

Systematic review: green tea and gastrointestinal cancer risk

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SUMMARY

Background: Gastrointestinal cancer is one of the leading causes of cancer mortality in the world. Therefore, numerous efforts are being made to find chemoprotective substances able to reduce its incidence. Amongst these, green tea, one of the most popular beverages world-wide, has been reported to provide protective effects against gastrointestinal cancer.

Aim: To critically evaluate all epidemiological studies reporting an association between green tea consumption and a reduced risk of gastrointestinal cancer.

Methods: Epidemiological studies of green tea consumption in relation to gastrointestinal cancer or preneoplastic lesions were identified through computerized

literature searches using the following databases: Medline (Pubmed), Embase, Amed, CISCOP, Phytobase and Cochrane Library. Only epidemiological studies indicating the type of tea (green tea) and the site of either cancer or precancerous lesions (stomach or intestine) were included. No language restrictions were imposed. **Results:** Twenty-one epidemiological investigations met our inclusion/exclusion criteria.

Conclusion: These studies seemed to suggest a protective effect of green tea on adenomatous polyps and chronic atrophic gastritis formations. By contrast, there was no clear epidemiological evidence to support the suggestion that green tea plays a role in the prevention of stomach and intestinal cancer.

INTRODUCTION

Cancer of the gastrointestinal tract is one of the most common forms of neoplastic disease affecting humans. The incidence of gastrointestinal cancer varies greatly in various parts of the world and amongst various peoples. Colon and rectal cancers are common in most Western countries; by contrast, the greatest percentage of stomach cancers occurs in China (38%), Korea, South American countries and Japan.^{1–3} In part, these variations may be due to differences in diet. An excess intake of protein and fat increases the risk of gastroin-

testinal cancer; beer consumption is a risk factor for rectal cancer; excessive consumption of salt or meat (beef and veal) increases the risk of stomach, colon and rectal cancer.^{4, 5} Some foods, such as dietary fibre, vegetables, fruit and soy, have been shown to induce a chemoprotective (curative and/or preventive) action on the gastrointestinal tract.⁶ Similarly, green tea, one of the most commonly consumed beverages in the world, has been reported to provide protective effects against gastrointestinal cancer.

Green tea, obtained from the steamed or pan-fried leaves of *Camellia sinensis*, contains polyphenolic components, which have been postulated to be protective against cancer. Epigallocatechin-3-gallate is the major polyphenolic constituent of green tea.⁷ Numerous animal and *in vitro* experiments have been carried out

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either on green tea or epigallocatechin-3-gallate. Green tea possesses antimicrobial, immunostimulant and anti-inflammatory capacities.⁸ In addition, green tea and epigallocatechin-3-gallate have shown protective effects against cardiovascular disease and preventive/curative effects against various kinds of cancer.^{9, 10} Although the mechanisms of the antimicrobial, immunostimulant and anti-inflammatory effects have been identified, the molecular mechanisms of the chemopreventive effects of green tea are still uncertain. The purpose of this systematic review was to critically evaluate all epidemiological studies reporting an association between green tea consumption and a reduced risk of gastrointestinal cancer.

METHODS

Epidemiological studies of green tea consumption in relation to gastrointestinal cancer or preneoplastic lesions were identified through computerized literature searches using the following databases: Medline (PubMed), Embase, Amed, CISCOM, Phytobase and Cochrane Library (all from inception to June 2003). In addition, searches were performed on 13 cancer and seven tea websites. Furthermore, manufacturers of green tea supplements were asked to contribute published and unpublished studies, and our own files were considered as well. All bibliographies retrieved were screened for further relevant publications. The search terms used for the search were: green tea, *Camellia sinensis*, tea, thea, gruner tee, matsucha and epigallocatechin. For the Medline, Phytobase and CISCOM searches, these keywords were combined with the words tumour, cancer, adenoma*, polyp, gastritis or precancerous lesion* (asterisks refer to all words that contain 'lesion' or 'adenoma'; for database searches). Only epidemiological studies indicating the type of tea (green tea) and site of either cancer or precancerous lesions (stomach or intestine) were included. Papers that failed to report the number of individuals (cases and controls) involved in the study and the level of green tea consumption (amount or frequency of green tea consumed) were excluded. No language restrictions were imposed. All articles were read in full. Data relating to the number of subjects (sample size), study design, green tea consumption levels and results were extracted by the first author and validated by other authors. A meta-analytical approach was considered, but was deemed to be inappropriate due to the heterogeneity of the primary data.

