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Relationship between green tea drinking and the risk of colorectal cancer; a systematic review and meta-analysis

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Abstract

Introduction: Green tea drinking is one of the traditional methods to prevent colorectal cancer (CRC). The present study proposes a systematic review and meta-analysis approach to investigate the relationship between green tea drinking and CRC risk.
Materials and Methods: The literature survey has been carried out using the previously published studies in the Google Scholar search engine and various electronic databases, including Scopus, Cochrane, Web of Science, Embase, and PubMed. The review process has continued until July 13, 2021. Besides, the Q test and I^2 index were employed to evaluate the heterogeneity of the studies. STATA 14 software has been conducted to analyze the gathered dataset. It is essential to note that the significance level for statistical tests was set to 5% (P value < 0.05).
Results: The results of 18 studies accomplished on 44,992 patients aged 19-80 years have been used to compute the relative risk of green tea consumption in CRC (OR [odds ratio] = 0.99; 95% CI: 0.83-1.18), colon (OR=0.97; 95% CI: 0.85-1.10), and rectum (OR=1; 95% CI: 0.86-1.16). Although green tea consumption was a protective factor in Asia and the United States, it was considered a risk factor in Australia. The general population studies classified green tea as a risk factor for CRC, while hospital studies considered this product as a protective factor.
Conclusion: The findings showed that green tea had the most significant effect on reducing the colon cancer risk, while it had the minimum influence on CRC. Additionally, it did not affect rectal cancer. It is essential to note that these relationships were not statistically significant.
Registration: The current protocol was also registered on PROSPERO (#CRD42021276257, https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021276257).

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Introduction

Over the last decades, the diagnosis and treatment of colorectal cancer (CRC) have considerably improved, and its emergence signifies an upward trend (1). Indeed, medication treatments with nonsteroidal anti-inflammatory drugs (e.g., aspirin) were efficient approaches to prevent CRC. However, these treatments are accompanied by significant side effects (2).

Different types of tea (e.g., green, oolong, and black) are produced from the leaves of the *Camellia sinensis* plant, which is known as a potential preventive agent against cancer. It mainly contains epigallocatechin gallate, which has the highest anti-carcinogenic effect on tea among the main catechins (3). Some studies stated that green tea could beneficially affect CRC due to its polyphenol content (4).

Key point
The results of 18 studies performed on 44,992 patients aged 19-80 years have been employed to calculate the relative risks of drinking green tea in CRC (OR=0.99; 95% CI: 0.83-1.18), colon (OR=0.97; 95%CI: 0.85-1.10), and rectum (OR=1; 95% CI: 0.86-1.16). Although green tea drinking was a protective factor in Asia and the United States, it was considered a risk factor in Australia. The general population studies classified green tea as a risk factor for CRC, while hospital studies considered green tea as a protective factor.

Although experimental studies demonstrated that green tea had a significant role in reducing the CRC risk, previous epidemiological studies reported contradictory results (5).

Objectives

Since previous studies reported contradictory results about the influence of green tea on

CRC risk, this study was conducted by systematic review and meta-analysis.

Materials and Methods

Study protocol

The present study investigated the relationship between green tea consumption and CRC risk. This meta-analysis has been performed based on the PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analysis) reporting guidelines, representing a specific procedure for systematic review and meta-analysis studies.

Search strategy

The search process has been performed considering all studies dealing with the relationship between green tea consumption and CRC risk without the time and language restrictions. This process has been carried out through electronic databases (e.g., Scopus, Cochrane, Web of Science, Embase, and PubMed) and applying several keywords (i.e., green tea, cancer, colorectal, colon, rectum, systematic review and meta-analysis, and their MeSH equivalents). Moreover, a combination of these keywords has been considered with AND & OR operators. It is necessary to note that the search process has been updated until July 13, 2021. Finally, the search process has been completed by searching the mentioned keywords in the Google Scholar search engine, and its first five pages have been selected for this study. The manual search has been accomplished by reviewing the reference list of all studies included in the meta-analysis process.

