control
Interventions	N/A
Outcomes	Incidence Adjusted for age, smoking, alcohol, fruit and vegetable consumption
Cancer type & time of follow-up	Gastric cancer (6 to 9 years follow-up)
Sponsor	Grants-in-Aid for Scientific Research; Ministry of Education, Science, Sports and Culture, Japan

Fujino 2002 (*Continued*)

Notes	Men: > 3 cups/week RR = 1.00 ≤ 3 cups/week RR = 0.82 (95% CI, 0.41 to 1.64) Green tea consumption every day: RR = 1.11 (95% CI, 0.75 to 1.63) Women: > 3 cups/week RR = 1.00 ≤ 3 cups/week RR = 1.74 (95% CI, 0.71 to 4.26) Green tea consumption every day: RR = 1.43 (95% CI, 0.78 to 2.62) No p-values provided

Galanis 1998

Methods	Case-control study within a cohort study of Japanese population living in Hawaii, USA
Participants	11,907 cohort participants 108 cases, sub-cohort control
Interventions	N/A
Outcomes	Incidence Adjusted for age, gender years of education, place of birth
Cancer type & time of follow-up	Gastric cancer (14.8 years follow-up)
Sponsor	not declared
Notes	All None RR = 1.00 1 cup / day RR = 1.3 (95% CI, 0.7 to 2.1) ≥ 2 cups / day RR = 1.5 (95% CI, 0.9 to 2.3) p = 0.10 Men None RR = 1.00 1 cup / day RR = 1.2 (95% CI, 0.6 to 2.5) ≥ 2 cups / day RR = 1.6 (95% CI, 0.9 to 2.9) p = 0.11 Women None RR = 1.00 1 cup / day RR = 1.3 (95% CI, 0.6 to 2.9 ≥ 2 cups / day RR = 1.3 (95% CI, 0.6 to 2.6) p = 0.50

Gao 1994

Methods	Case-control study, population-based in China
Participants	902 cases, 1,552 controls
Interventions	N/A
Outcomes	Association of green tea consumption with cancer risk Matched according to sex and age Adjusted for age, smoking, alcohol, education, birthplace
Cancer type & time of follow-up	Esophageal cancer
Sponsor	Not declared
Notes	Men: 1 to199 tea leaves in grams/month OR = 0.79 (95% CI, 0.53 to 1.17) ≥200 tea leaves in grams/month OR = 0.79 (95% CI, 0.56 to 1.13) p = 0.20 Women: 1 to 149 tea leaves in grams/month OR = 0.77 (95% CI, 0.39 to 1.53) ≥150 tea leaves in grams/month OR = 0.34 (95% CI, 0.17 to 0.69) p<0.01

Goto 1990

Methods	Case-control study, population-based in Japan
Participants	71 cases, 142 controls
Interventions	N/A
Outcomes	Association of green tea consumption with cancer risk Matched for age and area of residence
Cancer type & time of follow-up	Pancreatic cancer
Sponsor	Not declared
Notes	”Drinking green tea almost every day” OR = 0.34 (95% CI, 0.17 to 0.67) p<0.01

Hoshiyama 2002

Methods	Case-control study within a cohort study in Japan
Participants	72,851 cohort participants 359 cases, sub-cohort control
Interventions	N/A
Outcomes	Mortality, cancer specific Adjusted for age
Cancer type & time of follow-up	Gastric cancer (8 years mean follow-up)
Sponsor	Ministry of Education, Science, Sports and Culture of Japan
Notes	**Alle + Männer + Frauen** Men: 1 or 2 cups/day: RR = 1.6 (95% CI 0.9 to 2.9) 3 or 4 cups/day: RR = 1.1 (95% CI 0.6 to 1.9) 5 to 9 cups/day: RR = 1.0 (95% CI 0.5 to 2.5) 10 or more cups/day: RR = 0.8 (95% CI 0.4 to 1.6) p = 0.669 Women: 1 or 2 cups/day: RR = 1.1 (95% CI 0.5 to 2.5) 3 or 4 cups/day: RR = 1.0 (95% CI 0.5 to 2.5) 5 to 9 cups/day: RR = 0.8 (95% CI 0.4 to 1.6) 10 or more cups/day: RR = 0.8 (95% CI 0.3 to 2.1) p = 0.488

Huang 1999

Methods	Case-control study, Hospital-based in Japan
Participants	850 cases, 28,619 controls
Interventions	N/A
Outcomes	Association of green tea consumption with cancer risk Not matched but first visit outpatient without cancer served as controls Adjusted for age and gender
Cancer type & time of follow-up	Gastric cancer
Sponsor	Grant-in-Aid for Cancer Research, Ministry of Health and Welfare in Japan
Notes	> 6 cups/day vs never OR = 0.9 (95% CI 0.73 to 1.11) 3 to 5 cups/day vs never OR = 1.08 (0.90 to 1.24) 1 to 2 cups/day vs never OR = 0.88 (0.73 to 1.05) No p-values provided

Ide 2007

Methods	Case-control study within a cohort study in Japan
Participants	50,221 cohort participants 37 cases, sub-cohort control
Interventions	N/A
Outcomes	Incidence Adjusted for age, gender, smoking, alcohol, daily intake of various foods
Cancer type & time of follow-up	Oral cancer (follow-up mean of 10.3 years)
Sponsor	The Ministry of Education, Science, sports and Culture of Japan
Notes	All: < 1 cup/day HR = 1.00 1 to 2 cups/day HR = 0.65 (95% CI, 0.22 to 1.94) 3 to 4 cups/day HR = 0.69 (95% CI, 0.28 to 1.71) ≥ 5 cups green tea/day HR 0.44 (95% CI: 0.19 to 1.04) p = 0.07 Men: < 1 cup/day HR = 1.00 1 to 2 cups green tea/day HR 0.79 (95% CI: 0.18 to 3.57) 3 to 4 cups green tea/day HR 0.81 (95% CI: 0.22 to 3.03) ≥ 5 cups green tea/day HR 0.61 (95% CI: 0.18 to 2.06) p = 0.42 Women: < 1 cup/day HR = 1.00 1 to 2 cups green tea/day HR 0.51 (95% CI: 0.10 to 2.68) 3 to 4 cups green tea/day HR 0.60 (95% CI: 0.17 to 2.10) ≥ 5 cups green tea/day HR 0.31 (95% CI: 0.09 to 1.07) p = 0.08

Inoue 1994

Methods	Case-control study, hospital-based in Japan
Participants	668 cases, 668 controls
Interventions	N/A
Outcomes	Association of green tea consumption with cancer risk matched for sex, age and first time of hospital visit Adjusted for gender;
Cancer type & time of follow-up	Gastric cancer
Sponsor	Grant-in-Aid for Cancer Research, Ministry of Health and Welfare, Japan

Inoue 1994 (*Continued*)

Notes	Green tea consumption every day or less: OR = 1.09 (95% CI, 0.83 to 1.43) No p-value provided

Inoue 1998

Methods	Case-control study, hospital-Based in Japan
Participants	1,706 cases, sub-cohort control
Interventions	N/A
Outcomes	Association of green tea consumption withdigestive tract cancer risk Not matched but first visit outpatients without cancer as controls Adjusted for gender, age, smoking, alcohol, exercise, fruit, rice and meat consumption
Cancer type & time of follow-up	Digestive tract cancer
Sponsor	Grant-in-Aid for Cancer Research, Ministry of Health and Welfare, Japan
Notes	Esophagus cancer: Green tea consumption Rarely OR = 1.00 Occasionally OR = 1.02 (95% CI, 0.5 to 2.1) 1 to 3 cups/day OR = 1.07 (95% CI, 0.58 to 2.00) 4 to 6 cups/day OR = 0.96 (95% CI, 0.5 to 1.83) ≥ 7 cups/day OR = 1.14 (95% CI, 0.55 to 2.34) Stomach cancer Green tea consumption Rarely OR = 1.00 Occasionally OR = 1.00 (95% CI, 0.77 to 1.44) 1 to 3 cups/day OR = 0.96 (95% CI, 0.70 to 1.32) 4 to 6 cups/day OR = 1.01 (95% CI, 0.74 to 1.39) ≥ 7 cups/day OR = 0.69 (95% CI, 0.48 to 1.00) (p<.05) Colon cancer Green tea consumption Rarely OR = 1.00 Occasionally OR = 0.62 (95% CI, 0.36 to 1.05) 1 to 3 cups/day OR = 0.64 (95% CI, 0.42 to 1.00) 4 to 6 cups/day OR = 0.76 (95% CI, 0.49 to 1.17) ≥ 7 cups/day OR = 0.77 (95% CI, 0.47 to 1.26) Rectum cancer Green tea consumption Rarely OR = 1.00 Occasionally OR = 1.41 (95% CI, 0.7 to 2.83) 1 to 3 cups/day OR = 1.04 (95% CI, 0.55 to 1.98) 4 to 6 cups/day OR = 1.42 (95% CI, 0.75 to 2.69) ≥ 7 cups/day OR = 1.25 (95% CI, 0.62 to 2.51)

