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Coffee and Tea Consumption and Gastric Cancer: a pooled analysis in an international consortium of epidemiological studies

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Consumo di caffè e tè e cancro gastrico: un'analisi aggregata in un consorzio internazionale di studi epidemiologici

Sommario

L'obiettivo principale della mia ricerca di dottorato era esaminare l'effetto del consumo di caffè e tè sul rischio di cancro gastrico. Il caffè e il tè sono tra le bevande più popolari al mondo dopo l'acqua e si prevede che il loro consumo aumenterà in media del 17% nei prossimi anni. Il World Cancer Research Fund e l'American Institute for Cancer Research (WCRF/AICR) hanno concluso, nel loro rapporto più recente (2018), che non ci sono dati sufficienti per trarre conclusioni sulla relazione tra consumo di caffè e tè e cancro gastrico. Per stimare questa relazione sono state aggregate analisi dei singoli partecipanti in un unico consorzio globale di studi epidemiologici sul cancro gastrico, il progetto Stomach cancer Pooling (StoP). Il progetto StoP comprendeva trenta studi caso-controllo (CC) e cinque studi caso-controllo nidificati all'interno degli studi di coorte (NCC), provenienti da diciassette paesi diversi in tutto il mondo. Per ogni studio, il consumo di caffè e tè è stato valutato utilizzando questionari sulla frequenza alimentare (FFQ) autosomministrati, oppure somministrati dall'intervistatore prima della diagnosi per i casi di cancro gastrico o prima dell'insorgenza della malattia, ricovero ospedaliero per controlli ospedalieri o reclutamento per controlli basati sulla popolazione. I dati sull'assunzione di caffè erano disponibili in diciotto studi, che includevano 8,198 casi di cancro gastrico e 21,419 controlli; per quanto riguarda il tè, ventidue studi contenevano un totale di 9,438 casi di cancro gastrico e 20,451 controlli. Il consumo di caffè e tè è stato misurato in base al numero di tazze, orari o frequenza di consumo riportati in ogni studio e ulteriormente espresso nell'unità standard di tazze al giorno. Caffè con caffeina e decaffeinato sono stati considerati separatamente, così come la loro assunzione combinata. Le varie tipologie di tè riportati sono state calcolate come assunzioni totale di tè. Inoltre sono state valutate la temperatura e la forza del tè consumato. Modelli a effetti misti lineari generalizzati logistici che includono i termini per sesso, età, design dello studio, infezione da *Helicobacter pylori* (*H. pylori*) e molti altri dei principali fattori di rischio riconosciuti per il cancro gastrico sono stati utilizzati per stimare le associazioni tra cancro gastrico e consumo di caffè e tè,

attraverso analisi di modellazione sia a due che a una fase. Sono state inoltre condotte analisi di sottogruppi attraverso strati di diversi fattori e relazioni dose-risposta. Sono stati applicati anche modelli multinomiali a effetti misti per stimare gli OR e i corrispondenti CI al 95% del cancro gastrico in base al sito anatomico (cardiaco e non cardiaco) e al tipo istologico (intestinale, diffuso e misto/non specificato dalla categorizzazione di Lauren) per il tè normale bevitori e forti bevitori di caffè. L'eterogeneità tra gli strati è stata valutata dal test Q di Cohran e dal test I2 tra gli studi. I risultati hanno mostrato un'associazione leggermente inversa (OR: 0.92, CI 95%: 0.82-1.05) tra consumo di tè e cancro gastrico, ma nessuna associazione rilevante (OR: 1.03, CI 95%: 0.94-1.13) tra consumo di caffè e cancro gastrico. I bevitori regolari di tè avevano un rischio di cancro del cardias gastrico più basso (OR: 0.64, 95% CI: 0.49-0.84), rispetto ai forti bevitori di caffè, che invece erano positivamente associati (OR: 1.61, 95% CI: 1.27-2.05) con il cancro del cardias gastrico. Contrariamente all'assunzione di tè, che era più fortemente legata a un minor rischio nei paesi asiatici (OR: 0.67, CI 95%: 0.49-0.91, in studi da Cina e Giappone), non c'erano prove di differenze regionali nell'effetto del consumo di caffè sul rischio di cancro gastrico. Il consumo di tè caldo o molto caldo non ha aumentato il rischio di cancro gastrico, mentre bere tè caldo o freddo è stato correlato a un rischio inferiore.

Infine discuto anche altri progetti di ricerca che ho intrapreso durante i miei studi di dottorato. Questi includono altre analisi dietetiche all'interno del consorzio del progetto Stomach Cancer Pooling, il mio lavoro con la Hellenic Health Foundation per valutare la dieta abituale della popolazione adulta greca e un progetto che ho svolto durante il mio periodo di ricerca di sei mesi presso l'Harvard T.H. Chan School of Public Health, riguardante l'associazione tra consumo di olio d'oliva e cancro alla prostata nello studio di US Healthcare Professionals Follow-Up Study (HPFS) e
nella parte greca dello studio di coorte European Prospective Investigation into Cancer and Nutrition (EPIC-Greece).

Coffee and Tea Consumption and Gastric Cancer: a pooled analysis in an international consortium of epidemiological studies

Abstract

The main focus of my doctoral research was to examine the effect of coffee and tea drinking on gastric (stomach) cancer risk. Coffee and tea are among the most popular drinks worldwide after water, and their consumption is expected to rise by an average of 17% over the next several years. The World Cancer Research Fund and the American Institute for Cancer Research (WCRF/AICR) concluded in their most recent report (2018) that there is insufficient data to draw any conclusions about the relationship between coffee and tea consumption and gastric cancer. To estimate their relationship with gastric cancer risk, individual-participant pooled analyses in a unique global consortium of epidemiological studies on gastric cancer - the Stomach cancer Pooling (StoP) project- were carried out. The StoP project included thirty case-control (CC) studies and five nested case-control within the cohort (NCC) studies, from seventeen different countries worldwide. For each study, coffee and tea consumption were assessed using self- or interviewer-administered food frequency questionnaires (FFQ) prior to the diagnosis of gastric cancer cases or prior to the onset of disease, hospital admission for hospital-based controls, or recruitment for population-based controls. Data on coffee intake were available from eighteen studies, which included 8,198 gastric cancer cases and 21,419 controls, while on tea twenty-two studies totaled 9,438 gastric cancer cases and 20,451 controls. Coffee and tea consumption was measured by the number of cups, times, or frequency of consumption reported in each study and further expressed in the standard unit of cups per day. Coffee was considered either caffeinated coffee or decaffeinated coffee separately, as well as their combined intake. Various types of tea reported were calculated as total tea intake. In addition, the temperature and strength at which tea was consumed were assessed. Logistic generalized linear mixed-effects models including terms

for sex, age, study design, *Helicobacter pylori* (*H. pylori*) infection, and several other main recognized risk factors for gastric cancer were used to estimate the associations between gastric cancer and coffee and tea consumption, through both two- and one-stage modeling analyses. Subgroup analyses across strata of several factors and dose-response relationships were also carried out. Multinomial mixed-effects models were also applied to estimate the ORs and corresponding 95% CIs of gastric cancer by the anatomical site (cardia and non-cardia) and histological type (intestinal, diffuse, and mixed/unspecified by Lauren categorization) for regular tea drinkers and high coffee drinkers. Heterogeneity between strata was evaluated by Cohran's Q test and by the I2 test between studies. The results showed a slightly inverse association (OR: 0.92, 95% CI: 0.82–1.05) between tea drinking and gastric cancer but no relevant association (OR: 1.03, 95% CI: 0.94-1.13) between coffee consumption and gastric cancer. Regular tea drinkers had a lower gastric cardia cancer risk (OR: 0.64, 95% CI: 0.49-0.84), than heavy coffee drinkers, who were positively associated (OR:1.61, 95% CI: 1.27–2.05) with gastric cardia cancer. Contrary to tea intake, which was more strongly linked to lower risk in Asian countries (OR: 0.67, 95% CI: 0.49-0.91, in studies from China and Japan), there was no evidence of regional differences in the effect of coffee consumption on the risk of gastric cancer. Consuming hot or very hot tea did not increase the risk of gastric cancer, drinking warm or cold tea was related to a lower risk.

Last but not least, I also discuss additional research projects I have undertaken through my doctoral studies. These include other dietary analyses within the Stomach Cancer Pooling project consortium, my work with the Hellenic Health Foundation to evaluate the usual diet of the Greek adult population, and a project I carried out during my six-month visiting research period at Harvard T.H. Chan School of Public Health on the association between olive oil consumption and prostate cancer in the US Health Professionals Follow-up Study (HPFS) and the Greek part of the European Prospective Investigation into Cancer and Nutrition (EPIC-Greece) cohort study.

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Background and context

Gastric cancer, commonly known as stomach cancer, is the fifth most common cancer worldwide. More than 1 million new cases were diagnosed globally in 2020, accounting for 6% of all new cancer cases, excluding non-melanoma skin cancer (1, 2) . The number of new deaths from gastric cancer was estimated at 768,793 deaths in 2020, accounting for 7.7% of cancer deaths among men and women worldwide making it the fourth most common cause of cancer death (2) (**Figure 1**). Gastric cancer is more common in older adults, with an average age of diagnosis at 68 years old, and it is predicted that by 2040, the number of incident gastric cancer cases among those aged 70 years and older will nearly double (2). According to the latest Globocan report, about 1.8 million new cases and about 1.3 million deaths from gastric cancer will happen (2).

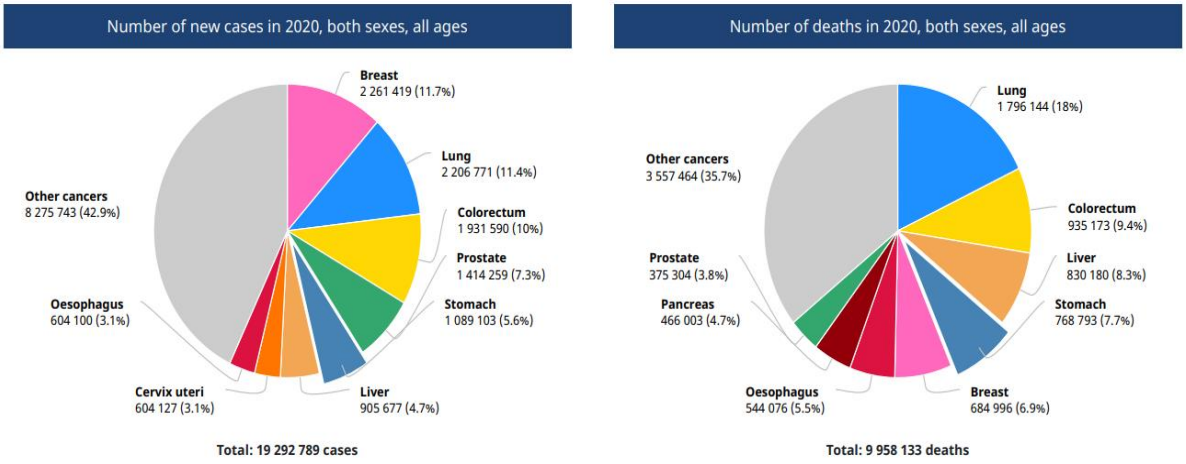


Figure 1. Number of new cancer cases and deaths from cancer in 2020. Globocan, 2020 (2).

The trends in mortality and incidence of gastric cancer are differentiated by sex and geographical region. There are almost twice men than women who have been given gastric cancer diagnoses (**Figure 2**). It is the fourth most frequent cancer in males (7.7% of all cancer cases) and the seventh most frequent cancer in women (4.2% of all cancer cases in women). Higher incidence rates of gastric cancer were found in Eastern Asia, followed by Eastern Europe, while the lowest was in African regions. Men in Japan (32.5%) and women in Mongolia (13.2%) were among those with the highest incidence rates, compared to men and women in Northern America and Northern Europe who had lower rates (2) (**Figure 2**).

Mortality rates for gastric cancer are higher among men in eastern and central Asia, such as Iran, Kyrgyzstan, Turkmenistan, and Latin America (2).