Inclusion and exclusion criteria

Inclusion criteria consisted of epidemiological studies (i.e., case-control or cohort studies), articles that estimated the association between green tea consumption and CRC risk, and those that had enough information for the statistical analysis of data. Besides, several studies were excluded from this meta-analysis; the studies that qualitatively expressed the effect of green tea on CRC, low-quality studies based on the STROBE checklist (6), case report studies, studies with no full text, studies that investigated the relationship between coffee or black tea and CRC, studies that examined the influence of green tea on the other types of cancer, and studies with insufficient information for the data analysis.

Qualitative evaluation of studies

The authors examined the quality of the articles through the STROBE checklist. This checklist includes 22 different parts. The score ranges of 1-15, 16-30, and 31-44 denote poor, average, and high qualities, respectively. In this case, the cut-off point has been set to 15. However, all studies were of good quality.

Data extraction

The authors designed a checklist to extract data from articles. This checklist contained information such as author name, number of samples, number of men and women, age group, publication year, study setting, type of study, duration and amount of consuming green tea, and relative risk of green tea consumption in CRC and its upper and lower limits.

Statistical analysis

The odds ratio (OR) index has been used to investigate the effect of green tea on the risk of developing CRC compared to the control group. Besides, the OR logarithm has been utilized to combine the results of different studies. The heterogeneity of the studies has been evaluated using the I^2 index and Cochran's Q test. In the I^2 index, the heterogeneity is divided into three categories, including low (<25%), moderate (25-75%), and severe (>75%). The random-effects model has been used (I^2 = 79.1%) to conduct the analysis. STATA 14 software has been employed for the data analysis. The significance level of the tests was set to 5% (i.e., *P* value <0.05). Meta-regression was utilized to assess the relationships between relative risk of green tea consumption in CRC, sample size, and publication year.

Results

Study selection

A total of 695 articles were first identified by searching in the mentioned databases. Then, 302 duplicate studies were eliminated by reviewing their titles. Afterward, the abstracts of the remaining 393 articles were reviewed. Among these studies, 258 articles were eliminated according to the exclusion criteria. Furthermore, 117 out of the remaining 135 articles were eliminated due to incomplete information or lack of full text. Finally, 18 articles met the study criteria. These articles were of good quality and entered the meta-analysis process (Figure 1). The specifications of the reviewed articles are given in Table 1.

The selected studies (n = 18) were performed on 44 992

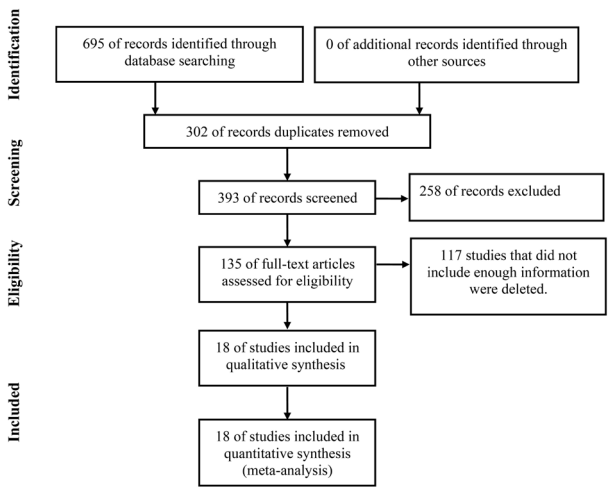

Figure 1. The process of entering the studies into the systematic review and meta-analysis

Table 1. Specifications of the articles entered the systematic review and meta-analysis