RESULTS

Twenty-one epidemiological investigations met our inclusion/exclusion criteria.^{11–31} Thirty-two epidemiological investigations on gastrointestinal cancer were excluded for one of the following reasons: did not distinguish the type of tea;^{32–55} the cancer-preventive effects of green tea were not analysed for selected types of cancer;⁵⁶ no quantitative data were reported on the amount or frequency of green tea consumption.^{57–63} Fourteen epidemiological studies were carried out on the risk of stomach cancer/precancerous lesions^{11–24} and three on the risk of colorectal cancer/precancerous lesions^{25–27} (Tables 1 and 2). Four epidemiological studies assessed the risk of stomach and colorectal cancer/preneoplastic lesions together (Table 3).^{28–31}

Green tea consumption and gastric cancer/preneoplastic lesions

Two cross-sectional studies, two hospital-based case-control studies, five population-based case-control studies, one population-hospital-based case-control study and four cohort studies were identified (Table 1). Four of these studies originated from China and 10 from Japan.

The cross-sectional studies were carried out on residents of a Japanese village (known for its green tea production), who had a low mortality due to gastric cancer,¹¹ and on self-defence officials (men) near to retirement age,¹² in order to examine the independent relation of green tea consumption to *Helicobacter pylori* infection and chronic atrophic gastritis. Information on green tea consumption and other dietary habits, obtained by self-administered questionnaire, included the frequency and amount. Kuwahara *et al.* assessed the reproducibility of a postal questionnaire at an interval of 5–8 months.¹² Information on the presence of *H. pylori* infection and/or chronic atrophic gastritis was obtained by serological methods carried out on blood samples of all subjects. Adjustments were made for sex, age, *H. pylori* status and consumption of coffee, soybean products, raw vegetables and salted food¹¹ (all lifestyle factors significantly associated with green tea consumption) or for *H. pylori*, rank and cigarette smoking.¹² The relative risks (RRs) and odd ratios (ORs) were calculated using, as reference category, the lowest level of green tea consumption. Although Shibata *et al.* found that a high green tea consumption

Table 1. Epidemiological studies of the relationship between green tea consumption and gastric cancer risk

Reference	Country and observation period	Subject number	Subject age	Green tea consumption level	OR or RR* (95% CI)	Results	Additional information
Cross-sectional studies							
Shibata <i>et al.</i> ¹¹	Japan (Kyushu) 1997	636 subjects	Mean ages: male, 59.14 female, 60.44	0–9 cups/day ≥ 10 cups/day	0.59 (0.42–0.86)	High green tea consumption (more than 10 cups per day) significantly reduces the risk of CAG	Self-administered questionnaire on lifestyle habits including the consumption of green tea, coffee, salted food, raw vegetables, soybean products and smoking status
Kuwahara <i>et al.</i> ¹²	Japan (Fukuoka) January 1993 to December 1997	566 men (retirement)	50–55 years	< 3 cups/day 3–4 cups/day ≥ 5 cups/day	0.7 (0.5–1.2)	Green tea consumption was associated with a (non-significant) small decrease in the risk of CAG	Self-administered questionnaire including information on smoking status, alcohol use, dietary habits (33 food items) and other lifestyle characteristics
Hospital-based case-control studies							
Kato <i>et al.</i> ¹³	Japan April 1985 to March 1989	427 GC cases 1414 atrophic gastritis cases 3014 controls	Mean age not reported (< 29 and > 70)	< 1 cup/day 1–3 cups/day ≥ 4 cups/day	Males: CAG: 1.00 (0.78–1.29) GC: 1.01 (0.70–1.47) Females: CAG: 1.19 (0.93–1.51) GC: 0.81 (0.51–1.27)	No association between green tea, GC and atrophic gastritis	Self-administered questionnaire included items on symptoms, medical history, family history, dietary habits (frequency of intake), smoking and drinking habits and psychological factors
Huang <i>et al.</i> ¹⁴	Japan (Tokai) 1990–95	887 GC cases 28 619 controls	20–79 years	Never 1–2 cups/day 3–5 cups/day > 6 cups/day	0.9 (0.73–1.11)	High consumption of green tea (more than 6 cups/day vs. never drinking) decreased the risk of GC. However, 3–5 cups/day increased the OR	Self-administered questionnaire. An interviewer checked all written responses at the time of collection of the questionnaire. The questionnaire included family history, beverage and food intake, smoking and drinking habits and general health status
Population-based case-control studies							
Hoshiyama and Sasaba ¹⁵	Japan (Saitama) August 1984 to July 1990 (cases) July 1986 to December 1990 (controls)	251 male GC cases 483 male controls	Mean age not reported (< 54 and > 65)	Low: ≤ 4 cups/day Intermediate: 5–7 cups/day High: ≥ 8 cups/day	Single GC: 0.9 (0.6–1.3) Multiple GC: 1.6 (0.7–3.9)	No association between green tea and stomach cancer risk	Interviews included information on frequency of intake of 12 food items, 12 food groups, cigarettes and alcohol consumption. Interviews were done before diagnostic procedures