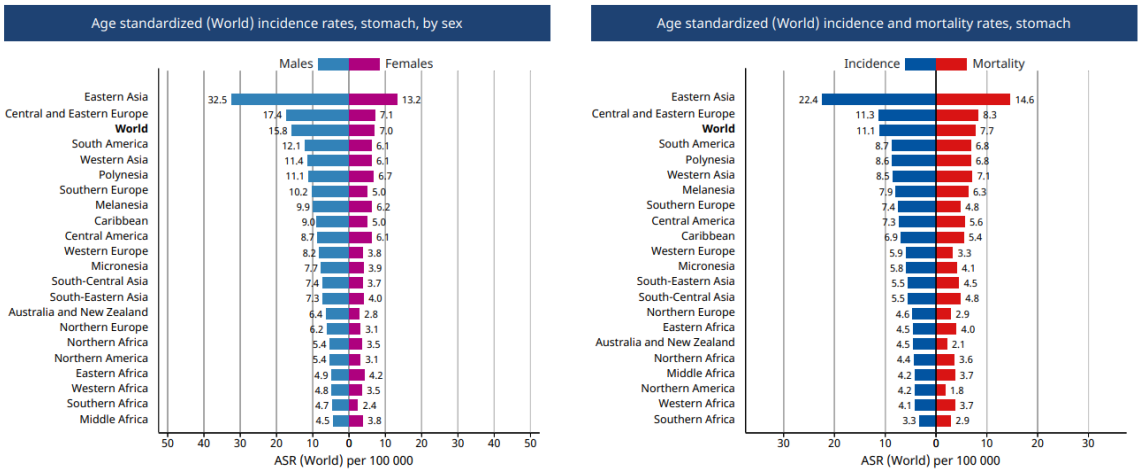


Figure 2. Age-standardized incidence and mortality rates of gastric cancer by sex and geographical region. Globocan, 2020 (2).

Gastric cancer is classified into two different types according to where anatomically in the stomach the tumor is located. Gastric cardia cancer is found in the top part of the stomach closest to the esophagus near the gastroesophageal junction, while non-cardia cancer is found in all other areas closest to the lower parts of the stomach (3). Globally, non-cardia cancer is more prevalent than cardia cancer, with East and Central Asia having the highest incidence rates. A higher proportion of cardia cancers is more common in Europe and the United States (4). Age-standardized incidence and mortality rates of gastric non-cardia cancer have decreased mainly due to reduced *Helicobacter pylori* (*H. pylori*) prevalence, which is strongly associated with this type of cancer (4, 5). On the other hand, rates of gastric cardia cancer have been seen to increase. Cardia cancer is more common in high-income countries like the United Kingdom and the United States and is three times more frequent in men than in women (1). Gastric cancer is also classified as either intestinal or diffuse. The intestinal type is more prevalent in men and older patients, and it has a better prognosis because cancer cells are more likely to respond to targeted medication therapy. The diffuse type is less frequent than the intestinal type, can affect people of any age or gender, spreads more quickly, and is harder to treat (1, 3).

Gastric cancer has a generally poor prognosis due to the fact that symptoms usually appear at a late stage including abdominal pain, vomiting, weight loss, and blood in the stool.

However, due to screening, early detection, and more effective treatment options, gastric cancer survival rates have progressively increased over the years (5). Survival rates are higher in high-income countries because of the advanced services aforementioned above. In Europe and the United States, the 5-year survival rates for gastric cancer range between 25-28% respectively, and they rise to 63% if the tumor is discovered at an early stage (6).

The decrease in the incidence of gastric cancer worldwide has also been associated with improvements in food preservation techniques, such as refrigeration, which are connected to a decrease in the consumption of salt-preserved foods and an increase in the consumption of fresh fruit and vegetables (7). *H. pylori* infection, a gram-negative bacterium that dwells in the human stomach, has been strongly related to non-cardia cancer and interacts with other risk factors like salt intake (8, 9). There is considerable evidence for the interaction of *H. pylori* infection and high salt intake in cases of non-cardia cancer. Eating foods preserved by salting, for example, dried fish or pickled vegetables, which are commonly prepared in East Asia, has been linked to increased rates of non-cardia cancer (1).

A number of dietary and lifestyle factors have been linked to carcinogenesis, making nutrition and lifestyle important cancer risk factors. For example, the intake of red and processed meat, alcohol, and smoking habits have been associated with increased cancer risk, whereas the intake of fruit and vegetables has been suggested to be protective against cancer risk. However, the role of many dietary and lifestyle risk factors in cancers like gastric cancer role has not been well quantified. There are many dietary factors with limited and inconclusive evidence of gastric cancer risk that may be associated with overall gastric cancer or according to the gastric subtype. According to a World Cancer Research Fund/American Institute for Research summary review of epidemiological data on diet, nutrition, physical activity, and stomach cancer, there is no conclusive evidence for the role of several dietary food groups such as cereals, nuts, and seeds, fish, coffee, tea, or nutrients such as dietary fiber, total fat, and protein on gastric cancer risk (1).

This dissertation aimed to investigate and quantify the association between coffee and tea drinking and gastric cancer through pooled analyses of individual data using data from a unique global consortium of epidemiological studies on gastric cancer, the Stomach Cancer Pooling (StoP) Project. The first two chapters of the current dissertation go into detail about the role of coffee and tea consumption on the risk of gastric cancer in the StoP project. The

third chapter gives a summary of the role of other dietary factors in gastric cancer risk, carried out through additional analyses in the same pooling dataset, while the fourth and fifth chapters briefly describe research activities implemented through the collaboration with the Hellenic Health Foundation and during my six-month visiting research period at the Department of Nutrition at Harvard T.H. Chan School of Public Health.

The Stomach Cancer Pooling (StoP) Project

The study of risk factors in cancer pathogenesis is essential for developing preventive methods and identifying high-risk patients. In 2012, a number of epidemiological studies on gastric cancer joined together to create the Stomach Cancer Pooling (StoP) Project consortium (http://stop-project.org) (10). Through pooled analyses of individual-level data, the StoP project seeks to investigate the contribution of lifestyle, environmental and genetic factors to gastric cancer risk. The StoP Project is coordinated by the Department of Clinical Sciences and Community Health of the University of Milan and received ethical approval from the Review Board of the University of Milan (reference 19/15 on 01/04/2015).

The StoP Project is the largest consortium of epidemiological studies on gastric cancer globally and to date, it includes original data from thirty-five countries conducted in Europe, Asia, and the Americas (**Table 1**). The latest release of the dataset (version 3.2) of the StoP project includes thirty case-control (CC) studies and five nested case-control within cohort (NCC) studies from fifteen countries, for a total of around 13,500 cases of gastric cancer and 32,000 controls. The characteristics of studies participating in the StoP project are shown in Table 1.

The eligible studies were first searched through electronic databases like Medline and Embase, backward citation tracking, and personal connections. The inclusion criteria required studies to have a case-control (CC) or nested case-control within cohort (NCC) study design and at least 80 incident-histologically confirmed gastric cancer cases (10). If a study met the above criteria, the principal investigators were contacted and invited to join the consortium. To participate principal investigators had to provide a signed data transfer agreement (DTA), the original dataset, original dietary questionnaires, and a description form of the study to the coordinating center at the University of Milan. Those who did not want to share the original datasets, provided a subset of core variables including socioeconomic, lifestyle characteristics and known risk factors of gastric cancer such as age, sex, education, social class, smoking habits, family history of gastric cancer, etc., as well as, they provided locally-computed estimates to use them in a two-stage meta-analysis (10).

The collected datasets were harmonized based on a predetermined format outlined in the project's codebook at the pooling center at the University of Milan. For each participant, a new identification number was computed by combining the study number, the case-control status, and the participant's initial identification number. The harmonized data were classified into the following categories: sociodemographic characteristics, smoking status, alcohol consumption, physical activity, and nutritional intake (10).

The StoP Project uses a sizable dataset with distinctive information from various geographical regions throughout the world to assess various dietary, non-dietary, and genetic risk factors for gastric cancer risk. The collaborative framework of the project, which comprises a vast amount of data, is its main strength. This will make it possible to analyze risk factors' contribution to the development of gastric cancer in general, as well as by histological types (intestinal vs. diffuse type) and subsites of gastric cancer (cardia vs. non-cardia), with enough statistical power. Studies have shown that pooled individual-level data analysis has important advantages over systematic reviews (11). Using individual-level data makes it possible to harmonize data collection and analysis, maintain consistency between adjustment terms and multivariate models, and efficiently examine heterogeneity and interaction between covariates (12).

To date, the StoP project has examined the association between several dietary and lifestyle factors and the risk of gastric cancer including meat consumption, fruit and vegetable intake, citrus fruit, smoking, alcohol, and exposure to chemical and environmental factors. In more detail, high intakes of red meat, processed and total meat were associated with 24%, 23% and 30% increased risk of gastric cancer, respectively (13). In particular, red and processed meat with an intake of 150 g/day and 50 g/day were more strongly associated with gastric cancer (OR: 1.85, 95% CI: 1.56-2.20, OR: 1.38, 95% CI: 1.28-1.49, respectively) (13). Consumption of six portions of fruit or non-citrus fruits a day and ten portions of vegetables had a protective effect on gastric cancer (OR: 0.64, 95% CI: 0.57-0.73, OR: 0.71, 95% CI: 0.61-0.83, and OR: 0.51, 95% CI: 0.43-0.60, respectively) (14). Higher intake of citrus fruit consumption, namely oranges, lemons, tangerines, grapefruits, and citrus fruit juices, was inversely associated with gastric cancer risk (OR: 0.80, 95% CI: 0.73-0.87), and the magnitude of the association was not differentiated between cardia and non-cardia cancer subsites (15). Heavy alcohol drinkers (4-6 drinks per day) had a lower risk of gastric cancer (OR: 1.26, 95% CI: 1.08-1.48), and the risk was higher for those who consumed more than six alcoholic drinks

(OR: 1.48, 95% CI: 1.29-1.70) and patients with gastric cardia cancer (OR: 1.61, 95% CI: 1.11–2.34) (16). Compared to never smokers, smoking cigarettes and smoking more than twenty cigarettes per day were both associated with a higher risk of gastric cancer (OR: 1.25, 95% CI: 1.11-1.40 and OR: 1.32, 95% CI: 1.10-1.58, respectively). In addition, a smoking history of more than forty years was related to an OR of 1.33 (95% CI: 1.14-1.54) (17). The aforementioned risk factors showed stronger associations with gastric cardia cancers (18). There have been suggestions that certain occupations and their related chemical and environmental exposures were negatively or favorably associated with gastric cancer, overall or by histological type. Gastric cancer risk was reduced for "desk jobs" compared to jobs that were exposed to dust and high-temperature conditions. Exposure to substances like coal derivatives, pesticides, aromatic amines, and radiation was linked to a 1.5-2.9 fold increased risk of diffuse-type cancer (19).

Among the future investigations of the StoP project is to examine the role of rare exposures on gastric cancer risk, as well as the prevalence of risk factors in understudied populations such as patients with gastric cardia cancer or those with young-onset gastric cancer. The consortium also plans to integrate more studies from Asia, create a polygenic-risk score for gastric cancer using genome-wide modeling, and apply survival analyses and machine learning techniques to better predict and prognose the risk of developing gastric cancer (10).

Table 1 Main characteristics of the studies agreed to participate in the Stomach Cancer Pooling (StoP) Project.

Study ID	Country	Period	Study type	Cases	Controls
1	Italy	1985-1997	CC, hospital-based	769	2,081
2	China	1987-1989	CC, hospital-based	266	533
3	Italy	1997-2007	CC, hospital-based	230	547
4	Italy	2006-ongoing	CC, hospital-based	160	444
5	Italy	1985-1987	CC, population-based	1016	1,159
6	Greece	1981-1984	CC, hospital-based	110	100
7	Canada	1994-1997	CC, population-based	1,182	5,039
8	China	2000	CC, population-based	206	415
9	Russia	1996-1997	CC, hospital-based	450	611
10	Iran	2004-2005	CC, population-based	217	394
11	Iran	2005-2007	CC, population-based	286	304
12	China	1991-1993	CC, population-based	711	711
13	China	1995	CC, population-based	133	433
14	USA	1992-1994	CC, hospital-based	132	132
15	USA	1980-1990	CC, hospital-based	87	261
16	Portugal	1999-2006	CC, population-based	692	1,667
17	Sweden	1998-2010	Cohort, nested CC	88	352
18	Iran	2001-2004	CC, hospital-based	119	119
19	Sweden	1998-2010	Cohort, nested CC	161	644
20	Spain	2008-2012	CC, hospital-based	441	3,440
21	Sweden	1989-1995	CC, hospital-based	514	1164
22	Spain	1995-1999	CC, hospital-based	401	455
23	Mexico	2004-2005	CC, population-based	248	478
24	Mexico	1989-1990	CC, population-based	220	752
25	Mexico	1994-1996	CC, hospital-based	234	468
26	Brazil	1991-1994	CC, hospital-based	226	226
27	Brazil	1991-1994	CC, hospital-based	93	186
28	Japan	1998-2002	CC, hospital-based	153	303
29	Latvia	2007-ongoing	CC, hospital-based	215	430
30	USA	1998-1993	CC, population-based	170	502
31	Greece	1994-1999	Cohort, nested CC	82	410
32	Finland	1985-1988	CC, population-based	462	462
33	USA	1995-1996	Cohort, nested CC	1,583	3,331
34	Brazil	2016-ongoing	CC, hospital-based	368	738

CC, Case Control.