First Author	Year of publication	Type of study	Continent	Country	Sample size	Number of female	Number of male	Source of Co	Age group (y)	Dose or time
Green (7)	2014	Case-Control	Australia	Australia	51	25	26	Population-based	40-79	<1 cup/mon
Green (7)	2014	Case-Control	Australia	Australia	24	11	13	Population-based	40-79	<1 cup/wk
Green (7)	2014	Case-Control	Australia	Australia	40	23	17	Population-based	40-79	≥1 cup/wk
Nechuta(8)	2012	Cohort	Asia	China	250	-	-	Population-based	40-70	2–3 cups/d
Wada (9)	2019	Cohort	Asia	Japan	7290	-	7290	Population-based	≥35	<Once/d
Wada (9)	2019	Cohort	Asia	Japan	1428	-	1428	Population-based	≥35	Once/d
Wada (9)	2019	Cohort	Asia	Japan	4088	-	4088	Population-based	≥35	2-3 time/d
Wada (9)	2019	Cohort	Asia	Japan	1151	-	1151	Population-based	≥35	≥4 time/d
Wada (9)	2019	Cohort	Asia	Japan	5893	5893	-	Population-based	≥35	< Once/d
Wada (9)	2019	Cohort	Asia	Japan	1612	1612	-	Population-based	≥35	Once/d
Wada (9)	2019	Cohort	Asia	Japan	7070	7070	-	Population-based	≥35	2-3 time/d
Wada (9)	2019	Cohort	Asia	Japan	1799	1799	-	Population-based	≥35	≥4 time/d
Kim (10)	2019	Case-Control	Asia	Korea	368	-	-	Population-based	56.3	≤0.01 g/d
Kim (10)	2019	Case-Control	Asia	Korea	378	-	-	Population-based	56.3	0.02-25.49 g/d
Kim (10)	2019	Case-Control	Asia	Korea	176	-	-	Population-based	56.3	≥25.5 g/d
Budhathoki (11)	2015	Case-Control	Asia	Japan	166	-	-	Population-based	40-79	<25.7 mL/d
Budhathoki (11)	2015	Case-Control	Asia	Japan	115	-	-	Population-based	40-79	≥25.7-113.6 mL/d
Budhathoki (11)	2015	Case-Control	Asia	Japan	233	-	-	Population-based	40-79	≥113.7-290.7 mL/d
Budhathoki (11)	2015	Case-Control	Asia	Japan	224	-	-	Population-based	40-79	>290.7 mL/d
Kato(12)	1990	Case-Control	Asia	Japan	223	84	139	Population-based	34-80	>1 times/d
Baron (13)	1994	Case-Control	Europe	Sweden	569	299	270	Population-based	68.6	≥cups/d
Ji (14)	1997	Case-Control	Asia	China	1815	-	-	Population-based	30-74	>8500 g/m
Tavani (15)	1997	Case-Control	Europe	Italy	3530	-	-	Hospital-based	19-79	-
Inoue (16)	1998	Case-Control	Asia	Japan	628	-	-	Hospital-based	61	≥7 cups/d
Munoz (17)	1998	Case-Control	America	Argentina	190	-	-	Hospital-based	23-79	≥1 cups/d
Slattery(18)	1999	Case-Control	America	USA	1993	904	1089	Population-based	30-79	>1 times/d
Woolcott (19)	2002	Case-Control	America	Canada	1866	-	-	Population-based	63	>5 cups/d
Zhang (20)	2002	Case-Control	Asia	China	102	-	-	Hospital-based	51.1	-
Il'yasova (21)	2003	Case-Control	America	USA	646	313	333	Population-based	40-80	≥2 times/d
Wu (22)	2011	Case-Control	Asia	China	421	203	218	Population-based	65.9	-
Zhang (23)	2011	Case-Control	Asia	China	478	-	-	Population-based	62.4	-
Li (24)	2011	Case-Control	Asia	China	175	-	-	Population-based	56.2	-

people between 1990 and 2019. The age group of the participants was ranged from 19 to 80 years. The results of these studies have been used to calculate the relative risks of green tea consumption in CRC (OR = 0.99; 95% CI: 0.83-1.18), colon (OR = 0.97; 95% CI: 0.85-1.10), rectum (OR = 1; 95% CI: 0.86-1.16), proximal colon (OR = 0.98; 95% CI: 0.44-2.19), distal colon (OR = 0.94; 95% CI: 0.61-1.45), and colorectal adenoma (OR = 1.11; 95% CI: 0.64-1.93) (Table 2, Figures 2-4).

Table 2 tabulates the subgroup analysis of the variables, participants, and continents.

Meta-regression results showed an upward trend regarding the relationship between the relative risk of green tea consumption in CRC and the number of study samples. However, the outcomes were not statistically significant ($P = 0.613$). In other words, studies with larger sample sizes have not reported a higher relative risk of green tea consumption in CRC (Figure 5).