Table 1. Continued

Reference	Country and observation period	Subject number	Subject age	Green tea consumption level	OR or RR* (95% CI)	Results	Additional information
Yu <i>et al.</i> ¹⁶	China (Hongkou, Nanhui) October 1991 to December 1993	711 GC cases 711 controls	Under 80 years Median age: 65 years	1–3 tea bags/day ≥ 4 tea bags/day	0.54 (0.33–0.88)	Low risk of stomach cancer associated with green tea drinking. A dose–response trend was observed	Interviews included information on type and strength of green tea used, its preparation method, alcohol drinking, cigarettes smoked, birthplace, personal and family past medical history, dietary intake and education level
Ji <i>et al.</i> ¹⁷	China (Shanghai) December 1, 1988 to November 30, 1989	1124 GC (770 males and 354 females) 1451 controls (819 males and 632 females)	20–69 years	Males: None ≤ 2000 g/year ≤ 3000 g/year > 3000 g/year Females: ≤ 1200 g/year > 1200 g/year	Males: 0.76 (0.55–1.27) Females: 0.81 (0.46–1.43)	Green tea drinking reduced the risk of gastric tumours in both sexes. The reduction did not reach statistical significance	Interviews elicited information on residential history, smoking and alcohol status, dietary habits, occupation, history of diseases and family history of diseases
Ye <i>et al.</i> ¹⁸	China (Fujian) May 1994 to July 1995	272 GC cases 233 male 39 female 544 controls	30–78 years	≤ 0.75 kg/year > 0.75 kg/year	0.58	Significant inverse association between GC and green tea consumption	Interviews included information on dietary habits, smoking, alcohol consumption, family history of diseases
Setiawan <i>et al.</i> ¹⁹	China January 1, 1995 to June 30, 1995	133 GC cases 166 CAG 433 healthy controls	Mean ages: 59.7 stomach cancer 46.8 controls	Never 1–21 cups/week > 21 cups/week	CAG: 0.52 (0.28–0.99) GC: 0.39 (0.15–1.01)	Significant inverse association between green tea drinking and cancer risk or CAG	Interviews included information on dietary habits, body weight, smoking, alcohol consumption, occupational history, medical history and family history of diseases
Population-hospital-based, case–control study Kono <i>et al.</i> ²⁰	Japan (Kyushu) 1979 to 1982	139 GC cases 2574 HC 278 PC	20–75 years	Low: ≤ 4 cups/day Intermediate: 5–9 cups/day High: ≥ 10 cups/day	> 10 cups/day vs. less HC: 0.5 (0.3–1.1) PC: 0.3 (0.1–0.7) P < 0.007	Significantly decreased risk of GC among subjects with high consumption of green tea	Blind interviews included information on occupation and dietary habits as well as smoking habit

Prospective cohort studies							
Galanis <i>et al.</i> ²¹	Japan (Hawaii) Questionnaire, 1975–80 Observation until 1994	5610 men 6297 women All without cancer	18 years and older	None 1 cup/day ≥ 2 cups/day	Males: 1.16 (0.9–2.9) Females: 1.3 (0.6–2.6)	Green tea consumption increased (not significant) the risk of stomach cancer	Self-administered questionnaire on lifestyle habits including 6 food and 4 beverages consumption, smoking status, alcohol drinking and family history of health and disease
Tsubono <i>et al.</i> ²²	Japan (Miyagi) January 1, 1984 to December 31, 1992	11 902 men 14 409 women All without cancer	40 years of age or older Mean: 46.4	< 1 cup/day 1–2 cups/day 3–4 cups/day ≥ 5 cups/day	Males: 1.16 (0.9–2.9) Females: 0.8 (0.5–1.3)	No association with risk of GC	Self-administered questionnaire including beverages, food and alcohol consumption, smoking status and personal and family history of disease. Questionnaire was checked by interviewers
Hoshiyama <i>et al.</i> ²³	Japan (Miyagi) From 1988 to 1990 Subjects were followed until the end of 1997	30 370 men 42 481 women	40–79 years	< 1 cup/day 1–2 cups/day 3–4 cups/day 5–9 cups/day ≥ 10 cups/day	Males: 1.00 (0.5–2.0) Females: 0.7 (0.3–2.0)	No association between green tea consumption and stomach cancer death	Self-administered questionnaire including dietary habits (consumption frequency of food and beverages), physical activity, drinking and smoking, occupation, level of education and family history of disease. The validity of the food frequency questionnaire was evaluated
Fujino <i>et al.</i> ²⁴	Japan Questionnaire, 1988–90 Observation until 1997	18 746 men 26 184 women	18 years of age or older in 1949	≤ 3 times/week > 3 times/week Every day	Males: 1.11 (0.75–1.63) Females: 1.43 (0.78–2.62)	No association between green tea consumption and stomach cancer death	Self-administered questionnaire including smoking, alcohol consumption, diet (fruit, vegetables etc.), sporting activities, medical history and level of education

CAG, chronic atrophic gastritis; CI, confidence interval; GC, gastric cancer; HC, hospital controls; OR, odds ratio; PC, population controls; RR, relative risk.