❖

From the published paper: Martimianaki G, Bertuccio P, Alicandro G, Pelucchi C, Bravi F, Carioli G, et al. Coffee consumption and gastric cancer: a pooled analysis from the Stomach cancer Pooling Project consortium. Eur J Cancer Prev. 2022 Mar 1;31(2):117-127. doi: 10.1097/CEJ.0000000000000680. PMID: 34545022; PMCID: PMC8972971 .

Chapter I. Coffee consumption and gastric cancer: a pooled analysis from the Stomach cancer Pooling (StoP) Project consortium

Introduction

With an annual average consumption of 1.27 kg per person, which climbed by 18.7 percent between 2014 and 2017, coffee is one of the most consumed beverages worldwide (20). Coffee is a complex mixture composed of numerous substances that may relate to gastric cancer. Studies have shown that its antioxidants mainly phenolic compounds, diterpenes, melanoidins, and vitamin precursors may inhibit the development of cancer, whereas other substances like aromatic hydrocarbons and heterocyclic amines which are formed during the processing of the coffee beans can promote carcinogenesis (21-25).

Since the 1960s, a number of epidemiological studies have analyzed the relationship between coffee drinking and the risk of gastric cancer. The outcomes of the studies on coffee consumption and gastric cancer are mixed. A recent summary overview of epidemiological studies on coffee consumption and cancer risk suggested that there was no conclusive relationship between coffee intake and overall gastric cancer risk (21). In 2018, the World Cancer Research Fund/American Institute for Research reported that there was insufficient proof to relate coffee to gastric cancer (26).

Although the majority of studies have suggested a weak relationship between coffee consumption and gastric cancer risk, the evidence is still debatable. Therefore, a pooled analysis of gastric cancer studies with individual participant data was implemented to more thoroughly explore and quantify the relationship between coffee drinking and gastric cancer.

Methods

Study population

The StoP Project consortium's v.3.1 dataset release was used in this analysis. The v.3.1 dataset included thirty-four studies and about 13,500 stomach cancer cases and 32,000 controls. Twenty-one of the studies had data on caffeinated and/or decaffeinated coffee intake. Three studies, two from Italy (27) and one from Mexico (28), were eliminated because they had more than 60% of missing values on coffee consumption. Therefore, for a total of eighteen studies with data on coffee intake two were conducted in Greece (29, 30), three in Italy (31-33), one in Canada (34), one in Russia (35),

three in the USA (36-38), one in Portugal (39), two in Spain (40, 41), Mexico (42, 43) and two in Brazil (44, 45), and one study in Japan (46). Only two of the eighteen studies—one from the USA (36) and one from Greece (29)—were nested case-control within cohort studies. Seven of the studies—two from Italy (32, 33), one from Russia (35), two from Spain (40, 41), and two from the USA (36, 38)—had data on the intake of decaffeinated coffee. Sixteen of the studies provided information on the amount of coffee consumed (**Supplemental Table I-1**). One study from Greece (29) did not provide the original dataset on coffee consumption but only locally computed estimates.

Assessment of coffee intake

Coffee consumption was measured using face-to-face interview-administered (twelve studies) or self-administered (six studies) food frequency questionnaires (FFQs). Participants were asked to report how much coffee they generally consumed, in total or by coffee type (caffeinated or decaffeinated), prior to the diagnosis for gastric cancer cases or study enrollment for controls.

Coffee consumption was given by the studies either as cups or grams or times consumed per day, week, or month (**Supplemental Table I-2**). Taking into account the quantity, frequency, and number of coffee cups or times the amount of coffee consumed in the standard unit of cups per day for each study was calculated. When coffee consumption was reported in frequency categories (for example 2-3 times per week), the number of cups or times drank was diverted by dividing the average number of coffee cups or times reported by the average number of days indicated in the frequency category. For the current analysis, the following three variables were computed: Caffeinated coffee, decaffeinated coffee, and their combined intake as total coffee. When I couldn't find in the FFQ a particular variable for caffeinated coffee, the various types of coffee reported separately were combined together. For example, in studies conducted in Italy (33) and in Russia (35), the summary consumption of espresso and cappuccino or of black-instant coffee, coffee with milk, and instant coffee with milk were assigned as caffeinated coffee consumption, respectively.

Total coffee drinkers, including both the consumption of caffeinated and decaffeinated coffee, were classified as never or rare drinkers and ever coffee drinkers. Never or rare drinking included participants who reported they never drank coffee or who consumed less than one cup per day, whereas ever coffee drinking included the consumption of one or more cups per day. The amount of total coffee consumed was categorized in two ways. The first one included eight categories: <1 cup/day: never or rare drinkers, ≥1 to <2 cups/day, ≥2 to <3 cups/day, ≥3 to <4 cups/day, ≥4 to <5

cups/day, ≥5 to <6 cups/day, ≥6 to <7 cups/day and ≥7 cups/day, while the second variable had four categories of drinking: <1 cup/day: never or rare drinkers, ≥1 to < 3 cups/day, ≥3 to <5 cups/day and ≥5 cups/day. Similar were the categories when was considered only caffeinated coffee. Since decaffeinated coffee consumption was not as frequently reported as caffeinated coffee, I used the four following categories of drinking: never or rare drinkers as 1 cup/day, 1 to 2 cups/day, 2 to 3 cups/day, and 3 cups/day.

Statistical analysis

The percentage of gastric cancer cases and controls was calculated by selected participant characteristics such as age, sex, study-specific socioeconomic status (low, intermediate, high), tobacco smoking (never smoker, former smoker, current smoker low, current smoker intermediate; current smoker high), alcohol drinking (≤ 12 g/day. >12 and < 48 g/day, ≥ 48 g/day), history of gastric cancer in first degree relatives (yes, no), tertiles of total fruit and vegetable intake, and salt intake (study-specific low, intermediate and high, respectively).

A two-stage analysis was used to estimate the summary pooled odds ratios (OR) and 95% confidence intervals (CIs) between total coffee consumption and gastric cancer (30) to include both studies that provided original data (seventeen studies) and those that provided local estimates only, one study from Greece (29). The two-stage meta-analysis is composed of two parts of analysis. First, the ORs and the corresponding 95% CIs of gastric cancer were estimated for each study separately using multivariable unconditional or conditional logistic regression models. Conditional logistic regression models were used to estimate the ORs and 95% CIs of the matched cased control studies (**Supplemental Table I-1**). Then, using meta-analysis the study-specific ORs and 95% CIs were pooled together using a logistic random-effects mixed model to calculate the summary pooled effects estimate. The meta-analysis was conducted in R 3.6.3 (R Core Team, 2021) with the "metaphor" package (47).

To assess the ORs and 95% CIs of gastric cancer and the amount of total, caffeinated and decaffeinated coffee consumed across consumption categories sixteen studies were analyzed pooling all the data together (48). Two studies were excluded from this one-stage analysis: the first one provided only locally computed estimates (29) and the second one did not report the amount of coffee consumed (30). The one-stage ORs and the 95% CIs of gastric cancer were computed by generalized linear mixed-effects models with a logistic link function and a random intercept for each study using

the "lme4" library and the GLMER procedure in R 3.6.3. (R Core Team, 2021). In addition, a stratification analysis across strata of sex, age (<65 and over 65 years), geographic area (Europe, Asia, America), socioeconomic status (low, intermediate, high), smoking status (never smokers, former smokers, current smokers), alcohol drinking (1 drink per day, 1-3 drinks per day, 4 drinks per day), total fruit and vegetable intake (low, intermediate, high), salt intake (low, intermediate, high), family history of gastric (yes, no), and *H. pylori* infection (yes, no), was also done. Heterogeneity between the different strata of variables was computed using Cochran's Q test (49). ORs of gastric cancer by anatomical subsite (cardia and non-cardia) and histological type (intestinal and diffuse by Lauren classification), were calculated by multinomial mixed-effects models of GLIMMIX procedure in SAS 9.4 (SAS Institute Inc, Cary, NC). To estimate the dose-response relationship between caffeinated coffee and gastric cancer a one-stage linear random-effects model with natural cubic splines and four knots at fixed percentiles of caffeinated coffee (25^{th}, 50^{th}, 75^{th}, and 90^{th}) distribution was used (50). Caffeinated coffee intake was considered in the model as a continuous variable, ranging from 0 to 7 or more cups of coffee per day. The dose-relationship was computed in R 3.6.3 (R Core Team, 2021) with the "splines" package.

The reference category for the one-stage and two-stage approaches was never or rare coffee drinkers. All models were adjusted to account for sex, five-year age groups (< 40, 40-44, 50-54, 55-59, 60-64, 65-69, 70-74, 75 or older), socioeconomic status (study-specific low, intermediate, high), smoking status (never, former, current low, current intermediate, current high), alcohol consumption (never, 1 drink per day, 1-3 drinks per day, 4 drinks per day), salt intake (study-specific low, intermediate, high), total fruit and vegetable intake (study-specific low, intermediate, high) and family history of gastric cancer (yes, no). Missing values in the covariates were retained in the models by either including them in a separate category of the corresponding variables or by including them in the lower levels of the categories when there was a proportion lower than 1% missing.

Results

Participants

The characteristics of gastric cancer patients and controls are shown in **Table I-1**. Fifty-one and forty-eight percent of the cases and controls respectively came from European studies, forty-seven and fifty percent from studies conducted in North and South America, while only 2 percent were cases from Japan which was the only Asian study in the current analysis. Male cases (65.7%) were more than control ones (57.4 %), 65 years or older (55.3%) versus 48.3 % of controls and had

reported a lower socioeconomic level (47.2%). In addition, cases reported more often to be heavy drinkers (14.3%), high current smokers (7.6%), and with a family history of gastric cancer (15.5%).

Table I-1 Percentages of gastric cancer cases and controls [a] by selected covariates.