Besides, the results of meta-regression analysis demonstrated an upward relationship between the relative risk of green tea consumption in CRC and the year of study from 1990 to 2019. However, this relationship was not statistically significant ($P = 0.244$). In other words, the relative risk of green tea consumption in CRC has not increased significantly over time (Figure 6).

Discussion

This meta-analysis investigated 18 studies with 44 992 samples. The relative risks of green tea consumption in CRC, colon, and rectum were (OR = 0.99; 95% CI: 0.83-1.18), (OR = 0.97; 95% CI: 0.85-1.10), and (OR = 1; 95% CI: 0.86-1.16), respectively. In the present study, green tea consumption did not reduce the risks of colorectal, colon, and rectal cancers. Indeed, these outcomes were not statistically significant. Several meta-analyses have been performed to find the relationship between green tea consumption and the risk of various cancers.

Sun et al (25) developed a meta-analysis considering 25 articles in 11 countries on three continents (i.e., North America, Asia and Europe). The results of combining eight studies showed that green tea reduced the risk of colon cancer (OR = 0.82; 95% CI = 0.69-0.98). Besides, they found a protective effect of green tea on three case-control studies of colon cancer (OR = 0.74; 95% CI = 0.60-0.93). The authors investigated the results of these studies on rectal cancer regardless of the type of study (case-control

Table 2. Relative risk between green tea consumption and cancer considering the variables, participants, and continents

Subgroups			OR (95% CI)	I^2 (%)	*P* value	Effect	Significant
Colorectal	Type of study	Case-control	0.92 (0.67, 1.27)	86.3	<0.001	Protector	No
		Cohort	1.04 (0.90, 1.20)	42.8	0.105	Risk factor	No
	Population	Population-based	1.04 (0.87, 1.25)	79.1	<0.001	Risk factor	No
		Hospital-based	0.62 (0.33, 1.15)	69.1	0.072	Protector	No
	Continent	America	0.80 (0.60, 1.07)	100	-	Protector	No
		Asia	0.99 (0.80, 1.23)	83.8	<0.001	Protector	No
		Australia	1.02 (0.77, 1.35)	0	0.914	Risk factor	No
Colon	Type of study	Case-control	0.92 (0.76, 1.11)	72.2	<0.001	Protector	No
		Cohort	1.03 (0.86, 1.23)	43.6	0.100	Risk factor	No
	Population	Population-based	0.95 (0.83, 1.09)	56.8	0.004	Protector	No
		Hospital-based	1.03 (0.67, 1.57)	66.9	0.082	Risk factor	No
	Continent	America	1.10 (0.88, 1.37)	4.1	0.352	Risk factor	No
		Asia	0.91 (0.77, 1.07)	61.4	0.003	Protector	No
		Europe	1.15 (0.95, 1.39)	29.8	0.233	Risk factor	No
Rectum	Type of study	Case-control	0.97 (0.79, 1.20)	66.2	0.001	Protector	No
		Cohort	1.04 (0.86, 1.26)	13.7	0.325	Risk factor	No
	Population	Population-based	0.98 (0.83, 1.16)	53.9	0.005	Protector	No
		Hospital-based	1.15 (0.99, 1.34)	0	0.819	Risk factor	No
	Continent	America	1.15 (0.79, 1.67)	0	---	Risk factor	No
		Asia	1.01 (0.83, 1.2)	58	0.006	Risk factor	No
		Australia	1.08 (0.72, 1.62)	0	0.635	Risk factor	No
		Europe	0.83 (0.41, 1.68)	86.9	0.006	Protector	No
Proximal Colon			0.98 (0.44, 2.19)	0	0.770	Protector	No
Distal Colon			0.94 (0.61, 1.45)	0	0.605	Protector	No
Colorectal Adenoma			1.11 (0.64, 1.93)	0	0.845	Risk factor	No