* For the highest levels of intake.

Table 2. Epidemiological studies of the relationship between green tea consumption and intestinal cancer risk

Reference	Country and observation period	Subject number	Subject age	Green tea consumption level	OR or RR* (95% CI)	Results	Additional information
Cross-sectional study							
Kono <i>et al.</i> ²⁵	Japan (Fukuoka) October 1986 to December 1988	Men early retirement: 80 cases (adenomatous polyps of the sigmoid colon) 1148 HC	49–56 years	Low: < 3 cups/day Intermediate: 3–4 cups/day High: ≥ 5 cups/day	0.69 (nr)	The risk of adenomatous polyps decreased with increasing consumption of green tea, although the OR was not statistically significant	Self-administered questionnaire with a supplementary interview for unanswered questions. The questionnaire included smoking and drinking habits, and so on. In addition, dietary questions included frequency of consumption and amount consumed. Reproducibility of dietary assessment was tested with an interval of 1–2 months
Population-based case–control studies							
Kato <i>et al.</i> ²⁶	Japan June 1986 to March 1990	746 cancer cases: 132 colon cancer, 91 rectal cancer (2 cases had both cancers), 525 colorectal adenoma 578 controls	39–75 years	Daily intake (number of cups is not reported)	ADENOMA: Proximal: 0.82 (0.56–1.19) Distal: 0.62 (0.46–0.82) Rectum: 0.61 (0.40–0.92) CANCER: Colon: 0.61 (0.41–0.91) Rectum: 1.32 (0.78–2.23)	Inverse association with the risk of colorectal adenoma and colon cancer. Increased risk with rectal cancer	Self-administered questionnaire (sent by mail to controls). It included items on frequency of intake of 25 foods, several lifestyle habits, medical and family histories and change in dietary habits. Reproducibility of the answers checked
Ji <i>et al.</i> ²⁷	China (Shanghai) October 1990 to June 1993	2266 cancer cases: 931 colon, 884 rectum and 451 pancreas 1552 controls	30–74 years	Non-drinker\ Regular drinker: Monthly intake (g): 1–199, 200–299 and ≥ 300 (men); 1–200 and ≥ 200 (women)	Males: Colon: 0.82 (0.52–1.28) Rectum: 0.72 (0.46–1.13) Females: Colon: 0.67 (0.41–1.10) Rectum: 0.57 (0.34–0.97)	Inverse association in rectal cancer (men) and in colon and rectal cancers (women) was observed with increasing amount of green tea consumption	Large study. Interviews included information on green tea consumption, dietary practices, consumption of cigarettes and alcohol, medical history, family cancer history, occupation, physical activity. Height and weight were also recorded

CI, confidence interval; HC, hospital controls; nr, not reported; OR, odds ratio; RR, relative risk.

* For the highest levels of intake.

Table 3. Epidemiological studies of the relationship between tea consumption and gastric-intestinal cancer risk