	Cases		Controls	
	N	%	N	%
Total	8,198	100.0	21,419	100.0
Study center				
Europe	4,191	51.0	10,470	48.9
Greece 1 (30)	110	1.3	100	0.5
Greece 2 (29)	82	1.0	410	1.9
Italy 1 (32)	769	9.4	2,081	9.7
Italy 2 (33)	230	2.8	547	2.6
Italy 4 (31)	1,016	12.4	1,159	5.4
Portugal (39)	692	8.4	1,667	7.8
Russia (35)	450	5.5	611	2.9
Spain 1 (40)	441	5.4	3,440	16.1
Spain 2 (41)	401	4.8	455	2.1
Asia				
Japan 3 (46)	153	1.9	303	1.4
Americas	3,854	47.0	10,646	49.7
Brazil 1 (45)	226	2.8	226	1.1
Brazil 2 (44)	93	1.1	186	0.9
Canada (34)	1,182	14.4	5,039	23.5
Mexico 1 (42)	248	3.0	478	2.2
Mexico 2 (43)	220	2.7	752	3.5
USA 1 (38)	132	1.6	132	0.6
USA 3 (37)	170	2.1	502	2.3
USA 4 (36)	1,583	19.3	3,331	15.6
Sex	5,385	65.7	12,304	57.4
Male				
Female	2,813	34.3	9,115	42.6
Age				
Missing	41	0.5	18	0.1
<40	240	2.9	1,462	6.8
40-44	256	3.1	1,144	5.3
45-49	458	5.6	1,549	7.2
50-54	615	7.5	1,774	8.3
55-59	885	10.8	2,161	10.3
60-64	1,167	14.2	2,943	13.7
65-69	1,626	19.8	3,779	17.6
70-74	1,698	20.7	3,672	17.1
≥75	1,212	14.8	2,917	13.6
Socioeconomic status (study-specific)	184	2.2	309	1.5
Missing				
Low	3,873	47.2	7,946	37.1
Intermediate	2,759	33.7	7,638	35.6
High	1,382	16.9	5,526	25.8
Tobacco smoking	384	4.7	563	2.6
Missing				
Never	3,092	37.7	9,094	42.5

Former	2,843	34.7	7,098	33.1
Current				
Low	512	6.2	1,603	7.5
Intermediate	745	9.1	1,790	8.4
High	622	7.6	1,271	5.9
Alcohol drinking	366	4.5	1513	7.1
Missing				
Never	2,107	25.7	5,582	26.1
Low (≤12 g/day)	2,165	26.4	7,237	33.8
Intermediate (>12 and ≤ 47 g/day)	2,388	29.1	5,010	23.4
High (>47 g/day)	1,172	14.3	2,077	9.7
History of gastric cancer in first-degree relatives[b]				
Missing	828	17.0	1,714	15.0
No	3,296	67.5	8,922	78.2
Yes	759	15.5	773	6.8
Fruit and vegetable intake (study-specific tertiles)				
Missing	179	2.2	745	3.5
Low	2,616	31.9	6,244	29.2
Intermediate	2,620	32.0	7,034	32.8
High	2,783	33.9	7,396	34.5
Salt intake (study-specific tertiles)[c]				
Missing	159	2.3	997	5.0
Low	2,794	40.0	7,501	38.0
Intermediate	2,221	31.8	6,192	31.4
High	1,816	26.0	5,060	25.6

[a] Percentages may not add to 100% due to rounding.

[b] The studies Canada (34), Greece 2 (29), Mexico 1 (42), Mexico 2 (43), and USA 4 (36) did not collect data on family history of gastric cancer.

[c] The studies Greece 1 (30), Greece 2 (29), and Italy 4 (31) did not collect data on salt intake.

Coffee consumption and gastric cancer

The results from the two-stage analysis including the study-specific and summary pooled ORs for gastric cancer and total coffee drinkers versus never or rare drinkers are shown in **Figure I-1**. Total coffee consumption was not associated with gastric cancer risk (OR: 1.03, 95% CI: 0.94-1.13).

The distribution of cases and controls according to the reported amounts for caffeinated, decaffeinated, and total coffee consumption are presented in **Table I-2**. About 63% of cases and 62% of controls reported consumption of ≥1 cup per day of caffeinated coffee, and about 70% of cases and 68% of controls reported consumption of ≥1 cup per day of total coffee. Compared with never or rare drinkers, the one-staged pooled ORs were 1.20 (95% CI: 0.91-1.58) and 1.01 (95% CI: 0.78-1.31) for ≥7 cups per day of caffeinated and total coffee, respectively.

Table I-2 shows the distribution of gastric cancer cases and controls based on the reported amounts of caffeinated, decaffeinated, and overall coffee intake. About 70% of cases and 68% of controls reported consuming one or more cups of total coffee per day. Approximately 63% of cases and 62% of controls reported consuming one or more cups of caffeinated coffee only per day. The one-stage pooled ORs of gastric cancer for consumption of one or more cups of caffeinated coffee per day ranged from 0.84 to 0.94 and from 0.88-0.96 for total coffee respectively and were non-statistically significant. The OR of gastric cancer for drinking seven cups of caffeinated coffee drinking daily was 1.20 (95% CI: 0.91-1.58) and 1.01 (95% CI: 0.78-1.31) for total coffee, compared with never or rare drinkers. Approximately 15% of gastric cancer cases and 19% of controls reported drinking decaffeinated coffee. Compared to never or rare drinkers, the one-stage pooled ORs were 0.85 (0.69-1.05) for one cup per day, 1.19 (0.89-1.60) for two cups per day, and 1.19 (95% CI: 0.76-1.85) for the consumption of three or more cups of decaffeinated coffee per day.

Figure I-1 Study-specific and summary pooled ORs and 95% CIs of gastric cancer for total coffee drinkers compared with never or rare drinkers. Results include studies that provided locally computed estimates.

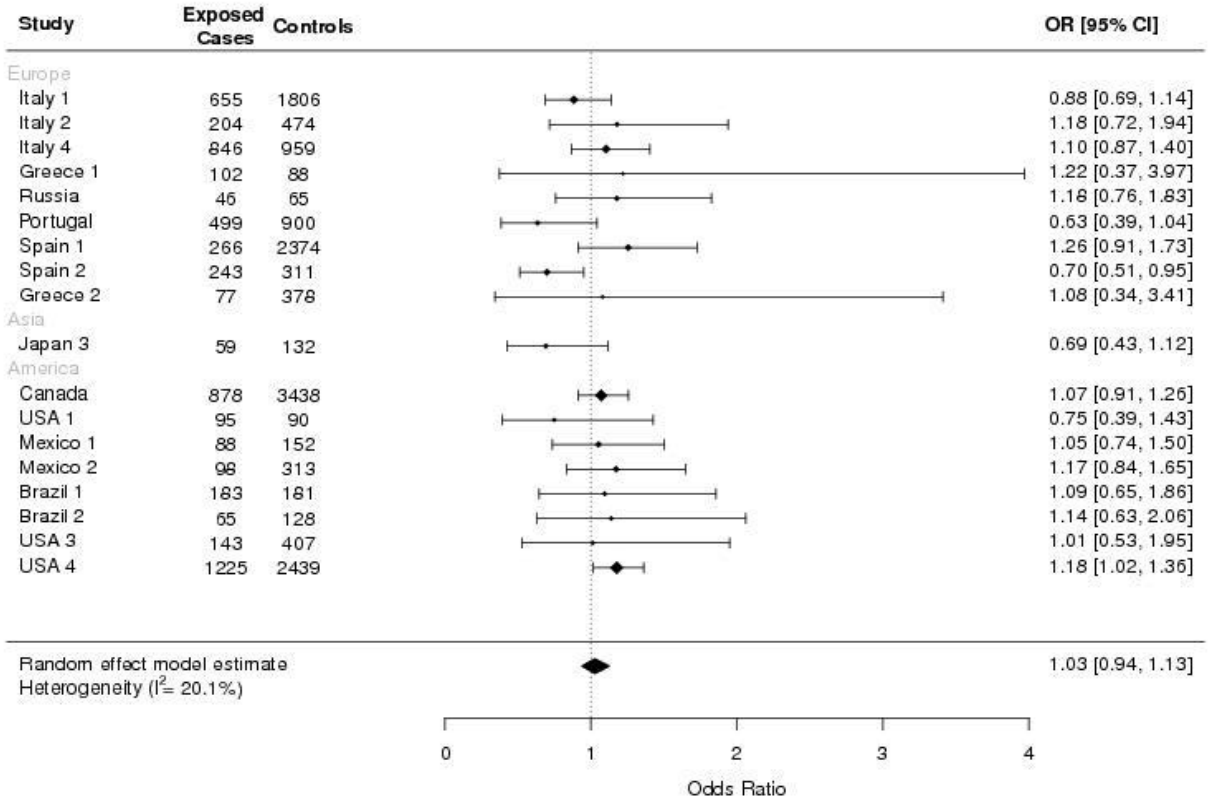


Table I-2 Number and percentage of gastric cancer cases and controls[a] by coffee consumption levels, and pooled ORs and 95% CIs for gastric cancer and coffee consumption. Results do not include studies provided locally computed estimates.

	Cases		Controls		
	N	%	N	%	OR (CI 95%)[b]
Caffeinated coffee	8,006		20,909		
Never or rare	2,726	34.0	6,753	32.3	1 [Reference]
1 cup per day	1,441	18.0	3,752	17.9	0.84 (0.73-0.95)
2 cups per day	1,874	23.4	5,125	24.5	0.91 (0.80-1.04)
3 cups per day	582	7.3	1,345	6.4	0.87 (0.74-1.03)
4 cups per day	608	7.6	1,590	7.6	0.87 (0.71-1.07)
5 cups per day	111	1.4	281	1.3	0.95 (0.72-1.25)
6 cups per day	215	2.7	513	2.5	0.94 (0.68-1.31)
≥7 cups per day	172	2.1	318	1.5	1.20 (0.91-1.58)
Missing values	277	3.5	1,232	5.9	
Decaffeinated coffee[c]	4,006		10,597		
Never or rare	3,274	81.7	8,227	77.6	1 [Reference]
1 cup per day	262	6.5	989	9.3	0.85 (0.69-1.05)
2 cups per day	252	6.3	717	6.8	1.19 (0.89-1.60)
≥3 cups per day	101	2.5	258	2.4	1.19 (0.76-1.85)
Missing values	117	2.9	406	3.8	
Total coffee	8,006		20,909		
Never or rare	2,128	26.6	5,462	26.1	1 [Reference]
1 cup per day	1,615	20.2	3,901	18.7	0.88 (0.77-1.01)
2 cups per day	2,112	26.4	5,673	27.1	0.94 (0.82-1.08)
3 cups per day	629	7.9	1,433	6.9	0.96 (0.81-1.13)
4 cups per day	698	8.7	1,811	8.7	0.93 (0.76-1.14)
5 cups per day	121	1.5	353	1.7	0.96 (0.74-1.25)
6 cups per day	223	2.8	568	2.7	0.88 (0.64-1.20)
≥7 cups per day	195	2.4	430	2.1	1.01 (0.78-1.31)
Missing values	285	3.6	1,278	6.1	

[a] Percentages may not add to 100% due to rounding.

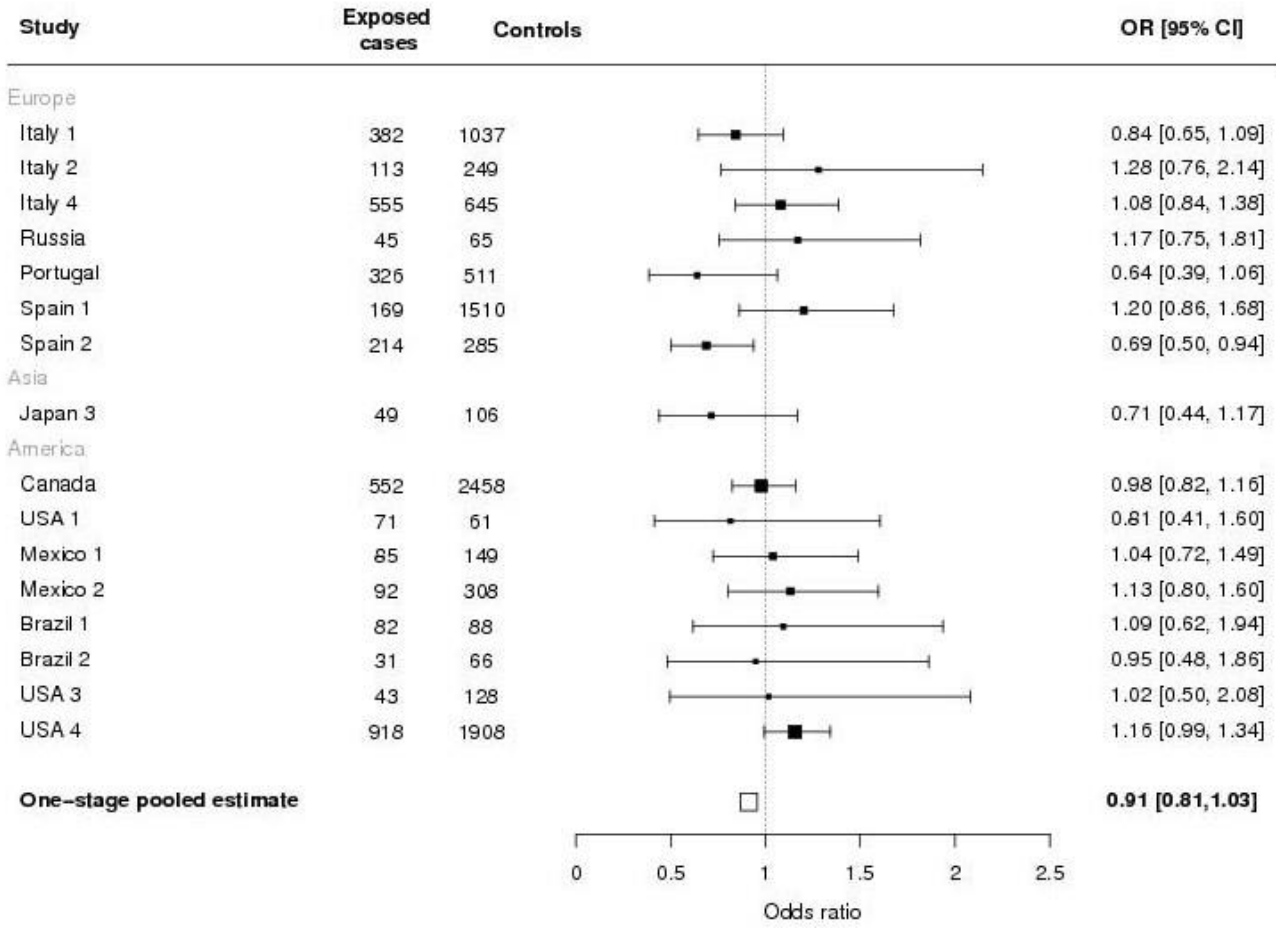
[b] One-stage pooled ORs estimated by a mixed-effects model and adjusted for sex, age category, social class, smoking status, salt intake, fruit intake and vegetable, alcohol intake, and family history of gastric cancer.