Inoue 2008

Methods	Case-control study within a population-based cohort study in Japan
Participants	63,257 cohort participants 380 cases, 662 controls
Interventions	N/A
Outcomes	Incidence Adjusted for age, year of recruitment, dialect group, level of education, black tea intake, BMI, age when period became regular, number of live births
Cancer type & time of follow-up	Breast cancer (time of follow-up unclear)
Sponsor	Not declared
Notes	Green tea consumption: none or < weekly OR = 1.00 weekly to < daily OR = 0.65 (95% CI, 0.45 to 0.94) daily OR = 1.00 (95% CI, 0.82 to 1.22) p = 0.41

Ishikawa 2006

Methods	Case-control study through a pooled analysis of two prospective cohort studies,Japan
Participants	78,950 cohort participants 78 cases, sub-cohort control
Interventions	N/A
Outcomes	Incidence Adjusted for age, smoking, alcohol, tea and coffee consumption
Cancer type & time of follow-up	Esophageal cancer
Sponsor	Not declared
Notes	Pooled hazard ratio for both cohorts: Never or occasionally HR = 1.00 1 to 2 cups/day:HR = 1.03 (95% CI 0.46 to 2.28) 3 to 4 cups/day: HR = 1.13 (95% CI 0.53 to 2.42) 5 cups or more/day: HR = 1.67 (95% CI 0.89 to 3.16) p = 0.04

Ji 1996

Methods	Case-control study, Population-based in China
Participants	1,124 cases, 1,451 controls
Interventions	N/A
Outcomes	Association of green tea consumption and cancer risk Matched for age and sex Adjusted for age, monthly family per capita income and educational level
Cancer type & time of follow-up	Gastric cancer
Sponsor	Not declared
Notes	**Alle + Männer + Frauen** Men: ≤ 1200 g green tea leaves/year OR = 1.06 (95% CI, 0.76 to 1.49) > 1200 to ≤ 2000 g/year OR = 1.15 (95% CI, 0.82 to 1.61) > 2000 to ≤ 3000 g/year OR = 0.88 (95% CI, 0.64 to 1.24) > 3000 g/year OR = 0.76 (95% CI, 0.55 to 1.27) p = 0.2 Women: ≤ 1200 g/year OR = 0.74 (95% CI, 0.45 to 1.21) > 1200 g/year OR = 0.81 (95% CI, 0.46 to 1.43) p = 0.24

Ji 1997

Methods	Case-control study, population-based in China
Participants	2,266 cases, 1,552 controls
Interventions	N/A
Outcomes	Association of green tea consumption with cancer risk
Cancer type & time of follow-up	Pancreatic and colorectal cancer Matched for age and sex Adjusted for age, income, education, smoking, place of birth, diet, BMI, physical activity
Sponsor	Not declared
Notes	Men: Colon cancer Non-drinkers OR = 1.00 1 to 199 g green tea leaves/month OR = 1.13 (95% CI, 0.80 to 1.61) 200 to 299 g green tea leaves/month OR = 0.92 (95% CI, 0.62 to 1.37) ≥ 300 g green tea leaves/month OR = 0.82 (95% CI, 0.52 to 1.28)

Ji 1997 (*Continued*)

	p = 0.38 Rectum cancer Non-drinkers OR = 1.00 1 to 199 g green tea leaves/month OR = 0.99 (95% CI,) 200 to 299 g green tea leaves/month OR = 0.66 (95% CI,) ≥ 300 g green tea leaves/month OR = 0.72 (95% CI,) p = 0.04 Pancreas cancer Non-drinkers OR = 1.00 1 to 199 g green tea leaves/month OR = 1.23 (95% CI, 0.69 to 1.41) 200 to 299 g green tea leaves/month OR = 0.57 (95% CI, 0.43 to 0.99) ≥ 300 g green tea leaves/month OR = 0.63 (95% CI, 0.46 to 1.13) p = 0.04 Women Colon cancer Non-drinkers OR = 1.00 1 to 200 g green tea leaves/month OR = 0.83 (95% CI, 0.57 to 1.21) > 200 g green tea leaves/month OR = 0.67 (95% CI, 0.41 to 1.10) p = 0.07 Rectum cancer Non-drinkers OR = 1.00 1 to 200 g green tea leaves/month OR = 0.51 (95% CI, 0.33 to 0.79) > 200 g green tea leaves/month OR = 0.57 (95% CI, 0.34 to 0.97) p = 0.001 Pancreas cancer Non-drinkers OR = 1.00 1 to 199 g green tea leaves/month OR = 0.47 (95% CI, 0.25 to 0.89) > 200 g green tea leaves/month OR = 0.53 (95% CI, 0.25 to 1.09) p = 0.008

Jian 2007

Methods	Case-control study in China
Participants	130 cases, 274 controls
Interventions	N/A
Outcomes	Association of green tea consumption with cancer risk No detailsreported on matching Adjusted for age, height, weight, BMI, locality, education, income, marital status, family history of prostate cancer, physical activities, intakes of fat and calories
Cancer type & time of follow-up	Prostate cancer

Jian 2007 (*Continued*)

Sponsor	Not declared
Notes	0 g green tea leaves/day OR = 1.00 0.3 to 2.9 g green tea leaves /day OR = 0.45 (95% CI, 0.25 to 0.82) 3.0 to 4.9 g green tea leaves/day OR = 0.24 (95% CI, 0.10 to 0.57) ≥ 5 g green tea leaves/day OR = 0.13 (95% CI, 0.05 to 0.32) No p-values provided

Kato 1990a

Methods	Case-control study, Population-based in Japan
Participants	746 cases, 578 controls
Interventions	N/A
Outcomes	Association of green tea consumption with cancer risk Matched for age, sex and municipality Adjusted for age, gender and residence
Cancer type & time of follow-up	Colorectal cancer
Sponsor	Grant-in-Aid for Cancer Research, Ministry of Health and Welfare, Japan
Notes	Daily green tea drinkers versus less than daily green tea drinkers: Colon cancer RR = 0.61 (95%CI, 0.41 to 0.91) Rectal cancer RR = 1.32 (95% CI, 0.78 to 2.23) No p-values provided

Kato 1990b

Methods	Case-control study, Hospital-based in Japan
Participants	1,841 cases, 3,014 controls
Interventions	N/A
Outcomes	Association of green tea consumption with cancer risk Not matched Adjusted for age and residence
Cancer type & time of follow-up	Gastric cancer
Sponsor	Grant-in-Aid for Cancer Research, Ministry of Health and Welfare in Japan

Kato 1990b (*Continued*)

Notes	1 to 4 cups/day: RR = 1.04 (95% CI, 0.83 to 1.30) ≥ 5 cups/day: RR = 1.00 (0.78 to 1.29) No p-values provided

Key 1999

Methods	Case-control study within a cohort study in Japan
Participants	488,989 cohort participants 427 cases, sub-cohort control
Interventions	N/A
Outcomes	Incidence Adjusted for age, residence at time of bombing and breast dose
Cancer type & time of follow-up	Breast cancer (10 years follow-up)
Sponsor	Japanese Ministry of Health and Welfare, US Department of Energy through National Academy of Science
Notes	≤ 1 cup green tea/day: RR = 1.00 2 to 4 cups green tea/day: RR = 1.02 (95% CI, 0.76 to 1.36) ≥ 5 cups green tea/day: RR = 0.86 (95% CI, 0.62 to 1.21) p = 0.284