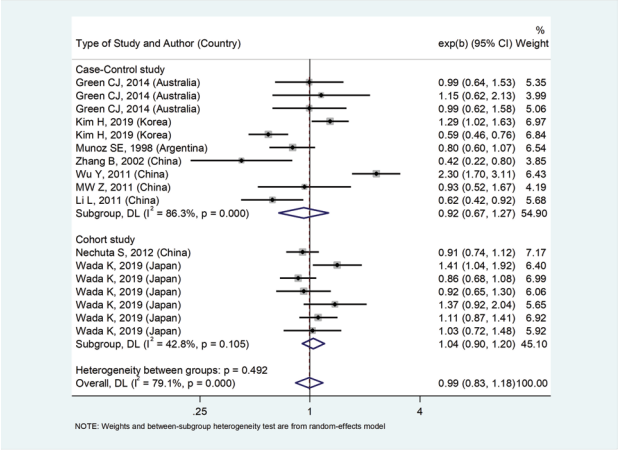

Figure 2. Relative risk between green tea consumption and colorectal cancer (95% CI).

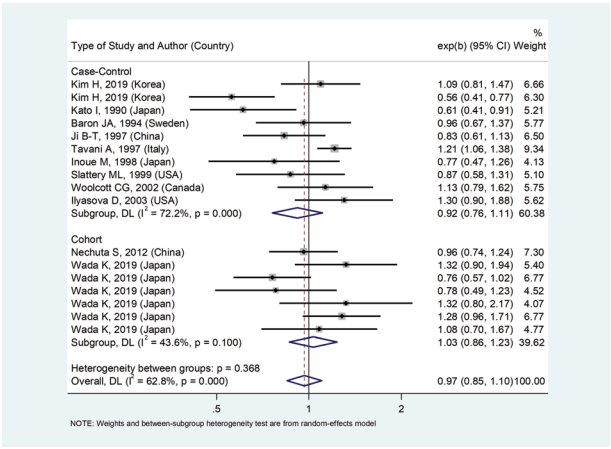

Figure 3. Relative risk between green tea consumption and colon cancer (95% CI).

versus cohort) (OR = 0.99; 95% CI = 0.71-1.37) and colon cohort studies (OR = 0.99; 95% CI = 0.79-1.24). In the same line, Wang et al (26) accomplished a meta-analysis considering 12 636 cases and 38 419 controls. The findings revealed that excessive consumption of green tea could reduce the risk of colon cancer. However, this relationship was not statistically significant (OR = 0.95; 95% CI: 0.81-1.11). They reported that the existing epidemiological data were not adequate to conclude about the protective effect of green tea against CRC in humans.

In addition, Wang et al (27) carried out a meta-analysis using the prospective cohort studies with 352,275 participants and 1675 cases of CRC. In these studies, the green tea consumption effect on CRC has been investigated. However, the final result was not statistically significant (RR = 0.90, 95% CI = 0.72-1.08). This finding is matched with the results of the present study. Different factors (e.g., dose, duration of consumption and individuals' age group) cause insignificant statistical outcomes. Therefore, it is suggested that these variables are considered for computing the relative risk in future studies (cohort or

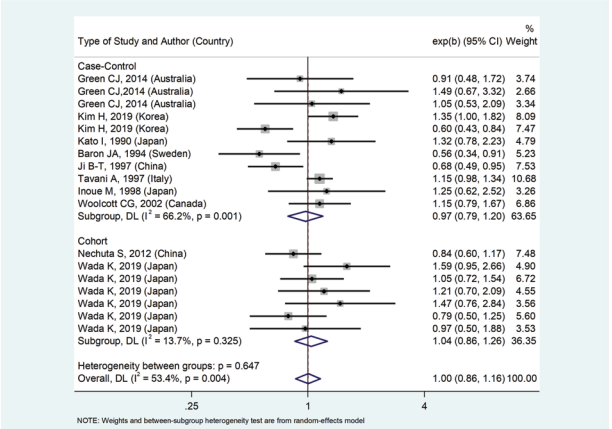

Figure 4. Relative risk between green tea consumption and rectal cancer (95% CI).