Reference	Country and observation period	Subject number	Subject age	Green tea consumption level	OR or RR* (95% CI)	Results	Additional information
Hospital-based case-control studies							
Tajima and Tominaga ²⁸	Japan (Nagoya) April 1981 to March 1984	93 stomach cancer 42 colon cancer 51 rectal cancer 186 controls	40–70 years	< 4 times/day ≥ 4 times/day	Stomach: 0.64 (nr) Colon: 0.97 (nr) Rectum: 0.91 (nr)	Lower risk of stomach cancer associated with green tea drinking (not significant)	Interviews included items on frequency of intake of numerous foods, several lifestyle habits and medical and family histories
Inoue <i>et al.</i> ²⁹	Japan (Nagoya) June 1990 to June 1995	1706 digestive tract cancer cases (185 oesophagus, 893 stomach, 362 colon, 266 rectum) 21 128 controls	40 years and over	Rarely Occasionally Daily: 1–3 cups/day 4–6 cups/day ≥ 7 cups/day	Stomach: 0.69 (0.48–1.00) Colon: 0.77 (0.47–1.26) Rectum: 1.25 (0.62–2.51)	A significantly decreased risk was observed for stomach cancer with high intake of green tea (≥ 7 cups/day), but not with colon or rectal cancer	Self-administered questionnaire included items on demographic characteristics, medical history, etc. It did not include socio-economic status. Multivariate analyses were carried out to exclude potential confounding factors
Prospective cohort studies (cancer incidence of some organs including stomach, colon and rectum)							
Nakachi <i>et al.</i> ³⁰	Japan (Saitama) 11 years' follow-up study, 1986–97	8552 individuals	Over 40 years	≤ 3 cups/day 4–9 cups/day ≥ 10 cups/day	Stomach: 0.69 (0.23–1.88) Colon/rectum: 0.56 (0.22–1.4)	High consumption of green tea (≥ 10 cups) decreased the RR of stomach and colorectal cancer	Self-administered questionnaire including 90 lifestyle factors (green tea consumption, cigarette consumption, alcohol use), history of diseases, present state of health, and types of medication used
Nagano <i>et al.</i> ³¹	Japan (Hiroshima and Nagasaki) Questionnaire, 1979–81 Observation until 31 December 1994	38 540 atomic bomb survivors (14 873 men and 23 667 women). No tumours at start of experiment	Mean ages: Males: 52.8 years Females: 56.8 years	0–1 cup/day 2–4 cups/day ≥ 5 cups/day	Stomach: 0.95 (0.76–1.2) Colon: 1.0 (0.76–1.4) Rectum: 1.3 (0.77–2.1)	Green tea consumption was not related to reduced cancer risks	Self-administered questionnaire including questions on consumption of 22 dietary items, smoking history, alcohol use, education levels and other personal characteristics

CI, confidence interval; nr, not reported; OR, odds ratio; RR, relative risk.

* For the highest levels of intake.

(10 cups/day) was associated with a significantly reduced risk of chronic atrophic gastritis, but not *H. pylori* infection.¹¹ Kuwahara *et al.* found only a weak (non-significant) inverse association between green tea consumption and both conditions.¹²

Two hospital-based case-control studies were carried out in Japan.^{13, 14} In both investigations, all cases were confirmed pathologically and controls were free of gastrointestinal diseases. Information on green tea consumption, as well as lifestyle habits and family history, was obtained through a self-administered questionnaire before the final diagnosis. Adjustments were made for sex, age and residence,¹³ or sex, age and gastric cancer family history.¹⁴ The RRs and ORs were calculated using, as reference category, subjects who drank less than 1 cup/day¹³ or non-drinking subjects.¹⁴ Although Kato *et al.* did not find an association between green tea consumption and gastric cancer or atrophic gastritis risk,¹³ Huang *et al.* showed that the frequent consumption of green tea (more than 6 cups/day) significantly decreased the risk of gastric cancer.¹⁴

Five population-based case-control studies were conducted in China¹⁶⁻¹⁹ and Japan.¹⁵ Cancer cases were confirmed histologically or by other methods.^{15, 17, 19} In some epidemiological studies, controls were randomly selected^{15, 17, 19} and matched according to age and sex^{16, 17} or home location.¹⁸ In all five investigations, information was obtained through interviews.¹⁵⁻¹⁹ Adjustments were made for age, sex, education, birth-place, alcohol drinking, cigarette smoking and fresh fruit, vegetable and preserved fruit intake;¹⁶ age, income, education level, diet, body mass index, occupation (for men and women) and alcohol consumption (for men only);¹⁷ age, sex, education, body mass index, pack-years of smoking and alcohol drinking;¹⁹ and age and smoking status.¹⁵ No adjustments were reported by Ye *et al.*¹⁸ The RRs and ORs were calculated using, as reference category, non-tea drinkers^{16, 17, 19} or low consumption of green tea.^{15, 18} Four of these five studies reported an inverse association between green tea consumption and the risk of gastric cancer.¹⁶⁻¹⁹ Yu *et al.*¹⁶ observed an increase in gastric cancer risk amongst drinkers of green tea at a boiling hot temperature. The investigation conducted in Japan did not report any association.¹⁵

One population-hospital-based case-control study was carried out in Japan in 1988 by Kono *et al.*²⁰ Cases were histologically diagnosed and hospital controls

were recruited; tests included barium study of the stomach, gastro-endoscopy and large bowel examination. Population controls were randomly selected and matched to cases by sex and age. Information from cases and hospital controls, as well as from population controls, on the frequency and amount of green tea consumption was obtained by interviews by public health nurses and hospital staff. Interviews on cases and hospital controls were performed before diagnostic procedures. The results were adjusted for smoking status, mandarin or orange intake and other fruit consumption. A further adjustment for sex, age and occupational class was also made. The RRs were estimated for intermediate and high consumption compared with low consumption. A significantly decreased gastric cancer risk with high consumption of green tea (10 or more cups/day) was observed in comparison with general population controls, but not in comparison with hospital controls.