Kikuchi 2006

Methods	Case-control study within a prospective cohort study in Japan
Participants	19,561 cohort participants 110 cases, sub-cohort control
Interventions	N/A
Outcomes	Incidence Adjusted for age, BMI, alcohol, smoking, marital status, daily calorie intake (continuous), daily calcium intake, walking duration, consumption frequencies of black tea and coffee and consumption frequencies of meat
Cancer type & time of follow-up	Prostate cancer (7 years follow-up)
Sponsor	A grant-in-aid of Third Term Comprehensive Control Research for Cancer from the Ministry of Health, Labour and Welfare, Japan

Kikuchi 2006 (*Continued*)

Notes	Green tea consumption (cups per day): <1 HR = 1.00 1 or 2 cups/day HR = 0.77 (95% CI, 0.42 to 1.40) 3 or 4 cups/day HR = 0.24 (95% CI, 0.69 to 1.94) ≥ 5 cups/day HR = 0.85 (95% CI, 0.50 to 1.43) p = 0.81

Koizumi 2003

Methods	Pooled analysis of 2 population-based prospective cohort studies in Japan
Participants	Cohort I: 31,345 participants Cohort II: 47,605 participants 733 cases, sub-cohort control
Interventions	N/A
Outcomes	Incidence Adjusted for gender, age, type of health insurance, parental history of gastric cancer, history of peptic ulcer, smoking, alcohol, tea consumption and that of other food (e.g. rice, pickled vegetables)
Cancer type & time of follow-up	Gastric cancer (follow-up cohort I: 9 years, cohort II: 7 years)
Sponsor	Not declared in this paper but in Tsubono 2001 - Supported in part by grants from the Japanese Ministry of Health and Welfare and the Japanese Ministry of Education, Science, and Culture
Notes	<1 cup/day: RR 1.00 1 or 2 cups/day: RR 1.01 (95%, CI 0.8 to 1.27) 3 or 4 cups/day: RR 0.89 (95%, CI 0.7 to 1.13) ≥5 cups/day: RR 1.06 (95%, CI 0.86 to 1.3) p = 0.61

Kono 1988

Methods	Case-control study, Hospital and population-based in Japan
Participants	139 cases, 2,852 controls
Interventions	N/A
Outcomes	Association of green tea consumption and risk of cancer matched for age and sex Adjusted for age, gender and occupational class
Cancer type & time of follow-up	Gastric cancer

Kono 1988 (*Continued*)

Sponsor	Grant-in-Aid, Ministry of Education, Science and Culture, Japan
Notes	Low green tea consumption: RR = 1.00 Intermediate green tea consumption: RR = 1.2 High green tea consumption: RR = 0.4 (p< 0.05) ≥10 cups/day versus less comparison with hospital controls: RR = 0.5 (95% CI, 0.3 to 1.1) (p = 0.10) comparison with general population controls: RR = 0.3 (95% CI, 0.1 to 0.7) (p = 0.007)

Kurahashi 2007

Methods	Case-control study within an prospective cohort study in Japan
Participants	49,920 cohort participants 404 cases, sub-cohort control
Interventions	N/A
Outcomes	Incidence Adjusted for age and residence
Cancer type & time of follow-up	Prostate cancer (follow-up 11 to14 years)
Sponsor	By a grant-in-aid for cancer research from the Ministry of Health, Labour and Welfare, Japan for the Third Term Comprehensive 10-year strategy for cancer control and by grants-in-aid for scientific research on priority areas form the Ministry of Education, Culture, Sports, Science and Technology for research on the risk of chemical substances
Notes	<1 cup/day: RR 1.00 1 to 2 cups/day: RR 1.12 (95% CI, 0.65 to 1.94) 3 to 4 cups/day: RR 0.86 (95% CI, 0.50 to 1.47) ≥ 5 cups/day: RR 0.60 (95% CI, 0.34 to 1.06) p = 0.03

Kuriyama 2006

Methods	Prospective cohort study in Japan
Participants	40,530 cohort participants 1,134 cases (deaths), sub-cohort control
Interventions	N/A
Outcomes	Mortality, cancer specific Adjusted for age at baseline, job status, years of education, BMI, engaging in sports or exercise, time spent walking, history of: hypertension, diabetes mellitus, gastric ulcer, smoking, alcohol, daily total energy intake, daily rice consumption bowls, or 5 bowls, daily consumption of miso

Kuriyama 2006 (*Continued*)

	soup, daily consumption of soybean products, total meat, total fish, dairy products, total fruits, and total vegetables and consumption of oolong tea, black tea, or coffee
Cancer type & time of follow-up	Various cancer types (gastric, lung, colorectal; 11 years follow-up)
Sponsor	Health Sciences Research Grant for Health Services, Ministry of Health, Labour, and Welfare, Japan
Notes	HRs of cancer mortality were not significant different from 1.00 in all green tea consumption categories compared with the lowest-consumption (referent) category Green tea consumption was inversely related with mortality due to all causes (including cancer). Inverse association was stronger in women Green tea consumption was associated with reduced mortality due to all causes and due to cardiovascular disease but not with reduced mortality due to cancer Green tea consumption (cups per day) a) <1 (=reference category) b) 1 or 2 c) 3 or 4 d) ≥5 All cancer mortality Green tea consumption (cups per day) a) <1: 65.656 person years, n. of deaths: n = 256 b) 1 or 2: 54.443 person years, n. of deaths: n = 229 c) 3 or 4: 55.290 person years, n. of deaths: n = 265 d) ≥5: 76.712 person years, n. of deaths: n = 384 All cancer mortality b =1.12 (95% CI, 0.89 to 1.41) c = 1.17 (95% CI, 0.94 to 1.46) d = 1.11 (95% CI, 0.90 to 1.37) Gastric cancer mortality b = 1.33 (95% CI, 0.86 to 2.40) c = 1.00 (95% CI, 0.64 to 1.58) d = 1.17 (95% CI, 0.78 to 1.76) Lung cancer mortality b = 1.03 (95% CI, 0.67 to 1.58) c = 1.05 (95% CI, 0.69 to 1.59) d = 1.18 (95% CI, 0.81 to 1.72) Colorectal cancer mortality b = 1.04 (95% CI, 0.59 to 1.82) c = 1.45 (95% CI, 0.87 to 2.41) d = 1.10 (95% CI, 0.67 to 1.82)

Li 2008

Methods	Case-control study within a population-based cohort study in Japan
Participants	41,440 cohort participants 302 cases, sub-cohort control
Interventions	N/A
Outcomes	Incidence Adjusted for age, gender, education level, marital status, passive smoking, BMI, walking duration, family history of cancer, smoking status, number of cigarettes smoked per day, years of smoking, alcohol drinking, total energy intake per day and daily consumption of soybean products, total meat, total fish, dairy products, total fruits and total vegetables and consumption of coffee
Cancer type & time of follow-up	Lung cancer (7 years follow-up)
Sponsor	By a grant-in-aid for Cancer Research and for the Third Term Comprehensive Ten-Year Strategy for Cancer Control, Ministry of Health, Labour and Welfare, Japan
Notes	All: < 1 cup/day: HR = 1.00 1 or 2 cups/day: HR = 1.14 (95% CI, 0.80 to 1.62) 3 or 4 cups/day: HR = 1.18 (95% CI, 0.83 to 1.66) ≥5 cups/day: HR = 1.17 (95% CI, 0.85 to 1.61) p = 0.48 Women: < 1 cup/day: HR = 1.00 1 or 2 cups/day: HR = 1.48 (95% CI, 0.71 to 3.10) 3 or 4 cups/day: HR = 1.11 (95% CI, 0.52 to 2.37) ≥5 cups/day: HR = 1.30 (95% CI, 0.65 to 2.60) p = 0.71 Men: < 1 cup/day: HR = 1.00 1 or 2 cups/day: HR = 1.05 (95% CI, 0.70 to 1.57) 3 or 4 cups/day: HR = 1.21 (95% CI, 0.82 to 1.79) ≥5 cups/day: HR = 1.17 (95% CI, 0.82 to 1.68) p = 0.32