[c] Information on decaffeinated coffee consumption was available for the studies Italy 1 (32), Italy 2 (33), Russia (35), Spain 1 (40), Spain 2 (41), USA 1 (38), and USA 4 (36).

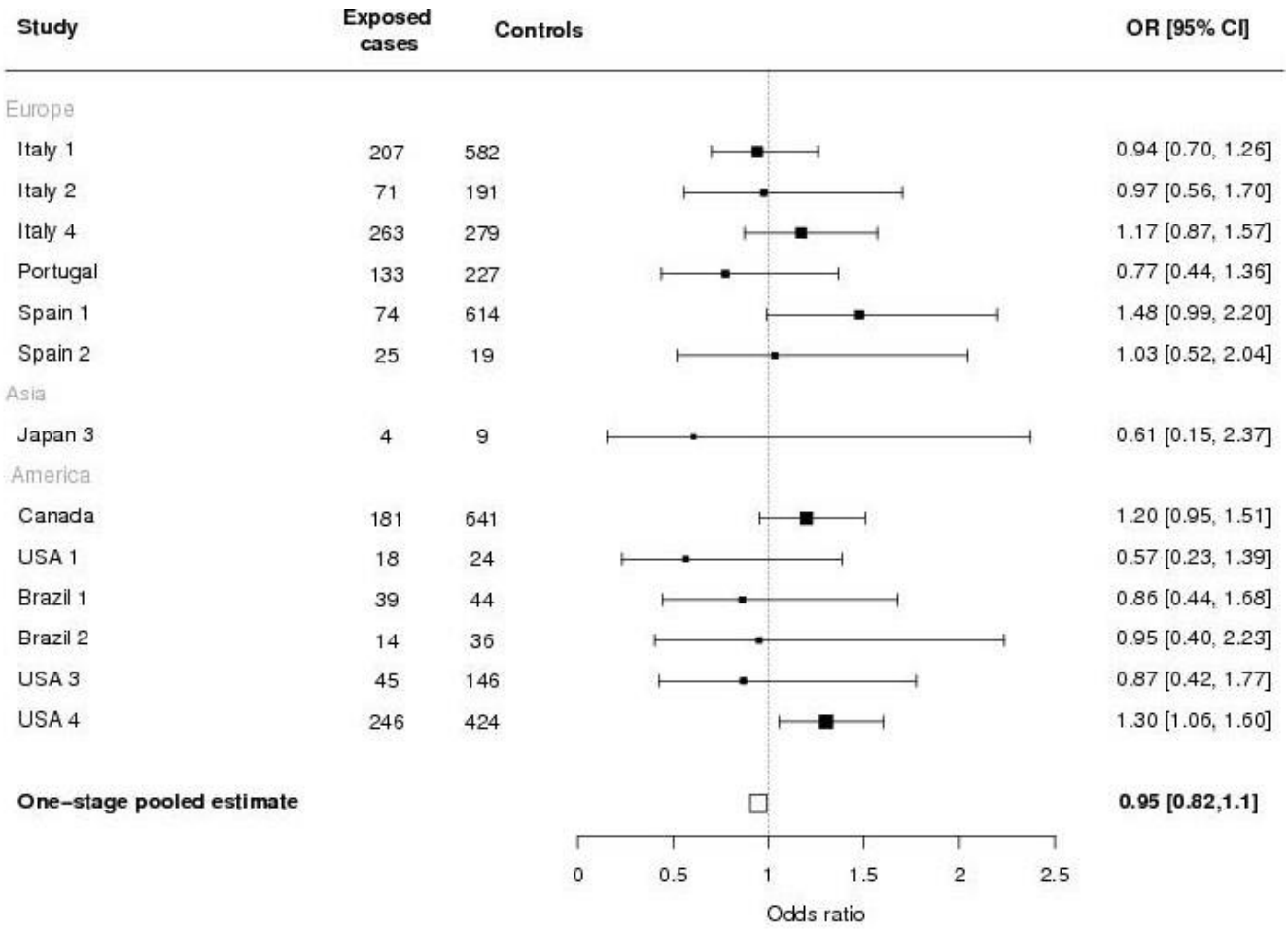
The forest plots of the adjusted pooled ORs, as well as the study-specific ORs, for gastric cancer according to categories of consumption of total coffee are shown in panels a, b, and c of **Figure I-2**. Compared with never or rare coffee drinkers, no association was found between categories of total coffee drinking and gastric cancer. The adjusted pooled OR estimates were 0.91 (95% CI: 0.81-1.03) for total coffee drinkers of 1-2 cups per day (**Panel a**), 0.95 (95% CI: 0.82-1.10) for total coffee drinkers of 3-4 cups per day (**Panel b**), and 0.95 (95% CI: 0.79-1.15) for total coffee drinkers of 5 or more cups per day (**Panel c**).

Figure I-2 Study-specific and one-stage pooled ORs and corresponding 95% CIs of gastric cancer for total coffee drinkers of 1-2 cups per day (a), 3-4 cups per day (b) and ≥5 cups per day (c) compared with never or rare drinkers. Results do not include studies provided locally computed estimates.

(a) Total coffee drinkers of 1-2 cups per day

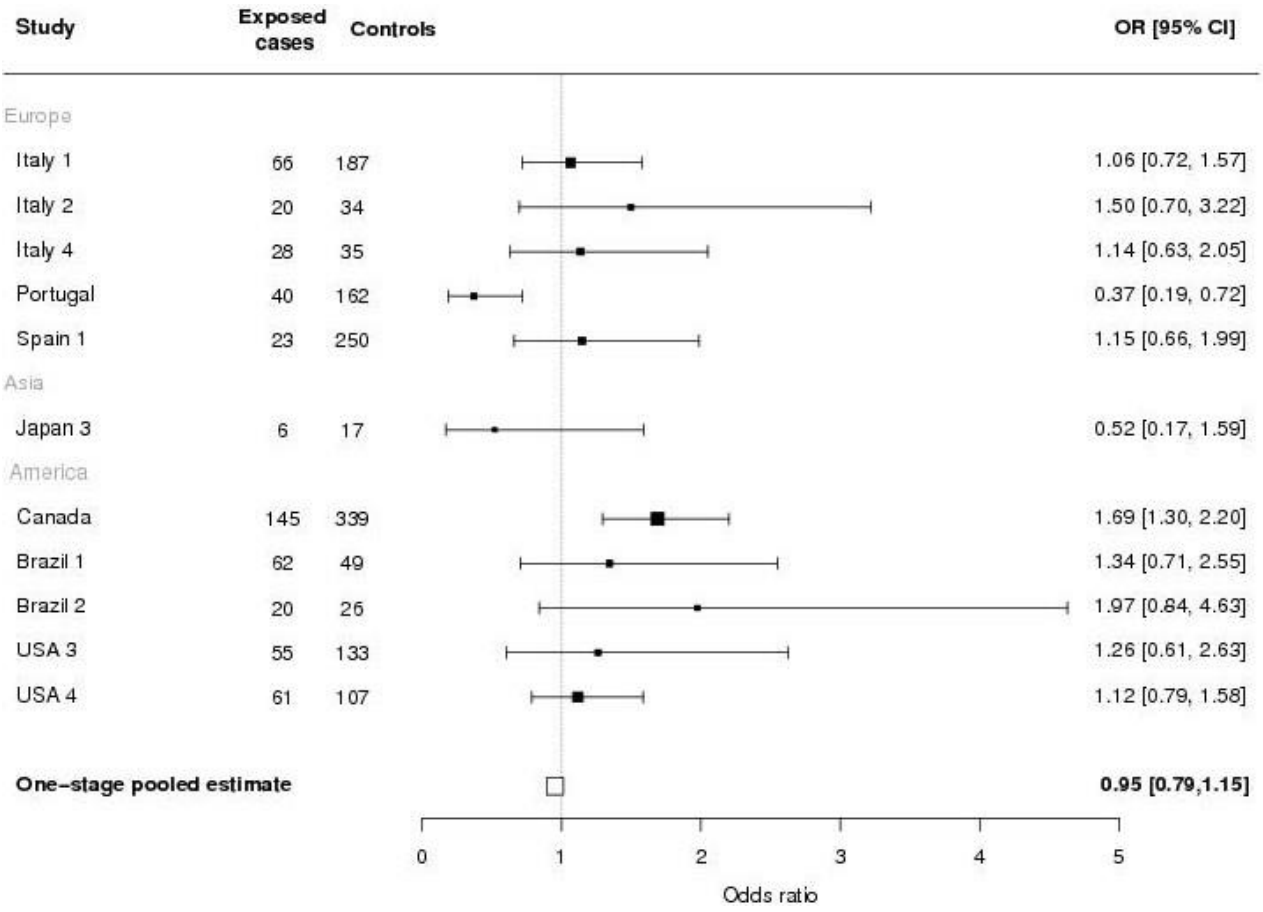


(b) Total coffee drinkers of 3-4 cups per day†



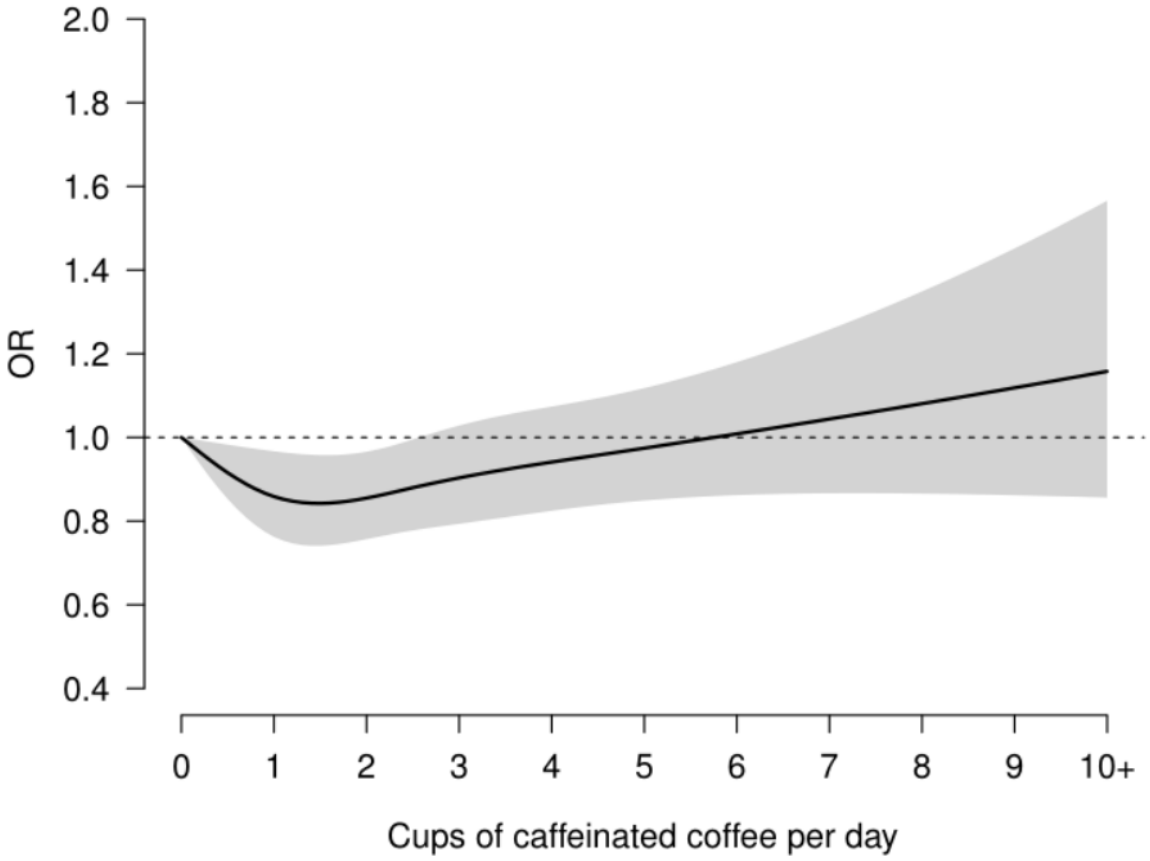
†Studies with more than five subjects in exposed cases or controls are shown.