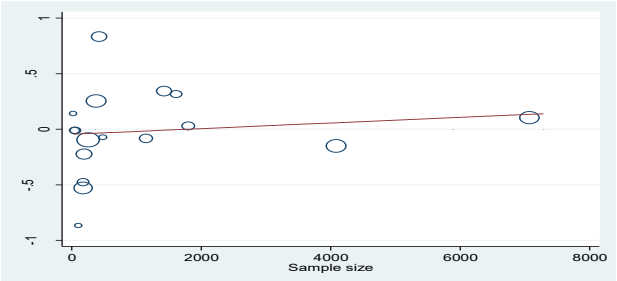

Figure 5. Meta-regression analysis of the relationship of "relative risk of green tea consumption with colorectal cancer" and sample size.

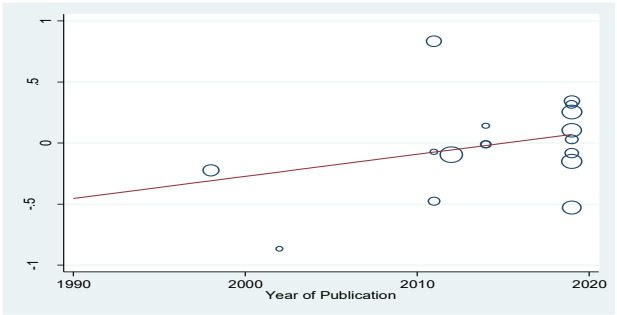

Figure 6. Meta-regression results of the relationship of "relative risk between green tea consumption and colorectal cancer", as well as the year of publication of the study.

case-control). Indeed, it is possible to observe a significant relationship at high doses or longer duration.

Conclusion

The present study showed that green tea consumption significantly reduced the risk of colon cancer. However, it had a minimum impact on reducing CRC risk. Additionally, it did not affect the risk of rectal cancer. Although the case-control studies classified green tea consumption as a protective factor for colorectal, colon, and rectal cancers, the cohort studies considered green tea consumption as a risk factor. It is worth mentioning that these relationships

were not statistically significant. Further, it was found that green tea consumption had a protective effect on CRC in Asia and the United States, while it was classified as a risk factor in Australia. In other words, the general population studies reported green tea consumption as a risk factor in CRC, while it was considered a protective factor in hospital studies. The findings showed that the relative risk of green tea consumption in colon/rectal cancers was a protective factor in the general population studies. However, some hospital studies considered it as a risk factor. If an analysis is performed based on continents, the relative risk of green tea consumption in colon cancer was a protective factor in Asia; since, it was considered as a risk factor in Europe and the United States. In addition, the relative risk of green tea consumption in rectal cancer was a protective factor in Europe. However, it was considered a risk factor in Asia, the United States, and Australia. It is essential to note that these relationships were not statistically significant.

Limitations of the study

Inaccessibility to the full text of some studies, the lack of uniform distribution of studies in the studied subgroups (continent and type of study), and lack of information about the relationship between green tea consumption and CRC based on gender. Besides, some studies had a wide age range, preventing the subgroup analysis based on age group variables. Since different doses of green tea consumption were considered in these studies, the measurement unit was not similar. Therefore, the results cannot be expressed based on the dose (low and high doses).

Authors' contribution

Conceptualization: Mohammad Azadbakht.
Data curation: Moloud Fakhri and Seyde Sedighe Yousefi.
Formal analysis: Mahmood Moosazadeh.
Funding acquisition: Moloud Fakhri.
Investigation: Mohammad Azadbakht.
Methodology: Hafez Fakheri and Moloud Fakhri.
Project administration: Moloud Fakhri.
Resources: Seyde Sedighe Yousefi.
Software: Mahmood Moosazadeh.
Supervision: Hafez Fakheri.
Validation: Moloud Fakhri.
Visualization: Hafez Fakheri.
Writing–original draft: All authors.
Writing–review & editing: All authors.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical considerations

This systematic review and meta-analysis were conducted in accord with the World Medical Association Declaration of Helsinki. The institutional ethical committee of Mazandaran University of Medical Sciences approved all study protocols (IR.MAZUMS.REC.1400.11466). The current protocol was also registered on PROSPERO (#CRD420.212.76257, https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD420.212.76257). Besides, ethical issues (including plagiarism, data fabrication, double publication) were completely observed by the authors.

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