Lin 2008

Methods	Case-control study within a prospective cohort study in Japan
Participants	77,850 cohort participants 292 cases (deaths), sub-cohort control
Interventions	N/A
Outcomes	Mortality, cancer specific Adjusted for age, sex, BMI, smoking, alcohol, diabetes history, gallbladder disease history

Lin 2008 (*Continued*)

Cancer type & time of follow-up	Pancreatic cancer (follow-up between 5 to 13 years)
Sponsor	Grant-in-Aid for Scientific Research on Priority Areas from Ministry of Education, Culture, Sports, Science and Technology of Japan
Notes	All: <1cup/day (reference category) 1 to 2 cups/day: RR 1.04 (95% CI 0.67 to 1.6) 3 to 4 cups/day: RR 1.14 (95% CI 0.8 to 1.63) 5 to 6 cups/day: RR 0.99 (95% CI 0.69 to 1.42) ≥ 7 cups/day: RR 1.23 (95% CI 0.84 to 1.8) p = 0.46 Men: <1cup/day (reference category) 1 to 2 cups/day: RR 0.79 (95% CI 0.42 to 1.51) 3 to 4 cups/day: RR 1.09 (95% CI 0.65 to 1.83) 5 to 6 cups/day: RR 0.88 (95% CI 0.53 to 1.48) ≥ 7 cups/day: RR 0.95 (95% CI 0.55 to 1.65) p = 0.90 Women: <1cup/day (reference category) 1 to 2 cups/day: RR 1.32 (95% CI 0.73 to 2.38) 3 to 4 cups/day: RR 1.20 (95% CI 0.73 to 1.97) 5 to 6 cups/day: RR 1.08 (95% CI 0.66 to 1.78) ≥ 7 cups/day: RR 1.54 (95% CI 0.91 to 2.60) p = 0.28

Luo 2007

Methods	Case-control study within a population-based cohort study in Japan
Participants	102,137 cohort participants 233 cases, sub-cohort control
Interventions	N/A
Outcomes	Incidence Adjusted for gender, age, BMI, leisure-time physical activity in terms of frequency of sports; smoking status, alcohol intake, history of diabetes; history of cholelithiasis; study area
Cancer type & time of follow-up	Pancreatic cancer (follow-up average of 11 years)
Sponsor	By a grant-in-aid for Cancer Research and for the Third Term Comprehensive Ten-Year Strategy for Cancer Control, Ministry of Health, Labour and Welfare, Japan. Author JL was partly supported by the SVENSKA SALLSKAPET FOR MEDININSK FOR SKNING (SSMF) and the Karolinska Institutet Travel Fund

Luo 2007 (*Continued*)

Notes	< 1 cup/day: HR = 1.1 (95% CI, 0.6 to 1.9) 1 or 2 cups/day: HR = 1.1 (95% CI, 0.7 to 1.9) 3 or 4 cups/day: HR = 1.2 (95% CI, 0.7 to 2.0) ≥5 cups/day: HR = 1.2 (95% CI, 0.7 to 1.9) p = 0.5

Mizuno 1992

Methods	Case-control study, Hospital-based in Japan
Participants	124 cases, 124 controls
Interventions	N/A
Outcomes	Association with green tea consumption and cancer risk Matched for age and gender Adjusted for gender, age and place of enrolment
Cancer type & time of follow-up	Pancreatic cancer
Sponsor	Grant-in-Aid for Cancer Research, Ministry of Health and Welfare, Japan
Notes	≥5 cups/day: OR = 1.94 (95% CI, 1.06 to 3.55) no p-values provided

Mu 2003

Methods	Case-control study, population-based in China
Participants	628 cases, 415 controls
Interventions	N/A
Outcomes	Association of green tea consumption with cancer risk
Cancer type & time of follow-up	Gastric, liver, esophageal cancer
Sponsor	Not declared
Notes	Consumption versus no consumption: Gastric cancer: OR = 0.44 (95% CI, 0.23 to 0.86) Liver cancer: OR = 0.65 (95% CI, 0.36 to 1.16) Esophageal cancer: OR = 1.00 Among alcohol drinkers Gastric cancer: OR = 0.23 (95% CI, 0.10 to 0.55) Liver cancer: OR = 0.25 (95% CI, 0.11 to 0.57) No p-values provided

Nagano 2001

Methods	Case-control study within a cohort study in Japan
Participants	38,540 cohort participants 4,069 cases, sub-cohort control
Interventions	N/A
Outcomes	Incidence Adjusted for gender, age, residence, radiation dose, smoking, alcohol, level of education and BMI
Cancer type & time of follow-up	Various types of cancer (13 to 15 years follow-up)
Sponsor	Radiation Effects Research Foundation, private non-profit foundation funded by Japanese Ministry of health and Welfare and US Department of Energy, National Academy of Sciences
Notes	< 1 cup/day RR = 1.00 2 to 4 times/day RR = 1.0 (95% CI, 0.01 to 1.1) ≥5 times/day RR = 0.98 (95% CI, 0.88 to 1.1)

Nakachi 2000

Methods	Case-control study within a cohort study in Japan
Participants	8,552 cohort participants 488 cases, sub-cohort control
Interventions	N/A
Outcomes	Incidence Adjusted for age, gender, smoking, alcohol, vegetable and rice intake
Cancer type & time of follow-up	Various types of cancer (11 years follow-up)
Sponsor	Grant-in-Aid for Cancer Research, MInistry of Education, Science, Sports and Culture, Japan and Ministry of Health and Welfare, Japan (Grant from Smoking Research Foundation)
Notes	Total: ≤ 3 cups/day: RR = 1.00 4 to 9 cups/day: RR = 0.81 (95% CI, 0.52 to 1.27) ≥10 cups/day: RR = 0.59 (95% CI, 0.35 to 0.98) Men: ≤ 3 cups/day: RR = 1.00 4 to 9 cups/day: RR = 1.00 (95% CI, 0.50 to 2.04) ≥ 10 cups/day: RR = 0.54 (95% CI, 0.22 to 1.34) Women: ≤ 3 cups/day: RR = 1.00 4 to 9 cups/day: RR = 0.92 (95% CI, 0.64 to 1.31)

Nakachi 2000 (*Continued*)

	≥ 10 cups/day: RR = 0.57 (95% CI, 0.34 to 0.98) No p-values provided

Sasazuki 2004

Methods	Case-control study within a cohort study in Japan
Participants	72,273 cohort participants 892 cases, sub-cohort control
Interventions	N/A
Outcomes	Incidence and mortality Adjusted for age, residence, smoking
Cancer type & time of follow-up	Gastric cancer (6 to 11 years follow-up)
Sponsor	Grant-in-Aid for Cancer Research, Ministry of Health, Labour and Welfare, Japan
Notes	Men: < 1 cup / day RR (Cohort I) = 1.00 RR (Cohort II) = 1.00 1 to 2 cups / day RR (Cohort I) = 0.95 (95% CI, 0.74 to 1.21) RR (Cohort II) = 0.94 (95% CI, 0.72 to 1.22) 3 to 4 cups / day RR (Cohort I) = 0.89 (95% CI, 0.71 to 1.13) RR (Cohort II) = 0.84 (95% CI, 0.65 to 1.08) > 5 cups / day RR (Cohort I) = 0.97 (95% CI, 0.77 to 1.22) RR (Cohort II) = 0.98 (95% CI, 0.77 to 1.25) Cohort I p = 0.81 Cohort II p = 0.65 Women: < 1 cup / day RR (Cohort I) = 1.00 RR (Cohort II) = 1.00 1 to 2 cups / day RR (Cohort I) = 0.93 (95% CI, 0.61 to 1.41) RR (Cohort II) = 0.85 (95% CI, 0.53 to 1.38) 3 to 4 cups / day RR (Cohort I) = 1.10 (95% CI, 0.75 to 1.60) RR (Cohort II) = 1.04 (95% CI, 0.68 to 1.58) > 5 cups / day RR (Cohort I) = 0.70 (95% CI, 0.47 to 1.05) RR (Cohort II) = 0.67 (95% CI, 0.43 to 1.04) Cohort I p = 0.15

Sasazuki 2004 (*Continued*)