(c) Total coffee drinkers of ≥5 cups per day†



†Studies with more than five subjects in exposed cases or controls are shown.

Figure I-3 Dose-response relationship between caffeinated coffee consumption and gastric cancer.



The results from the stratified analysis by categories of total coffee consumption are presented in **Table I-3** and **Figure I-4**. No heterogeneity was apparent for strata of sex, age, socioeconomic status, alcohol drinking, salt intake, family history of gastric cancer, *H. pylori* infection, type of controls and cancer histological type. Heterogeneity was significant in strata of geographical area ($Q=7.00$, $p<0.01$), smoking levels ($Q= 4.83$, $p=0.03$), fruit and vegetable intake ($Q=5.58$, $p=0.02$), and subsite of gastric cancer ($Q=12.60$, $p<0.001$). The stratified analysis showed a significant positive association between gastric cardia cancer (OR 1.61, 95% CI: 1.27-2.05) and consumption of ≥5 cups/day of total coffee. No association was found for non-cardia gastric cancer (OR 0.93, 95% CI: 0.77-1.12)

Table I-3 Pooled ORs and 95% CIs of gastric cancer by caffeinated coffee consumption levels and sex, age, and other main risk factors of gastric cancer.

	Never/Rare	1-2 cups of caffeinated coffee per day			3-4 cups of caffeinated coffee per day			≥5 cups of caffeinated coffee per day		
	Ca; Co	Ca; Co	OR[a] (95% CI)	Q (p)[b]	Ca; Co	OR[a] (95% CI)	Q (p)[b]	Ca; Co	OR[a] (95% CI)	Q (p)[b]
Overall	2726; 6753	3315; 8877			1190; 2935			498; 1112		
Sex				1.60 (0.21)			3.5 (0.06)			0.54 (0.46)
Men	1273; 2993	2492; 5567	0.97 (0.83-1.14)		964; 1972	1.04 (0.86-1.26)		406; 890	1.00 (0.79-1.25)	
Women	855; 2469	1235; 4007	0.83 (0.69-1.00)		363; 1272	0.77 (0.60-0.98)		133; 461	0.86 (0.62-1.20)	
Age				0.62 (0.43)			1.29 (0.26)			0.01 (0.91)
<65 years	945; 2856	1479; 4536	0.96 (0.81-1.13)		719; 1930	0.99 (0.81-1.21)		326; 871	0.93 (0.74-1.19)	
≥65 years	1183; 2605	2248; 5032	0.87 (0.73-1.03)		608; 1313	0.83 (0.66-1.04)		213; 478	0.91 (0.67-1.23)	
Socioeconomic status				4.44 (0.04)			0.58 (0.44)			2.59 (0.11)
Low	820; 1724	1844; 3564	0.83 (0.71-0.98)		644; 1166	0.91 (0.74-1.12)		206; 443	0.81 (0.61-1.07)	
Intermedia	875; 2188	1165; 3427	0.92 (0.74-1.13)		443; 1141	0.96 (0.74-1.25)		222; 526	1.05 (0.78-1.43)	
High	376; 1147	636; 2454	1.25 (0.88-1.79)		225; 908	1.08 (0.73-1.61)		107; 366	1.20 (0.75-1.92)	
Geographic area				1.70 (0.19)			0.72 (0.40)			7.00 (<0.01)
Europe	990; 1908	1804; 4302	0.89 (0.77-1.02)		774; 1912	0.97 (0.82-1.15)		181; 675	0.81 (0.64-1.03)	
Asia	91; 168	49; 106	0.72 (0.44-1.18)		4; 9	0.66 (0.17-2.59)		6; 17	0.44 (0.15-1.32)	
America	1047; 3386	1874; 5166	1.04 (0.77-1.40)		549; 1323	0.85 (0.60-1.21)		352; 659	1.32 (0.93-1.89)	
Smoking status				1.66 (0.20)			1.81 (0.18)			4.83 (0.03)
Never smokers	1012; 2931	1423; 4029	0.85 (0.73-1.01)		323; 942	0.85 (0.68-1.06)		91; 302	0.73 (0.53-1.02)	

Former smokers	649; 1507	1410; 3513	1.03 (0.80-1.31)		487; 1180	1.09 (0.81-1.45)		201; 465	1.21 (0.86-1.71)	
Current smokers	385; 891	729; 1794	0.92 (0.70-1.21)		457; 1043	0.98 (0.72-1.33)		200; 546	1.05 (0.74-1.48)	
Alcohol drinking				0.83 (0.36)			5.57 (0.02)			2.10 (0.15)
< 1 drink/day	1276; 3803	1933; 5755	0.89 (0.76-1.05)		593; 1759	0.87 (0.71-1.06)		296; 745	0.99 (0.77-1.27)	
1-3 drinks/day	453; 890	1222; 2564	0.87 (0.68-1.11)		478; 939	0.85 (0.63-1.15)		126; 307	0.76 (0.51-1.13)	
≥ 4 drinks/day	336; 497	477; 853	1.02 (0.77-1.35)		222; 392	1.36 (0.97-1.90)		86; 218	1.15 (0.76-1.74)	
Fruit and vegetable intake				1.19 (0.27)			0.17 (0.68)			5.58 (0.02)
Low	624; 1615	1231; 2830	0.82 (0.65-1.04)		460; 955	0.90 (0.68-1.19)		159; 448	0.69 (0.47-0.99)	
Intermediate	667; 1172	1265; 3270	0.90 (0.73-1.11)		433; 1129	0.92 (0.71-1.20)		163; 427	0.94 (0.67-1.31)	
High	833; 2028	1203; 3342	0.97 (0.80-1.18)		430; 1108	0.97 (0.76-1.25)		217; 448	1.22 (0.92-1.63)	
Salt intake[c]				0.46 (0.50)			1.29 (0.26)			1.05 (0.31)
Low	792; 2220	1318; 3420	0.94 (0.79-1.13)		395; 1117	0.86 (0.69-1.08)		202; 530	0.96 (0.73-1.26)	
Intermediate	712; 1752	992; 2996	0.87 (0.71-1.08)		353; 1010	0.93 (0.72-1.21)		136; 382	1.04 (0.75-1.46)	
High	450; 1278	860; 2500	0.86 (0.66-1.12)		316; 831	1.08 (0.78-1.49)		170; 398	0.79 (0.52-1.21)	
Family history of gastric cancer[d]				0.08 (0.78)			0.17 (0.68)			0.76 (0.38)
No	849; 1914	1349; 3746	0.94 (0.83-1.07)		576; 1744	0.95 (0.81-1.12)		259; 726	1.00 (0.82-1.23)	
Yes	191; 196	320; 325	0.89 (0.62-1.27)		151; 158	1.05 (0.67-1.64)		44; 41	1.32 (0.73-2.42)	
H. pylori infection[e]				0.07 (0.79)			0.69 (0.41)			0.08 (0.77)
No	263; 434	129; 302	0.92 (0.66-1.29)		27; 103	0.69 (0.38-1.24)		28; 61	0.84 (0.46-1.55)	
Yes	469; 980	515; 1546	0.97 (0.80-1.17)		174; 556	0.91 (0.70-1.19)		108; 307	0.76 (0.56-1.03)	

Type of controls				0.68 (0.41)			0.93 (0.33)			1.64 (0.20)
Hospital-based	885; 1341	987; 1957	0.90 (0.78-1.04)		379; 905	0.92 (0.76-1.10)		184; 325	1.14 (0.90-1.44)	
Population-based	1243; 4121	2740; 7617	1.01 (0.80-1.28)		948; 2339	1.08 (0.83-1.42)		355; 1026	0.88 (0.64-1.22)	
Subsite[f]				0.93 (0.34)			4.33 (0.04)			
Cardia	365; 5462	721; 9574	1.09 (0.94-1.26)		260; 3244	1.38 (1.15-1.67)		124; 1351	1.61 (1.27-2.05)	12.6 (<0.001)
Non-Cardia	1035; 5462	1859; 9574	1.00 (0.91-1.10)		650; 3244	1.09 (0.96-1.25)		217; 1351	0.93 (0.77-1.12)	
Histotype[g]				0.03 (0.87)			0.34 (0.56)			0.00 (1.00)
Intestinal	474; 5462	832; 9574	0.93 (0.79-1.10)		302; 3244	1.04 (0.84-1.28)		92; 1351	0.83 (0.62-1.12)	
Diffuse	362; 5462	447; 9574	0.91 (0.74-1.12)		157; 3244	0.94 (0.72 -1.21)		67; 1351	0.83 (0.59-1.18)	

[a] One-stage pooled ORs were estimated using mixed effect models adjusted, where available and feasible, for sex, age category, social class, smoking status, salt intake, fruit and vegetable intake, alcohol intake and family history of gastric cancer.

[b] p values for test of OR heterogeneity across strata.

[c] The study Italy 4 (31) did report data on salt intake.

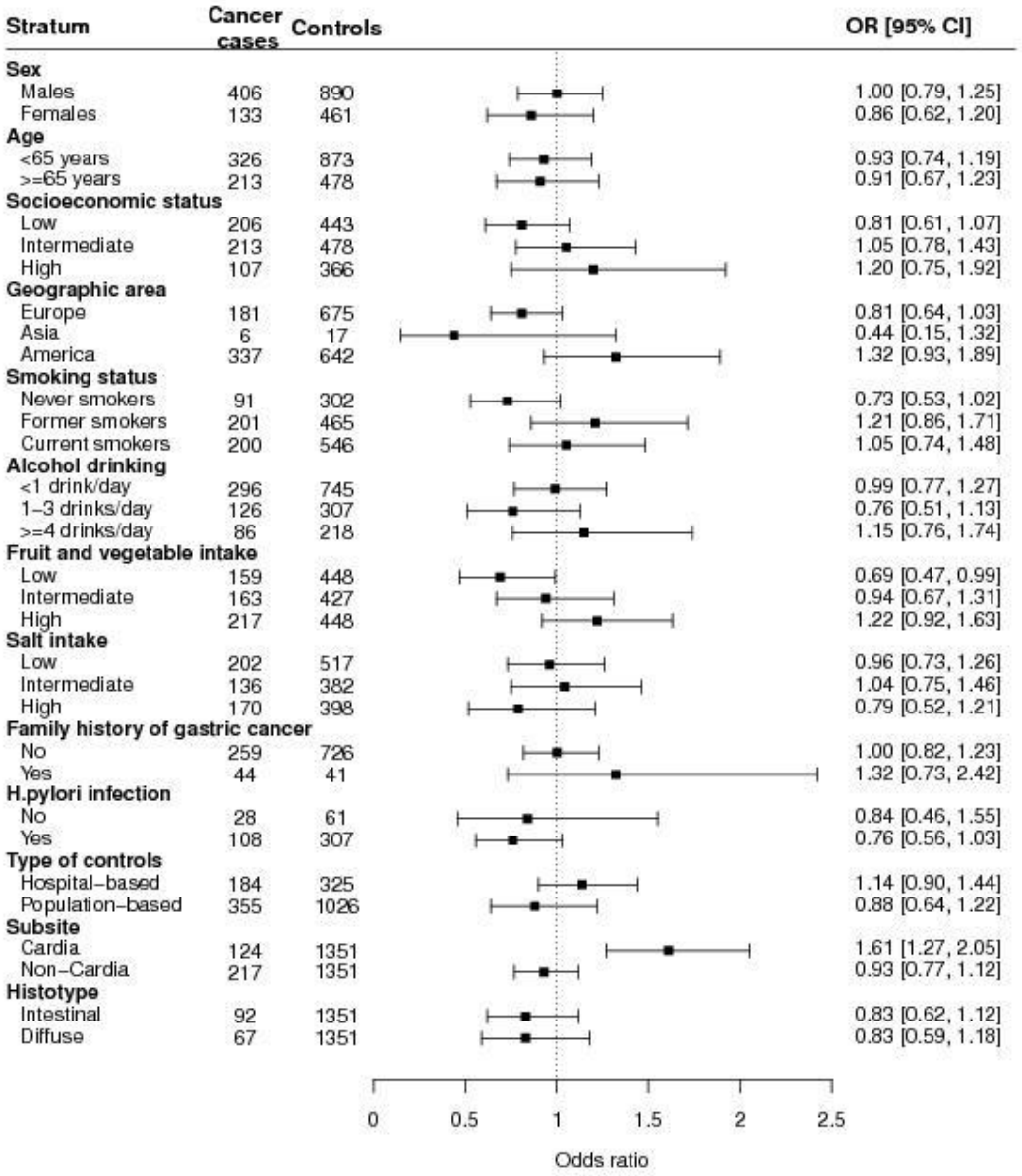
[d] The studies Canada (34), Mexico 1 (42), Mexico 2 (43) and USA 4 (36) did not collect data on family history of gastric cancer.