The four cohort studies were carried out in Japan.²¹⁻²⁴ Information on the frequency and amount of green tea consumed and on other lifestyle factors was obtained by a self-administered postal questionnaire. In one cohort study, the validity of the food frequency questionnaire was evaluated,²³ and in two of the four cohort studies the questionnaire was checked by interviewers.^{22, 23} In the first cohort study, 108 participants (44 women, 64 men) developed gastric cancer (follow-up period of 14.8 years on average);²¹ in the second study, 419 participants (123 women, 296 men) developed gastric cancer (follow-up period of 9 years);²² in the third study, 359 subjects (240 men and 119 women) died of stomach cancer (follow-up period of 7 years);²³ finally, in the last cohort study, 345 subjects (237 men and 108 women) died of stomach cancer (follow-up period of 7 years).²⁴ In all cohort studies, some adjustments were made: sex,²¹⁻²⁴ age,²¹⁻²⁴ years of education,^{21, 24} cigarette smoking (for men only),²¹⁻²³ alcohol consumption (for men only),^{21, 22} place of birth,²¹ history of peptic ulcer^{21, 23} and stomach cancer,²³ coffee consumption and several other foodstuffs.^{22, 23} The RRs were calculated using, as reference category, either non-tea drinkers²¹ or the lowest level of green tea consumption.²²⁻²⁴ Galanis *et al.*²¹ reported a non-significant trend indicating an increased risk of stomach cancer associated with green tea consumption. By contrast, the other three studies found no association between green tea consumption and stomach cancer incidence.²²⁻²⁴

Green tea consumption and intestinal cancer/precancerous lesions

One cross-sectional study²⁵ and two case-control studies,^{26, 27} both carried out in Japan, were located (Table 2). The cross-sectional study was conducted on men in early retirement with adenomatous polyps ($n = 80$) and in healthy normal men ($n = 1148$).²⁵ All subjects had colonoscopy of the rectum and sigmoid colon. Information on green tea consumption included the amount and frequency of consumption. Adjustments were made for smoking, alcohol consumption, social condition and strenuous exercise (age was similar in all subjects). Dietary confounding factors were not considered. The ORs were estimated for intermediate and high consumption compared with low consumption. The results showed that the risk of adenomatous polyps decreased with increasing consumption of green tea, although neither the ORs nor the trend was statistically significant.

In two case-control studies,^{26, 27} cases were histologically diagnosed and controls were randomly selected from the population and matched to cases by sex, age²⁷ and municipality.²⁶ Information on green tea consumption included the frequency of consumption (daily or less than 1 cup/day),²⁶ as well as the amount and duration of tea drinking.²⁷ Adjustments were made for sex, age and residence,²⁶ and for age, income, education, physical activity, body size and cigarette smoking.²⁷ Dietary confounding factors, such as fruit and vegetables and fresh red meat, were also considered in the analysis.²⁷ As the levels of green tea consumption varied considerably between men and women, all analyses were conducted separately for the sexes, and green tea consumption was categorized into three and two levels for men and women, respectively.²⁷ The RRs and ORs were calculated using, as reference category, subjects drinking less than 1 cup/day or non-tea drinkers, respectively. Kato *et al.* showed that a daily intake of hot green tea was inversely, but not significantly, associated with the risk of either distal colon and rectal adenomas or colon cancer.²⁶ A positive but non-significant association was found between green tea intake and rectal cancer.²⁶ Ji *et al.*²⁷ reported that, in men and women, there was a significant risk reduction with increasing monthly green tea consumption and lifetime consumption of green tea for rectal cancer and colon and rectal cancer, respectively.

Green tea consumption and gastrointestinal cancer/precancerous lesions

Two hospital-based case-control studies^{28, 29} and two cohort studies,^{30, 31} all carried out in Japan, were found (Table 3). In the hospital-based case-control studies, all cancer cases were histologically diagnosed. In one study, several controls, chosen by individual matching to each case for sex, age and time of interview, had complaints of the gastrointestinal tract, such as chronic gastritis.²⁸ Information on green tea consumption (including frequency and amount consumed) were obtained either by interview²⁸ or by a self-administered questionnaire checked by a single trained interviewer.²⁹ In the latter case, the information was obtained before the patients' diseases were identified. Data were adjusted for age and sex,²⁸ and for age, sex, year and season at first hospital visit, smoking, alcohol consumption, regular physical exercise, consumption of soft drinks and for some dietary confounding factors.²⁹ All analyses were conducted separately according to cancer site. The ORs and RRs were calculated using, as reference category, individuals who rarely drank green tea,²⁹ or those consuming less than 4 cups/day.²⁸ Both studies showed a reduced risk of stomach cancer associated with green tea drinking. This decreased risk was statistically significant only amongst individuals with a high consumption of green tea (≥ 7 cups/day).²⁹ No dose-response was noted with gastric cancer and no association with colon or rectal cancer was found.