	Cohort II p = 0.08

Setiawan 2001

Methods	Case-control study, population-based in USA
Participants	299 (of which n = 166 chronic gastritis) cases, 433 controls
Interventions	N/A
Outcomes	Association of green tea consumption with cancer risk Not matched controls Adjusted for age, gender, education, smoking, alcohol and BMI
Cancer type & time of follow-up	Gastric cancer
Sponsor	National Institute of Health, Department of Health and Human Services and University of California - Los Angeles Jonsson Comprehensive Cancer Care Center Foundation and Weissman Fund
Notes	Non-drinkers: OR = 1.00 1 to 21 cups/week OR = 0.70 (95% CI, 0.36 to 1.36) > 21 cups/week OR = 0.39 (95% CI, 0.15 to 1.01) p = 0.048

Song 2008

Methods	Case-control study, population-based in USA
Participants	781 cases, 1,263 controls
Interventions	N/A
Outcomes	Association of green tea consumption with cancer risk Adjusted for age, county, year of diagnosis/reference date, race/ethnicity, number of full-term pregnancies, duration of hormonal contraception, education, body mass index, smoking, tubal ligation/hysterectomy, and family history of breast/ovarian cancer
Cancer type & time of follow-up	Ovarian cancer
Sponsor	NIH grant, USA
Notes	Non-drinkers OR = 1.00 < 1 cup/day OR = 0.82 (95% CI, 0.66 to 1.04) ≥1 cups/day OR = 0.46 (95% CI, 0.26 to 0.84) p = 0.01 When Asian women were excluded from analysis:

Song 2008 (*Continued*)

	Non-drinkers OR = 1.00 < 1 cup/day OR = 0.81 (no CIs provided) ≥1 cups/day OR = 0.41 (no CIs provided) p = 0.003

Sonoda 2004

Methods	Case-control study, hospital-based in Japan
Participants	140 cases, 140 controls
Interventions	N/A
Outcomes	Association of green tea consumption with cancer risk Age-matched Adjusted for age, smoking and total energy intake
Cancer type & time of follow-up	Prostate cancer
Sponsor	Not declared
Notes	≤ 1 cup/day OR = 1.00 2 to 4 cups/day OR = 0.99 (95% CI, 0.48 to 2.03) 5 to 9 cups/day OR = 0.79 (95% CI, 0.38 to 1.63) ≥ 10 cups/day OR = 0.67 (95% CI, 0.27 to 1.64) p = 0.30

Sun 2007

Methods	Case-control study within a population-based prospective cohort study in Singapore
Participants	61,320 cohort participants 516 cases (colon cancer), 329 cases (rectal cancer), sub-cohort control
Interventions	N/A
Outcomes	Incidence Adjusted for gender, age at baseline interview, year of interview, dialect group, education, family history of colorectal cancer, history of diabetes, cigarette smoking, alcohol drinking, coffee drinking, weekly moderate physical activity, BMI, total energy, total fat, dietary fiber, calcium and vitamin C
Cancer type & time of follow-up	Colorectal cancer (follow-up average of 8.9 years)
Sponsor	National Cancer Institute, Bethesda, MD, USA

Sun 2007 (*Continued*)

Notes	Total: Non-drinker RR = 1.00 Drinker RR = 1.12 (95% CI, 0.97 to 1.29) Monthly RR = 1.05 (95% CI, 0.84 to 1.31) Weekly RR = 1.11 (95% CI, 0.92 to 1.35) Daily RR = 1.18 (95% CI, 0.97 to 1.45) p = 0.08 Men: Non-drinker RR = 1.00 Drinker RR = 1.31 (95% CI, 1.08 to 1.58) Monthly RR = 1.32 (95% CI, 0.98 to 1.78) Weekly RR = 1.25 (95% CI, 0.98 to 1.61) Daily RR = 1.36 (95% CI, 1.06 to 1.74) p = 0.009 Women: Non-drinker RR = 1.00 Drinker RR = 0.89 (95% CI, 0.71 to 1.12) Monthly RR = 0.79 (95% CI, 0.56 to 1.13) Weekly RR = 0.96 (95% CI, 0.71 to 1.31) Daily RR = 0.91 (95% CI, 0.63 to 1.32) p = 0.52

Suzuki 2004

Methods	Case-control study within a cohort study in Japan
Participants	35,004 cohort participants 222 cases, sub-cohort control
Interventions	N/A
Outcomes	Incidence Adjusted for age, types of health insurance, age at menarche, menopausal status age at first birth, parity, mother's history of breast cancer, smoking current alcohol drinking, BMI and consumption frequencies of black tea and coffee
Cancer type & time of follow-up	Breast cancer (7 years follow-up)
Sponsor	Not declared
Notes	< 1 cup/day: RR = 1.00 1 or 2 cups/day: RR = 0.87 (95% CI, 0.57 to 1.32) 3 or 4 cups/day: RR = 1.07 (95% CI, 0.73 to 1.57) ≥ 5 cups/day: RR = 0.84 (95% CI, 0.57 to 1.24) p = 0.69

Suzuki 2005

Methods	Case-control study within two prospective cohort studies in Japan
Participants	26,311 participants in cohort I 269 cases, sub-cohort control 39,604 participants in cohort II 247 cases, sub-cohort control
Interventions	N/A
Outcomes	Incidence Adjusted for sex, age, family history of CRC, smoking, Alcohol, BMI, consumption of black tea and coffee
Cancer type & time of follow-up	Colon and rectal cancer (follow-up cohort I: 9 years, cohort II: 7.5years)
Sponsor	Not declared
Notes	HR1= RR with all cases of CRC HR2 = RR with cases diagnosed in first 3 years of follow-up Colon: Multivariate HR1 >1 cups/day: 1.0 1 or 2 cups/day: 1.06 (0.74 to 1.52) 3 or 4 cups/day: 1.10 (0.78 to 1.55) 5 or more cups/day: 0.97 (0.7 to 1.35) p = 0.81 Multivariate HR2 >1 cups/day: 1.0 1 or 2 cups/day: 1.08 (0.72 to 1.62) 3 or 4 cups/day: 1.05 (0.71 to 1.57) 5 or more cups/day: 0.83 (0.57 to 1.21) p = 0.27 Rectal: Multivariate HR1 >1 cups/day: 1.0 1 or 2 cups/day: 1.85 (0.56 to 1.29) 3 or 4 cups/day: 0.70 (0.45 to 1.08) 5 or more cups/day: 0.85 (0.58 to 1.23) p = 0.31 Multivariate HR2 >1 cups/day: 1.0 1 or 2 cups/day: 0.73 (0.43 to 1.22) 3 or 4 cups/day: 0.62 (0.36 to 1.07) 5 or more cups/day: 0.90 (0.58 to 1.40) p = 0.67

Tajima 1985

Methods	Case-control study, hospital-based in Japan
Participants	186 cases, 186 controls
Interventions	N/A
Outcomes	Association of green tea consumption with cancer risk Matched for age and sex Adjusted for age and gender
Cancer type & time of follow-up	Gastric cancer
Sponsor	Grant-in-Aid for Cancer Research, MInistry of Health and Welfare, Japan
Notes	≥ 4 cups green tea/day versus less: Stomach cancer: RR = 0.64 Colon cancer: RR = 0.97 Rectal cancer: RR = 0.91 no CIs and no p-values provided

Tsubono 2001

Methods	Case-control study within a cohort study in Japan
Participants	26,311 cohort participants 419 cases, sub-cohort control
Interventions	N/A
Outcomes	Incidence Adjusted for gender; age; type of health insurance; history of peptic ulcer; cigarette smoking;alcohol consumption; daily consumption of rice; consumption of black tea and consumption of coffee; and consumption of meat, green or yellow vegetables, pickled vegetables, other vegetables, fruits, and bean-paste soup
Cancer type & time of follow-up	Gastric cancer (8 years follow-up)
Sponsor	Ministry of Health and Welfare, Japan and Ministry of Education, Science and Culture, Japan
Notes	≤ 1 cups/day: RR = 1.00 1 or 2 cups/day: RR = 1.1 (95% CI, 0.8 to 1.6) 3 or 4 cups/day: RR = 1.0 (95% CI, 0.7 to 1.4) ≥5 cups/day: RR = 1.2 (95% CI, 0.9 to 1.6)