[e] The studies Italy 1 (32), Italy 2 (33), Italy 4 (31), Canada (34), USA 1 (38), Mexico 2 (43), USA 3 (37), and USA 4 (36) did not collect data on H. pylori infection. The study Spain 2 (41) was not included because no information on *H. pylori* infection was available for controls.

[f] The studies Mexico 2 (43) and USA 3 (37) did not collect data on cancer subsite.

[g] The studies Italy 1 (32), Mexico 2 (43), Japan 3 (46) and USA 3 (37) did not collect data on histological type. Ca: Cases, Co: Control

Figure I-4 Pooled ORs and 95% CIs of gastric cancer for high total coffee consumption (≥5 cups per day) compared to never or rare coffee consumption by strata of selected risk factors of gastric cancer.



Discussion

The current study (51) found no significant relationship between caffeinated, decaffeinated, or total coffee consumption and gastric cancer. For low (1-2 cups per day) to moderate (3-4 cups per day) consumption of total coffee, there was only little evidence of an inverse non-significant association, but the highest level of consumption of total coffee (5 or more cups per day) was associated with a non-significant 20% increased risk of gastric cancer.

The above findings are consistent with previous published research. Meta-analyses of case-control studies or cohort studies suggested similar results (52-56). A meta-analysis of 14 case-control studies by Poorolajal et al in 2020 (55) reported no association between coffee drinking and gastric cancer (OR: 0.99, 95% CI: 0.88-1.11). Other meta-analyses between thirteen and fifteen prospective cohort studies suggested that a highest level of coffee consumption did not significantly associated with increased risk of gastric cancer (RR ranged between 1.13-1.18) (53, 56). Similarly, a systematic review and meta-analysis of nine cohort studies including 3,027 gastric cancer cases among 1,250,825 participants found a pooled HR of 1.05 (95% CI: 0.88-1.25) of gastric cancer for frequent coffee consumption versus infrequent consumption (54). Although the highest levels of consumption varied significantly across the studies included (from two to more than seven cups per day), a few meta-analyses that compared the highest and lowest levels of consumption discovered an association of a higher risk ranging from 1.16 to 1.24 (25, 57).

In the current analysis, a significant association between high coffee drinking and gastric cancer was only found. There are not many studies that have investigated the relationship between coffee consumption and gastric cardia cancer or gastric non-cardia cancer in the literature. High coffee drinking has been related in some studies to a 23–50% higher risk of developing cardia cancer (54, 57). Caffeine consumption has been suggested to stimulate gastric acid secretion (58, 59) and increase the risk of gastroesophageal reflux symptoms, such as heartburn and regurgitation (60), which are both related to increased cardia cancer risk (61).

The studies from America showed a non-significant 32% increase in risk, whereas studies from Europe revealed a 19% decrease in risk. The variation in the estimate of the effect's direction may be due to residual confounding as well as differences in the quantity and quality of coffee drunk in America and Europe (53). Depending on coffee consumption, the types of coffee, the amount of caffeine, the preparation, and the brewing techniques vary by geographic region. I was unable to take

these differences into account because the majority of the included studies missed such data. Additionally, there were differences in the approach adopted by the studies to quantify coffee consumption, including the quantity or frequency of cups consumed per day as well as the size of the cups.

Gastric cancer patients have higher rates of gastrointestinal issues like gastritis and it is frequently recommended for them to avoid or drink less coffee. Because of this, participants at risk of gastric cancer may have reduced the amount of their coffee intake before the disease occurred. This might assist in partially explaining the small inverse association between low and moderate intake because case-control studies only collect information a short time before the diagnosis. The one cohort study (36) that was considered in the analysis of coffee consumption showed that, in fact, the risk rose rather than decreased at lower consumption levels. The comparability of results between population- and hospital-based controls strengthens the validity of these findings.

Strengths and limitations

The current study is among the largest studies exploring the relationship between coffee consumption and gastric cancer. The analysis was based on a large sample size of fourteen case-control and two nested case-control cohort studies conducted worldwide. Information on the type of coffee consumed, caffeinated and decaffeinated, and a large number of risk factors of gastric cancer as confounders such as tobacco smoking, alcohol consumption, socioeconomic status, family history of gastric cancer, salt intake, and fruit and vegetable intake, were included. However, given that smoking is related to gastric cancer and that people who consume a lot of coffee are more likely to smoke, there may still be some residual confounding from smoking (17). All covariates were centrally-harmonized during the collection of the original datasets so as to not differ among the studies included. Also, separate analyses for gastric cardia cancer and non-cardia cancer, as well as by cancer histological type were performed.

However, heterogeneity may have been introduced by different types of coffee (e.g. instant coffee) containing different levels of compounds consumed among the studied populations. Most information on specific types of coffee or brewing method was not available. The variation in coffee cup sizes was not provided by most of the studies, which vary from country to country. I did not estimate the association between gastric cancer and the duration of coffee consumption because most studies did not provide this information.

In conclusion, based on a large pool of epidemiological studies conducted worldwide, not significant evidence of an association between coffee consumption and gastric cancer was found. An increased risk of gastric cardia cancer was only suggested among those consuming high amounts of coffee i.e. five or more cups of coffee per day (51).

❖

From the published paper: Martimianaki G, Alicandro G, Pelucchi C, Bonzi R, Rota M, Hu J, et al. Tea consumption and gastric cancer: a pooled analysis from the Stomach cancer Pooling (StoP) Project consortium. Br J Cancer. 2022 May 24. doi: 10.1038/s41416-022-01856-w. Epub ahead of print. PMID: 35610368 .

Chapter II. Tea consumption and gastric cancer: a pooled analysis from the Stomach cancer Pooling (StoP) Project consortium

Introduction

With global consumption of 6.3 billion kg in 2020 and a rise of 17.4% by 2025, tea is the second most popular beverage drunk worldwide after water (62). Tea is produced from the dried leaves of the Camellia sinensis plant. Tea is classified into several types such as green tea, black tea, oolong tea, and white tea, based on the degree of fermentation of the plant leaves. Black tea is the most popular variety of tea in Western nations and it gets its color and stronger flavor from the long fermentation of the leaves after they have been rolled and exposed to air to induce the oxidation process (63, 64).

Green tea is primarily consumed in East Asia and it has not gone through the same oxidation process as black tea or the partial fermentation procedure required to make oolong tea. Catechins, a type of flavonoid found in green tea leaves, are much more abundant than those found in black or other types of tea. The main four catechin types are epigallocatechin-3-gallate (EGCG), epigallocatechin, epicatechin-3-gallate (ECG), and epicatechin. The major catechin in green tea, accounting for more than 40% of it, is EGCG, which has been researched for its anti-inflammatory and anti-cancer effects. Depending on the preparation techniques, the amount of catechins in a typical cup of brewed green tea (250 mL) can range from 50 to 100 mg (63, 64). In vitro and in vivo studies suggested that EGCG catechins have anti-inflammatory properties that may help prevent chronic diseases like diabetes, heart disease, and some types of cancer. According to clinical research, EGCG therapies can inhibit the growth of tumors in a variety of organ sites, including the stomach (65).

Studies on the relationship between drinking tea and gastric cancer, however, found mixed results (66-76). Recent meta-analyses with data from cohort and case-control studies suggested insufficient evidence to indicate a relevant relationship between tea consumption and risk of gastric cancer (77-79). In addition, few investigations on tea and the anatomical region or histological type of cancer have been conducted (78, 80). The World Cancer Research Fund and American Institute for Cancer Research (WCRF/AICR) reported that there is not enough evidence to conclude that tea drinking may have a protective effect against gastric cancer (26). To better determine whether tea drinking is related to an increased risk of gastric cancer an individual participant pooled analysis of

studies participated in the global consortium of the Stomach cancer Pooling (StoP) Project was conducted.

Methods

Study population

This analysis is based on the third release (version 3.2) of the StoP project (10) which contained 34 case-control studies or nested case-control studies (cohort), including 12,753 cases of gastric cancer and 30,682 controls. The original data set and food frequency questionnaires (FFQ) of each study were searched for any information on tea, including total tea, green tea, black tea, and/or other types of tea. Finally, twenty-two studies were selected with information on tea intake, including 9,438 gastric cancer cases and 20,451 controls. Among these studies were from two from Greece (29, 30), three from Italy (31-33), one from Canada (34), one from Russia (35), one from Portugal (39), three from the USA (36-38), one from Spain (41), one from Japan (46), one from Mexico (42), three from Brazil (44, 45, 81), one from Iran (82), and four studies from China (66, 83-85). Studies more than 60% of missing values for tea intake such as one from Italy (27) were excluded from the analysis.

Assessment of tea intake

Participants through self-administered or interviewer-administered FFQs reported whether they drink or not tea, the frequency and the amount of tea consumed, the drinking temperature, the strength of flavor of the tea, and if they consumed various types of tea, where available (Supplemental Table II-2). The standard unit of tea consumption was defined as cups per day by considering the number of cups or times reported by each study. When tea consumption was reported in frequency categories (e.g. 1-2 times per week), the amount consumed into cups per day by taking the average number of teacups or times and dividing it by the average number of days stated in the corresponding frequency category, was calculated. If different types of tea were reported in the same study, they were considered together as total tea intake.

Total tea consumption was defined as non-regular tea drinkers versus regular drinkers. Non-regular drinkers were assigned those who reported zero tea consumption (such as two studies in Italy (31, 32), four studies in China (66, 83-85), one study in Canada (86), Russia (35), Portugal (39), Mexico (42), and Brazil (81), and two studies in the USA (36, 37)) or irregular consumption (< 1 cup per day) (such as one study in Italy (33), USA (38), and Spain (41), and two studies in Brazil (44, 45)

and Greece (29, 30)). Regular tea drinkers were assigned as those who reported the consumption of one or more cups of tea per day. Non-regular drinkers were defined in studies from Iran (82) and Japan (46) as those who consumed less than three and two cups per day, respectively, based on the minimum value of the corresponding teacup distribution. In addition, intake of tea was classified into levels of consumption in two ways. The first variable included the following categories based on the amount consumed: non-regular drinkers (0 or less than 1 cup per day), 1 to less than 2 cups per day, 2 to less than 3 cups per day, and 3 or more cups per day. The second variable was classified by study-specific criteria according to the distribution of tea consumption in each study and was grouped into the following three categories: non-regular tea drinkers (including non-drinkers), low, moderate, and high tea consumption (**Supplemental Table 3**). Six studies reported information on tea drinking temperature, which was grouped as non-tea drinkers, cold or warm, and hot or very hot, while the information "how strong tea was" was assessed by four studies, and the corresponding variables were classified into three categories: non-tea drinkers, regular, and strong or very strong tea (**Supplemental Table II-1**).