Two prospective studies examined the association between cancer risk and green tea consumption.^{30, 31} Information on the frequency and amount of green tea consumption and on other lifestyle factors was obtained by means of a self-administered postal questionnaire. At follow-up, 140 and 60 cancer cases of the stomach and colorectum had been recorded (11 years of follow-up),³⁰ and 901, 432 and 193 cancer cases of the stomach, colon and rectum (15 years of follow-up).³¹ Adjustments were made for age, sex, city, radiation exposure (the study was carried out on atomic bomb survivors), smoking, alcohol consumption, body mass index, education levels, calendar time and for some dietary factors,³¹ or for sex and lifestyle factors.³⁰ The RRs were calculated using, as reference category, the lowest level of green tea consumption. Nakachi *et al.* reported a non-significant decreased risk of stomach and colorectal cancer associated with a high consumption of green tea (≥ 10 cups/day).³⁰ By contrast, Nagano *et al.*

found no association between green tea consumption and stomach, colon or rectal cancer risk.³¹

DISCUSSION

Almost all experimental studies have demonstrated inhibitory effects of green tea and tea polyphenols on gastrointestinal carcinogenesis. Yet, the epidemiological studies evaluated above yield contradictory findings. In this review, we have examined the strengths and weaknesses of these studies in order to clarify whether a relationship exists between green tea intake and cancer risk.

The histopathological development of most colorectal and gastric cancers is well known. Colorectal cancer starts with the formation of adenomas, with varying degrees of malignant potential, leading finally to adenocarcinoma.⁶⁴ Gastric carcinogenesis has two pathways, both starting from gastritis and both leading to phenotypically different gastric tumour growth.^{65, 66} Thus, adenomatous polyps and atrophic gastritis are both precursor lesions of adenocarcinoma of the large bowel and gastric cancer, although the possibility should be considered that the factors leading to adenomatous polyps and chronic atrophic gastritis formation are different from those which lead to cancer development from the preneoplastic lesion. Therefore, in this paper, we have included epidemiological studies reporting the association between green tea consumption and the formation of adenomatous polyps or atrophic gastritis. Only two studies carried out in Japan have so far examined directly the relationship between green tea consumption and adenomatous polyps of the large bowel.^{25, 26} In these studies (a population-based case-control study and a cross-sectional study), a decreased risk of adenomatous polyps was associated with green tea drinking. This suggests that green tea can interrupt the sequence of colon/rectal cancer formation. Regrettably, the population-based case-control study had limitations. Some of the controls did not receive a colonoscopic examination, and therefore asymptomatic colorectal adenoma cannot be excluded.²⁶ Furthermore, no quantitative information on green tea consumption was provided. Although, qualitatively, cross-sectional studies are generally less credible than case-control studies, the cross-sectional study carried out by Kono *et al.* was particularly rigorous.²⁵ In this study, the reproducibility of dietary assessments was tested, a dose-related effect was

considered and multiple adjustments for confounding variables were made.²⁵

Two statistically significant results (one cross-sectional study and one population-based case-control study)^{11, 19} and one statistically insignificant result (cross-sectional study)¹² implied a decreased risk for atrophic gastritis with increased green tea consumption. The population-based case-control study was, however, open to selection bias (controls may have had undiagnosed chronic gastritis) and information bias (interviews were not blind).¹⁹ By contrast, the two cross-sectional studies were controlled for selection bias and recall bias,^{11, 12} although one investigation was prone to information bias (self-administered questionnaire).¹¹ A hospital-based case-control study produced conflicting results.²⁰ It was, however, open to selection and information bias (controls had diseases such as mild atrophic gastritis and the information on green tea consumption was obtained by a self-recorded questionnaire). In addition, this paper reported individuals who drank green tea at a hot temperature. Numerous studies have demonstrated a positive association between the intake of hot food and beverages and the increased risk of stomach cancer.^{16, 67} Therefore, the lack of an association between green tea consumption and atrophic gastritis in this case might have been due to the high temperature of the green tea consumed.

Collectively, these data show that green tea has a protective effect against both adenomatous polyps and chronic gastritis, suggesting that it may be considered as a potential preventive agent for individuals at high risk of developing stomach cancer.