Wakai 2004

Methods	Case-control study, hospital-based in Japan
Participants	124 cases, 620 controls
Interventions	N/A
Outcomes	Association of green tea consumption with cancer risk Matched for age and sex Adjusted for age, gender, smoking, year of first visit
Cancer type & time of follow-up	Urinary bladder cancer
Sponsor	Grant-in-Aid for Cancer Research, Ministry of Health, Labour and Welfare, Japan
Notes	<1 cup/day OR = 1.00 1 to 4 cups/day OR = 1.40 (95% CI, 0.74 to 2.62) 5 to 9 cups/day OR = 2.67 (95% CI, 1.44 to 4.94) p< 0.01 ≥10 cups/day OR = 1.18 (95% CI, 0.49 to 2.84) p = 0.024

Wang 1999

Methods	Case-control study, hospital-based in China
Participants	209 cases, 209 controls
Interventions	N/A
Outcomes	Association of green tea consumption with cancer risk
Cancer type & time of follow-up	Esophageal, cardiac and gastric cancer
Sponsor	Not declared
Notes	Esophageal cancer: OR = 0.20 Gastric cancer: OR = 0.28 no CIs or p-values provided

Wang 2007

Methods	Case-control study, population-based in Singapore
Participants	355 cases, 408 controls
Interventions	N/A

Wang 2007 (*Continued*)

Outcomes	Association of green tea consumption with cancer risk Matched for sex and age Adjusted for age, marital status and education years.
Cancer type & time of follow-up	Esophageal cancer (squamous cell carcinoma)
Sponsor	National Nature Science Foundation of China
Notes	Men: 0 cups/year OR = 1.00 < 30 cups/year OR = 1.312 (95% CI, 0.846 to 2.033) p = 0.225 ≥30 cups/day OR = 1.435 (95% CI, 0.908 to 2.268) p = 0.122 Women: 0 cups/year OR = 1.00 < 30 cups/year OR = 0.327 (95% CI, 0.064 to 1.677) p = 0.18 ≥30 cups/day OR = 0.182 (95% CI, 0.021 to 1.544) p = 0.118

Wu 2003

Methods	Case-control study, population-based of Asian Americans in USA
Participants	501 cases, 594 controls
Interventions	N/A
Outcomes	Association of green tea consumption with cancer risk Matched for age and ethnicity Adjusted for age, ethnicity, birth place, smoking and alcohol consumption
Cancer type & time of follow-up	Breast cancer
Sponsor	California Breast Cancer Research program and USC/Norris Comprehensive Cancer Center, USA
Notes	Non-drinker OR = 1.00 ≤ 85.7 ml/day OR = 0.73 (95% CI, 0.40 to 1.32) ≥ 85.7 ml/day OR = 0.47 (95% CI, 0.26 to 0.85)

Yang 2007

Methods	Case-control study within a prospective cohort study in China
Participants	69,710 cohort participants (women) 256 cases, sub-cohort control
Interventions	N/A
Outcomes	Incidence Adjusted for age; education; household income; cigarette smoking; alcohol drinking; physical activity; body mass index; menopausal status; nonsteroidal antiinflammatory drug use; vitamin supplement use; prior histories of colorectal polyps and chronic ulcerative colitis; family history of colorectal cancer; and intakes of total energy, vegetables, fruits, and red meat
Cancer type & time of follow-up	Colon and rectal cancer (follow-up 6 years)
Sponsor	USPHS grant and NIH intramural program, Division of Cancer Epidemiology and genetics
Notes	Non-drinker: RR = 1.00 1 to 4 g green tea leaves/day: RR = 0.70 (95% CI, 0.47 to 1.02) ≥ 5 g green tea leaves/day: RR = 0.56 (95% CI, 0.32 to 0.98) p = 0.01

Ye 1998

Methods	Case-control study, population-based in China
Participants	272 cases, 544 controls
Interventions	N/A
Outcomes	Association of green tea consumption with cancer risk Matched for age, sex and nationality
Cancer type & time of follow-up	Gastric cancer
Sponsor	"8.5" National Major Project, China
Notes	> 0.75 kg green tea leaves/year OR = 1.00 ≤ 0.75 kg green tea leaves/year OR = 1.72 (95% CI, 1.26 to 2.36) p< 0.01

Yu 1995

Methods	Case-control study, population-based in China
Participants	711 cases, 711 controls
Interventions	N/A
Outcomes	Association of green tea consumption with cancer risk Matched for age and gender Adjusted for age, gender, residence, education, birth place, alcohol, smoking
Cancer type & time of follow-up	Gastric cancer
Sponsor	Public Health Service Grant from NIH, Department of Health and Human Services, USA
Notes	Non-drinkers OR = 1.00 Drinkers OR = 0.71 (95% CI, 0.54 to 0.93) 1 to 3 batches green tea/day OR = 0.76 (95% CI, 0.57 to 1.03) ≥ 4 batches green tea/day OR = 0.54 (95% CI, 0.33 to 0.88) p = 0.006

Zhang 2002

Methods	Case-control study, hospital and population-based in China
Participants	254 cases, 652 controls
Interventions	N/A
Outcomes	Association of green tea consumption with cancer risk Matched for age and geographical area (all women) Adjusted for age, education, living area, BMI, tobacco smoking, alcohol consumption, coffee drinking, family income, marital status, menopause status, parity, tubal ligation, oral contraceptive use, physical activity, and family history of ovarian cancer
Cancer type & time of follow-up	Ovarian cancer
Sponsor	Main author partially supported by Australian federation of University Women
Notes	"Never or seldom" OR = 1.00 At most 1 time/week OR = 1.0 (95% CI, 0.24 to 0.73) Green tea consumption 2 to 6 times/week OR = 0.42 (95% CI, 0.23 to 0.7) Green tea consumption at least 1 time/day OR= 0.43 (95% CI, 0.3 to 0.63) p = 0.001

Zhang 2007

Methods	Case-control study, hospital-based, China
Participants	1,009 cases, 1,009 controls
Interventions	N/A
Outcomes	Association of green tea consumption with cancer risk Matched for age Adjusted for age, residential area, education, BMI, number of children breastfed, menopausal status, oral contraceptive use, hormone replacement therapy, biopsy-confirmed benign breast diseases, family history of breast cancer and total energy intake
Cancer type & time of follow-up	Breast cancer
Sponsor	First author supported through fellowship from National Health and Medical Research Council, Australia
Notes	**Alle + Männer + Frauen** 1 to 249 g green tea leaves/year OR = 0.87 (95% CI, 0.73 to 1.04) 250 to 499 g green tea leaves/year OR = 0.68 (95% CI, 0.54 to 0.86) 500 to 749 g green tea leaves/year OR = 0.59 (95% CI, 0.45 to 0.77) > 750 g green tea/year OR = 0.61 (95% CI, 0.48 to 0.78) p < 0.001

Zhong 2001

Methods	Case-control study, population-based in China
Participants	649 cases, 675 controls
Interventions	N/A
Outcomes	Association of green tea consumption with cancer risk Matched for age Adjusted for age, income, number of years of exposure to environmental tobacco smoke at work, high-risk occupation, family history of lung cancer, Vitamin C intake, cooking food at high temperature and respondent status
Cancer type & time of follow-up	Lung cancer
Sponsor	National Natural Science Foundation of China
Notes	Non-drinkers OR = 1.00 1 to 500 g green tea leaves/year OR = 0.80 (95% CI, 0.45 to 1.42) 501 to 1500 g green tea leaves/year OR = 0.62 (0.36 to 1.08) > 1500 g green tea leaves/year OR = 0.46 (95% CI, 0.22 to 0.96) No p-values provided

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Arts 2001	No distinction between green and black tea
Bianchi 2000	No distinction between green and black tea
Chyou 1995	No green tea
Hara 1984	All cancer patients
Hoshiyama 1992	No distinction between at least 2 amounts of frequency of green tea
Il'yasova 2003	No distinction between green and black tea
Imai 1997	This paper is summarised and contains added new data in the Nakachi et al 2000 paper
Inoue 1997	All cancer patients
Inoue 2001	Study does not address cancer
Ishizuka 2003	Measured gallstones
Jatoi 2003	All cancer patients
Kono 1991	Measured polyps of the colon
Kuwahara 2000	Measured atrophic gastritis
Lee 1990	Mixed reporting of results for oolong, black and green tea No distinction between at least 2 amounts of frequency of green tea consumption
Montella 2007	No distinction between green and black tea
Montella 2009	No distinction between green and black tea
Nagano 2000	Summarised and added new data in Nagano et al 2001
Nakachi 1998	All cancer patients
Nakachi 2003	Paper reviews Nakachi et al's 1998 study, all cancer patients
Oguni 1992	Abstract only, insufficient data
Ohno 1985	No amount of frequency of green tea consumption specified
Ohno 1995	"Okinawa tea" consumption, which is half-fermented oolong tea

(*Continued*)

Pisters 2001	All cancer patients
Ren 1991	Type of tea not specified
Shibata 2000	Measured atrophic gastritis
Shim 1995	Study does not address cancer
Sun 2002	No distinction between green and black tea No distinction between at least 2 amounts of frequency of green tea consumption
Tewes 1990	Amount of frequency of green tea consumption not specified
Tsubono 1997	Not related to cancer risk factors
Wakai 1993	All cancer patients
Wang 2002	No cancer (precancerous lesions)
Wu 2003a	Amount of frequency of green tea consumption not specified
Yu 1991	Amount of frequency of green tea consumption not specified, not green tea only
Zhang 2004	Follow-up study to Zhang 2002, all cancer patients
Zhang 2006	Results did not differentiate between black and green tea drinkers

DATA AND ANALYSES

This review has no analyses.

ADDITIONAL TABLES

Table 1. Risk of bias assessment for RCTs

Criterion		Description	Judgement
Adequate sequence generation?		Quote: "Volunteers were randomly assessed to a placebo- or GTCs-arm by simple randomization" Comment: Unclear how sequence was generated	Unclear
Allocation concealment?		Quote: "That same day, they were alternatively assigned to the placebo- or GTCs-arm and given the appropriate treatment." Comment: Probably not done	No
Blinding?	**"IPSS/ Qol Scores" (not clearly stated whether patient-reported or physician-assessed)**	Quote: "In the second arm, men received placebo (three identical capsules per day). To all subjects, capsules were given by the urologist according to the double blind method." Comment: Probably done	Yes
	Incidence of prostate cancer (primary outcome measure)	No explicit statement on blinded outcome assessment	Unclear
	PSA	Review authors do not believe this will introduce bias	Yes
Incomplete outcome data addressed?	**"IPSS/ Qol Scores" (not clearly stated whether patient-reported or physician-assessed)**	Quote: "patients, diagnosed with prostate cancer at the 6 months biopsy check, left the study" Comment: number of patients included in analysis not stated	Unclear
	Incidence of prostate cancer (primary outcome measure)	All randomized patients analysed	Yes
	PSA	Quote: "patients, diagnosed with prostate cancer at the 6 months biopsy check, left the	Unclear

Table 1. Risk of bias assessment for RCTs (*Continued*)

		study" Comment: number of patients included in analysis not stated	
Free of selective reporting?		All outcomes reported	Yes
Free of other bias?		Study controlled for total serum PSA at the time of enrollment, prostate volume at the time of enrollment, prostate volume at the end of study; e, total number of HG-PIN cores versus total cores taken at the time of enrollment, total number of HG-PIN cores taken at the end of study; total number of monofocal or plurifocal HG-PIN lesions by means of a multivariate analysis	Yes

Table 2. Methodological quality of cohort studies

Study	Cohort study			Case study		Total (out of 16)
	Selection	Comparability	Outcome	Selection	Exposure	
Chyou 1993	4	2	2	3	1	12
Fujino 2002	3	2	2	3	2	12
Galanis 1998	4	2	2	4	2	14
Hoshiyama 2002	3	2	2	3	2	12
Ide 2007	3	2	2	3	2	12
Inoue 2008	4	1	2	2	1	10
Ishikawa 2006	3	2	2	2	2	11
Key 1999	2	2	2	3	2	11
Kikuchi 2006	3	2	1	3	2	11
Koizumi 2003	3	2	2	3	1	11
Kurahashi 2007	3	2	3	3	2	13

Table 2. Methodological quality of cohort studies (*Continued*)

Kuriyama 2006	3	2	3	3	2	13
Li 2008	3	2	3	3	2	13
Lin 2008	3	2	3	3	2	13
Luo 2007	3	2	3	3	2	13
Nagano 2001	2	2	2	2	2	10
Nakachi 2000	2	2	2	1	1	8
Sasazuki 2004	3	2	3	3	2	13
Sun 2007	4	2	3	4	2	15
Suzuki 2004	3	2	2	3	2	12
Suzuki 2005	3	2	2	3	2	12
Tsubono 2001	3	2	2	3	2	12
Yang 2007	4	2	2	4	2	14

Table 3. Methodological quality of case-control studies

Study	Selection	Comparability	Exposure	Total (out of 9)
Bonner 2005	3	2	1	6
Gao 1994	2	2	2	6
Goto 1990	3	2	1	6
Huang 1999	3	2	2	7
Inoue 1994	3	1	2	6
Inoue 1998	3	2	2	7
Ji 1996	1	2	1	4
Ji 1997	2	2	2	6
Jian 2007	3	2	3	8
Kato 1990a	3	2	2	7

Table 3. Methodological quality of case-control studies (*Continued*)

Kato 1990b	3	1	2	6
Kono 1988	2	2	0	4
Mizuno 1992	0	2	1	3
Mu 2003	3	1	0	4
Setiawan 2001	4	2	1	7
Song 2008	3	2	2	7
Sonoda 2004	3	1	2	6
Tajima 1985	3	2	2	7
Wakai 2004	3	2	2	7
Wang 1999	2	1	0	3
Wang 2007	4	2	1	7
Wu 2003	3	2	2	7
Ye 1998	3	2	1	6
Yu 1995	3	2	2	7
Zhang 2002	3	2	2	7
Zhang 2007	3	2	2	7
Zhong 2001	3	2	2	7

Table 4. Results - Randomised controlled trials

Study	Country	Cancer	Outcomes	Participants	Findings (risk associated with green tea consumption [1])		
					All	Women	Men
Bettuzzi 2006	Italy	Prostate	Incidence PSA values Quality of life Side-effects	60	[2]	-	yes

[1] "yes" = the consumtion of green tea was associated with a decreased cancer risk

Table 5. Results - Cohort studies

Study	Country	Cancer	Outcome	Participants	Findings (risk associated with green tea consumption)		
					All	Women	Men
Yang 2007	China	Colorectal	Incidence	69,710	- [1]	yes	-
Ide 2007	Japan	Oral	Incidence	50,221	yes	yes	no
Key 1999	Japan	Breast	Incidence	488,989	- [1]	no	-
Inoue 2008	Japan	Breast	Incidence	63,257	- [1]	no	-
Suzuki 2004	Japan	Breast	Incidence	35,004	- [1]	no	-
Suzuki 2005	Japan	Colorectal	Incidence	65,915	no	-	-
Ishikawa 2006	Japan	Esophageal	Incidence	78,950	inverse	-	-
Koizumi 2003	Japan	Gastric	Incidence	65,915	no	-	-
Tsubono 2001	Japan	Gastric	Incidence	26,311	no	-	-
Sasazuki 2004	Japan	Gastric	Incidence and mortality	72,273	-	yes (trend)	no
Fujino 2002	Japan	Gastric	Mortality	44,930	-	no	no
Hoshiyama 2002	Japan	Gastric	Mortality	72,851	-	no	no
Li 2008	Japan	Lung	Incidence	41,440	no	no	no
Nagano 2001	Japan	Various	Incidence	38,540	no	-	-
Nakachi 2000	Japan	Various	Incidence	8,552	yes	yes	no
Kuriyama 2006	Japan	Various	Mortality	40,530	no	-	-
Luo 2007	Japan	Pancreatic	Incidence	102,137	no	-	-
Lin 2008	Japan	Pancreatic	Mortality	77,850	no	no	no
Kikuchi 2006	Japan	Prostate	Incidence	19,561	- [2]	-	no

Table 5. Results - Cohort studies (*Continued*)