Two epidemiological studies showed a decreased risk of colon and rectal cancer associated with green tea consumption;^{27, 30} one study found an inverse association with the risk of colon cancer, but not rectal cancer,²⁶ and three studies found no association.^{28, 29, 31}

In almost all of these studies, selection and confounding bias was minimized (i.e. cases and controls were drawn from the same population; adjustment for certain factors). However, in two hospital-based case-control studies (both reporting no association), the controls were not free of disease.^{28, 29} Furthermore, most of the controls had complaints of the gastrointestinal tract (such as chronic gastritis and gastric polyps)²⁸ which, as outlined above, constitute risk factors for the development of gastric cancer. Moreover, one hospital-based case-control study was prone to information bias

because the data were collected in an unblind manner.²⁸ The third negative epidemiological study, because of its prospective nature, was free from recall and selection bias.³¹ However, no distinction was made between individuals drinking modest amounts and high amounts of green tea. The population-based case-control study reporting an inverse association between green tea consumption and colon cancer risk was inconclusive: no adjustments for confounding variables were performed, no quantitative information on green tea consumption was reported and, because information was obtained by a questionnaire survey, self-selection bias could not be excluded.²⁶ By contrast, a large population-based case-control study and a prospective cohort study (both reporting an inverse association of colon and rectal cancer with increasing amount of green tea consumption) yielded more conclusive results.^{27, 30} The large population-based case-control study was not open to selection and recall bias.²⁷ In this and in the prospective cohort study, adjustments were made for the major known causes of colorectal cancer.^{27, 30}

Nine of the 16 epidemiological studies found a reduced risk for gastric cancer with increased green tea consumption.^{14, 16–20, 28–30} One cohort study reported a positive association between green tea consumption and gastric cancer (not significant),²¹ and six found no association (four cohort studies and two case-control studies).^{13, 15, 22, 31} As a general rule, cohort studies are regarded as the most rigorous and methodologically pure for the identification, evaluation and understanding of risk factors associated with a disease. However, the value of a study depends not only on the type of design, but also on its size and overall quality. Our search identified six cohort studies which examined the association between cancer risk and green tea consumption. Of these, the smallest study observed a non-significant inverse association,³⁰ whereas the four largest studies observed no association;^{22–24, 31} one study found a non-significant positive association.²¹ Only one cohort study (reporting no association between green tea consumption and gastric cancer risk) showed limitations due to selection bias.²² All case-control studies, principally as a result of their retrospective nature, showed selection, information and confounding bias.

Overall, these data do not seem to suggest a protective effect of green tea on stomach cancer. The discrepancy in the results of some studies may be due, in part, to differences in the amount and temperature of green tea

consumed. Several case-control studies suggested either a protective effect of green tea at a high intake (> 10 cups daily), or an inverse dose-effect relationship. However, a well-designed recent cohort study found that even very high consumption of green tea (> 10 cups daily) was not associated with a lower risk of gastric cancer.²³

The biological mechanism of the protective effect of green tea on chronic atrophic gastritis or gastric cancer has been explained by the antioxidant activity of polyphenols contained in green tea. Polyphenols have a scavenging effect on active oxygen,^{68, 69} which promotes superficial gastritis (precursor lesion to chronic atrophic gastritis) and/or chronic atrophic gastritis.^{70, 71} In addition, green tea polyphenols have been reported to inhibit the release of tumour necrosis factor- α ,^{72, 73} which plays an important role in the occurrence of gastritis.^{74, 75} Furthermore, green tea has also been shown to: (i) block heterocyclic aromatic amines formed during the cooking of meat which play a role in the development of gastric and colorectal cancers;⁷⁶ (ii) inhibit urokinase activity, one of the most frequently over-expressed enzymes in human cancers; (iii) induce apoptosis and cell cycle arrest in human cancer cells;^{77, 78} (iv) inhibit the activity of enzymes involved in important pathways that regulate cell division and proliferation (e.g. protein kinase C); (v) induce phase I and phase II metabolic enzymes that increase the formation and excretion of detoxified metabolites of carcinogens.⁷⁸ All of these actions could be potential contributors to the inverse relationship observed between green tea intake and adenomatous polyps and chronic gastritis.

There is currently no clear epidemiological evidence to support the suggestion that green tea plays a role in the prevention of gastric and intestinal cancer. Further epidemiological research, designed specifically to study the effect of green tea on gastric and intestinal cancer, is needed. Because many green tea drinkers brew more than one cup of tea from each batch of dried leaves, in future studies, green tea consumption should be assessed in terms of the amount of active ingredient consumed in a given period. In addition, future epidemiological investigations should take into account the method of preparation of green tea, its strength and temperature.

The overall conclusion from this systematic review is that an inverse association does not seem to exist between green tea consumption and the risk of gastric and intestinal cancer.

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