Kurahashi 2007	Japan	Prostate	Incidence	49,920	- [2]	-	yes
Chyou 1993	Japan	Urinary tract	Incidence	7,995	- [2]	-	no
Sun 2007	Singapore	Colorectal	Incidence	61,320	inverse (trend)	no	inverse
Galanis 1998	USA	Gastric	Incidence	11,907	inverse (trend)	no	inverse (trend)

[1] only women investigated
[2] only men investigated

Table 6. Results - Case-control studies

Study	Country	Cancer	Participants	Findings (risk associated with green tea consumption)		
				All	Women	Men
Zhang 2007	China	Breast	2,018	- [1]	yes	-
Gao 1994	China	Esophageal	2,454	-	yes	no
Wang 1999	China	Esophageal, cardiac and gastric	418	yes	-	-
Wang 2007	Singapore	Esophageal	1,042	-	yes	no
Ji 1996	China	Gastric	2,575	-	yes	yes
Ye 1998	China	Gastric	816	yes	-	-
Yu 1995	China	Gastric	1,422	yes	-	-
Mu 2003	China	Gastric, liver, esophageal	1,043	yes	-	-
Bonner 2005	China	Lung	244	no	-	-
Zhong 2001	China	Lung	1,320	- [1]	yes	-
Song 2008	USA	Ovarian	2,017	- [1]	yes	-
Zhang 2002	China	Ovarian	706	- [1]	yes	-
Ji 1997	China	Pancreatic and colorectal	3,818	yes	yes	yes

Table 6. Results - Case-control studies (*Continued*)

Goto 1990	Japan	Pancreatic	213	yes	-	-
Mizuno 1992	Japan	Pancreatic	248	inverse	-	-
Jian 2007	China	Prostate	404	- [2]	-	yes
Sonoda 2004	Japan	Prostate	280	- [2]	-	no
Wakai 2004	Japan	Urothelial	744	inverse	-	-
Wu 2003	USA	Breast	1,095	- [1]	yes	-
Kato 1990a	Japan	Colorectal	1,324	yes/no [3]	-	-
Inoue 1998	Japan	Digestive tract	22,834	no	-	-
Huang 1999	Japan	Gastric	29,506	no	-	-
Inoue 1994	Japan	Gastric	1,336	no	-	-
Kato 1990b	Japan	Gastric	4,855	no	-	-
Kono 1988	Japan	Gastric	2,991	yes	-	-
Setiawan 2001	Japan	Gastric	732	yes	-	-
Tajima 1985	Japan	Gastric	376	no	-	-

[1] only women investigated
[2] only men investigated
[3] positive association for colon cancer/no association for rectal cancer

APPENDICES

Appendix 1. Ovid Search Strategy

Ovid Search Strategy modified for MEDLINE, EMBASE, Amed and PsychInfo
Last searched on 13/01/09
1 green tea.ti,ab,rw,sh.
2 camellia sinensis.ti,ab,rw,sh.
3 tea.ti,ab,rw,sh.
4 thea.ti,ab,rw,sh.
5 Gruner Tee.ti,ab,rw,sh.
6 matsu-cha.ti,ab,rw,sh.
7 mattsu-cha.ti,ab,rw,sh.
8 antiox$.mp.
9 anti-oxid$.mp.
10 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9
11 tumour.ti,ab,rw,sh.
12 cancer$.ti,ab,rw,sh.
13 oncol$.ti,ab,rw,sh.
14 malignant.ti,ab,rw,sh.
15 survival$.mp.
16 mortality$.mp.
17 11 or 12 or 13 or 14 or 15 or 16
18 trial$.ti,ab,rw,sh.
19 study.ti,ab,rw,sh.
20 cohort$.mp.
21 exp Cohort studies/
22 exp Clinical trials/
23 exp Clinical trial/
24 ((prospectiv$ or observation$) adj5 (research$ or data$ or stud$)).mp.
25 longitud$.mp.
26 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25
27 10 and 17 and 26

Appendix 2. Newcastle-Ottawa Quality Assessment Scale - Cohort Studies

NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE - COHORT STUDIES
Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability.
Selection
1) Representativeness of the exposed cohort
a) truly representative of the average ..... (describe) in the community (*)
b) somewhat representative of the average ..... in the community (*)
c) selected group of users eg nurses, volunteers
d) no description of the derivation of the cohort
2) Selection of the non exposed cohort
a) drawn from the same community as the exposed cohort (*)
b) drawn from a different source
c) no description of the derivation of the non exposed cohort
3) Ascertainment of exposure
a) secure record (eg surgical records) (*)
b) structured interview (*)
c) written self report

d) no description
4) Demonstration that outcome of interest was not present at start of study
a) yes (*)
b) no
Comparability
1) Comparability of cohorts on the basis of the design or analysis
a) study controls for ····· (select the most important factor) (*)
b) study controls for any additional factor (*) (This criteria could be modified to indicate specific control for a second important factor)
Outcome
1) Assessment of outcome
a) independent blind assessment (*)
b) record linkage (*)
c) self report
d) no description
2) Was follow-up long enough for outcomes to occur
a) yes (select an adequate follow up period for outcome of interest) (*)
b) no
3) Adequacy of follow up of cohorts
a) complete follow up - all subjects accounted for (*)
b) subjects lost to follow up unlikely to introduce bias - small number lost - > ···· % (select an adequate %) follow up, or description provided of those lost) (*)
c) follow up rate < ····% (select an adequate %) and no description of those lost
d) no statement

Appendix 3. Newcastle-Ottawa Quality Assessment Scale - Case Control Studies

NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE - CASE CONTROL STUDIES
Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Exposure categories. A maximum of two stars can be given for Comparability.
Selection
1) Is the case definition adequate?
a) yes, with independent validation (*)
b) yes, eg record linkage or based on self reports
c) no description
2) Representativeness of the cases
a) consecutive or obviously representative series of cases (*)
b) potential for selection biases or not stated
3) Selection of Controls
a) community controls (*)
b) hospital controls
c) no description
4) Definition of Controls
a) no history of disease (endpoint) (*)
b) no description of source
Comparability
1) Comparability of cases and controls on the basis of the design or analysis
a) study controls for ····· (Select the most important factor.) (*)
b) study controls for any additional factor (*) (This criteria could be modified to indicate specific control for a second important factor.)
Exposure
1) Ascertainment of exposure
a) secure record (eg surgical records) (*)

b) structured interview where blind to case/control status (*)
c) interview not blinded to case/control status
d) written self report or medical record only
e) no description
2) Same method of ascertainment for cases and controls
a) yes (*)
b) no
3) Non-Response rate
a) same rate for both groups (*)
b) non respondents described
c) rate different and no designation

WHAT'S NEW

Date	Event	Description
21 September 2016	Amended	Contact details updated.

HISTORY

Date	Event	Description
11 February 2015	Amended	Contact details updated.
27 March 2014	Amended	Contact details updated.

CONTRIBUTIONS OF AUTHORS

The following contributions will be made by the reviewers stated:

Link with editorial base and coordination of contributions from co-reviewers (KB)

Draft protocol (KB with contributions from all)

Run searches (KB, SKH)

Identify relevant titles (KB, MH, SKH)

Selection of included trials (KB, MH, SKH)

Extraction of data from trials (KB, GH, MH, SKH, SM)

Methodological quality assessment (KB, MH)

Interpretation of analysis (KB, MH)

Drafting final review (KB with contributions from all)

DECLARATIONS OF INTEREST

None known

SOURCES OF SUPPORT

Internal sources

- Pilkington Family Trusts, UK.

External sources

- AG Biologische Krebstherapie, Deutsche Krebshilfe, Bonn, Germany.
- Cochrane Gyneacological Cancer Review Group, UK.
- Nordic Cochrane Centre / ViFab, Denmark.

INDEX TERMS

Medical Subject Headings (MeSH)

*Camellia sinensis [chemistry]; *Tea [adverse effects]; Breast Neoplasms [prevention & control]; Flavonoids [pharmacology]; Gastrointestinal Neoplasms [prevention & control]; Liver Neoplasms [prevention & control]; Lung Neoplasms [prevention & control]; Neoplasms [epidemiology; mortality; *prevention & control]; Phenols [pharmacology]; Polyphenols; Prostatic Neoplasms [prevention & control]; Urogenital Neoplasms [prevention & control]

MeSH check words

Female; Humans; Male