Statistical analysis

The number and proportion of gastric cancer cases and controls was calculated by age, sex, socioeconomic status (low, intermediate, high), tobacco smoking (never smoker, former smoker, current smoker low, current smoker intermediate; current smoker high), alcohol drinking (≤ 1 drink per day, 1-3 drinks per day, ≥ 4 drinks per day, where 1 drink equals to 12 g of alcohol), history of gastric cancer in first degree relatives (yes, no), total fruit and vegetables intake (study-specific low, intermediate, high), and salt intake (study-specific low, intermediate and high, respectively).

The relationship between regular tea drinking versus non-regular drinking and gastric cancer was estimated by both a two-stage and a one-stage modeling analysis. A two-stage meta-analysis was performed to also include studies that provided locally computed estimates, like one study from Greece (29). In the first stage of the meta-analysis, multivariable conditional or unconditional logistic regression models for each study were estimated to calculate the odds ratios (ORs) and the 95% confidence intervals (CIs) of gastric cancer between regular tea drinkers and non-regular tea drinkers. In the second stage, the study-specific effect estimates were pooled together and through a random-effects model, the summary (pooled) OR was calculated (87). The I^2 statistic was used to measure the heterogeneity between studies in the two-stage analysis (88). The two-stage analysis was conducted in R 3.6.3 (R Core Team, 2021) using the "metaphor" package.

The relationship between levels of tea drinking and gastric cancer was calculated by one-stage analysis by pooling the data of twenty-one studies together. One study from Greece (29) was excluded because provided only locally computed estimates. To estimate the pooled ORs and the corresponding 95% CIs of gastric cancer across the categories of tea-drinking generalized linear mixed-effects models with a logistic link function and a random intercept for each study were used. The analysis was done using the GLMER procedure in R 3.6.3. (R Core Team, 2021) and the "lme4" library. By considering the tea levels variable as ordinal in the models the p values for trends and determined the significance of linear trends across the levels of tea intake were estimated. Furthermore, using a one-stage linear random-effects model with three knots at set percentiles of the distribution of tea intake (50th, 75th, and 90th), the dose-response relationship between the continuous variable of teacups and gastric cancer was calculated (50). The dose-relationship was computed in R 3.6.3 (R Core Team, 2021) with the "splines" package.

The one-stage analysis was also used to assess the relationship between tea drinking and gastric cancer across strata of selected variables. The effects of tea consumption, regular versus non-regular tea drinkers, were estimated across strata of geographic areas (Europe, America, Asia) salt (low, intermediate, high), family history of gastric cancer (no, yes), *H. pylori* infection (no, yes as determined by serology), type of controls (hospital-based, population-based), and study design (CC studies, NCC studies). Since green tea is the most popular type of tea in China and Japan, these studies were also examined separately. In order to estimate the ORs for each anatomical site (cardia and non-cardia) and histological type (intestinal, diffuse, and mixed/unspecified by Lauren categorization) of gastric cancer I used multinomial mixed-effects models and the GLIMMIX procedure in SAS 9.4 (SAS Institute Inc, Cary, NC). The Cochran's Q test evaluated the heterogeneity between strata effect estimates.

In both two- and one-stage analyses, the reference category was non-regular drinker and all models were adjusted for gender, age groups of five years (40, 40-44, 45-54, 55-64, 65-70, 70-74, and ≥75 years), socioeconomic status (study-specific low, intermediate, high), alcohol consumption (study-specific never, low, intermediate, high), family history of gastric cancer (no, yes), salt intake (study-specific low, intermediate, high), and intake of fruit and vegetables (study-specific low, intermediate, high). Missing values in the study-specific confounders were either included in the models as a separate category or by included in the lower categories of the variables when the proportion of missing was less than one percent. For sensitivity analysis the studies from Iran 1 (82) and Japan (46) were excluded to prevent for misclassification bias.

Results

Study participants

The number and percentage of gastric cancer cases and controls by sociodemographic and other lifestyle characteristics of participants are presented in **Table II-1**. About 40%, 18% and 42% of the cases were from European, Asian, and American studies, while about 34%, 14% and 52% of controls were from European, Asian and American studies, respectively. Cases were more than controls in terms of men (66.1% versus 59.6 %), age of 65 or older (52.8% versus 45.4%), lower socioeconomic class (50.6% versus 37.3%). Additionally, they were more likely to be heavy drinkers (15.0% versus 11.2%), high current smokers (8.2% versus 6.7%), and have a family history of gastric cancer (18.4% versus 8.3%).

Table II-1 Number and percentage of gastric cancer cases and controls† by socioeconomic and lifestyle characteristics of participants.

	Cases		Controls	
	N	%	N	%
Total	9,438	100.0	20,451	100.0
Study center				
Europe	3,750	39.7	7,030	34.4
Greece 1 (30)	110	1.2	100	0.5
Greece 2 (29)	82	0.9	410	2
Italy 1 (32)	769	8.1	2,081	10.2
Italy 2 (31)	230	2.4	547	2.7
Italy 4 (33)	1,016	10.8	1,159	5.7
Portugal (39)	692	7.3	1,667	8.2
Russia (35)	450	4.8	611	3
Spain 2 (41)	401	4.2	455	2.2
Asia	1,686	17.9	2,789	13.6
China 1 (66)	266	2.8	533	2.6
China 2 (83)	206	2.2	415	2
China 3 (84)	711	7.5	711	3.5
China 4 (85)	133	1.4	433	2.1
Iran 1 (82)	217	2.3	394	1.9
Japan 3 (46)	153	1.6	303	1.5
Americas	4,002	42.4	10,632	52.0
Brazil 1 (45)	226	2.4	226	1.1
Brazil 2 (44)	93	1	186	0.9
Brazil 3 (81)	368	3.9	738	3.6
Canada (34)	1,182	12.5	5,039	24.6
Mexico 1 (42)	248	2.6	478	2.3
USA 1 (36)	132	1.4	132	0.6
USA 3 (89)	170	1.8	502	2.5
USA 4 (37)	1,583	16.8	3,331	16.3

Sex	6,243	66.1	12,185	59.6
Men				
Women	3,195	33.9	8,266	40.4
Age				
<40	312	3.3	1,600	7.8
40-44	314	3.3	1,212	5.9
45-49	542	5.7	1,521	7.4
50-54	754	8.0	1,781	8.7
55-59	1,083	11.5	2,214	10.8
60-64	1,450	15.4	2,828	13.8
65-69	1,846	19.6	3,532	17.3
70-74	1,902	20.1	3,408	16.7
≥75	1,235	13.1	2,342	11.5
Socioeconomic status (study-specific)				
Low	4,704	50.6	7,529	37.3
Intermediate	3,107	33.4	7,451	36.9
High	1,478	15.9	5,215	25.8
Tobacco smoking				
Never	3,736	41.2	9,033	45.3
Former	3,100	34.2	6,372	32.0
Current				
Low	547	6.0	1,364	6.8
Intermediate	929	10.3	1,812	9.1
High	744	8.2	1,344	6.7
Alcohol drinking (g/day)[a]				
Never	2,602	31.3	5,997	32.5
<1 drink/day	2,075	25.0	5,964	32.4
1-3 drinks/day	2,387	28.7	4,388	23.8
≥4 drinks/day	1,249	15.0	2,069	11.2
Vegetable and fruit intake (study-specific tertiles)[b]				
Low	2,862	31.1	5,829	29.3
Intermediate	3,087	33.6	6,784	34.2
High	3,250	35.3	7,248	36.5
Salt intake (study-specific tertiles)[c]				
Low	2,957	40.4	7,202	41.7
Intermediate	2.529	34.6	5,675	32.8
High	1,830	25.0	4,413	25.5
Family history of gastric cancer[d]				
No	3,541	81.6	7,220	91.6
Yes	800	18.4	658	8.3
H. pylori infection[e]				
No	754	33.3	1361	31.9
Yes	1,511	66.7	2,900	68.1
Type of controls[f]				
Hospital-based	3,198	33.9	5,912	28.9
Population-based	6,240	66.1	14,539	71.1
Study design[g]				
Case-control	7,773	82.4	16,710	81.7
Nested case-control	1,665	17.6	3,741	18.3
Subsite[h]				
Cardia	1,607	28.4	20,451	100.0
Non-cardia	4,057	71.6	20,451	100.0
Histological type[i]				

Intestinal	1,897	29.3	20,451	100.0
Diffuse	1,218	18.8	20,451	100.0
Mixed/unspecified	3,368	51.9	20,451	100.0

† For some variables, the sum does not add to the total because of missing values in age (13 controls), social class (149 cases, 256 controls), tobacco smoking (382 cases, 526 controls), alcohol drinking (281 cases, 889 controls), family history of gastric cancer (1025 controls, 2071 cases), vegetable and fruit intake (106 cases, 157 controls) and salt intake (203 cases, 781 controls), or because the variables were not available for some studies.

a The studies China 3 (84) and China 4 (85) did not collect data on alcohol drinking.

b The study China 4 (85) did not collect data on vegetable and fruit intake.

c The studies Greece 1 (30), Greece 2 (29), China 3 (84), and Italy 4 (33) did not collect data on salt intake.

d The studies China 1 (66), Canada (34), China 3 (84), Mexico 1 (42), Greece 2 (29), and USA 4 (37) did not collect data on family history of gastric cancer.

e The studies China 2 (83), Russia (35), Iran 1 (82), China 4 (85), Portugal (39), Mexico 1 (42), Brazil 1 (45), Brazil 2 (44), Japan 3 (46), and Brazil 3 (81) collected data on *H. pylori* infection. The study Spain 2 (41) was not included because no information on *H. pylori* infection was available for controls.

f The studies Italy 4 (33), Canada (34), China 2 (83), Iran 1 (82), China 3 (84), China 4 (85), Portugal (39), Mexico 1 (42), and USA 3 (38) include population-based controls.

g The studies Greece 2 (29) and USA 4 (37) are nested case control studies (NCC).

h The studies China 1 (66), China 2 (83), China 3 (84), and China 4 (85) did not collect data on cancer subsite.

The findings from both one-stage and two-stage analyses for regular tea drinkers compared to non-regular tea drinkers are shown in **Figure II-1**. For regular tea drinkers compared to non-regular tea drinkers, the one-stage pooled OR was 0.91 (95 % CI: 0.85-0.97). The two-stage pooled OR for gastric cancer was 0.92 (95% CI: 0.82-1.05), with an estimated heterogeneity of I^2= 62% between the studies.

The **Table II-2** shows the distribution of cases and controls by levels of tea drinking and the one-stage pooled ORs for gastric cancer. About 57.6% of cases and 63% of controls in the twenty-one studies that provided information on tea drinking reported ever consumed tea, with a pooled OR of 0.91. (95% CI: 0.85-0.97). About 26.2% of cases and 30.6% of controls reported consuming one or more than one cup of tea per day in eighteen studies and the one-stage pooled ORs was 1.03 (95% CI: 0.94-1.12) compared to non-drinkers. For those who consumed two or more cups per day the OR was 0.98 (95% CI: 0.88-1.10), and 0.91 (95% CI:0.80-1.03) for three or more cups of tea per day. A non-significant trend in risk (P=0.27) was observed across categories of tea-drinking levels. When categories of tea consumption were specific to each study, the results were similar, with ORs of 0.92 (95% CI: 0.85-0.99) for low tea consumption, 0.98 (95% CI: 0.89-1.07) for intermediate consumption, and 0.90 (95% CI: 0.80-1.00) for high consumption. The trend in risk was not

statistically significant (P=0.10). Results across categories of tea-drinking temperature showed a significant inverse association (OR:0.65, 95% CI: 0.53-0.79) of gastric cancer for subjects drinking tea in cold or warm temperatures, and a non-significant excess risk (OR: 1.04, 95% CI: 0.87-1.23) of gastric cancer for subjects consuming tea in hot or very hot temperatures compared to non-tea drinkers. A null association was found between the consumption of strong or very strong tea and gastric cancer (OR:1.11, 95% CI: 0.89-1.39).

Figure II-1 Study-specific, adjusted one-stage and two-stage pooled ORs and 95% CIs of gastric cancer for regular tea drinkers compared with non-regular tea drinkers.

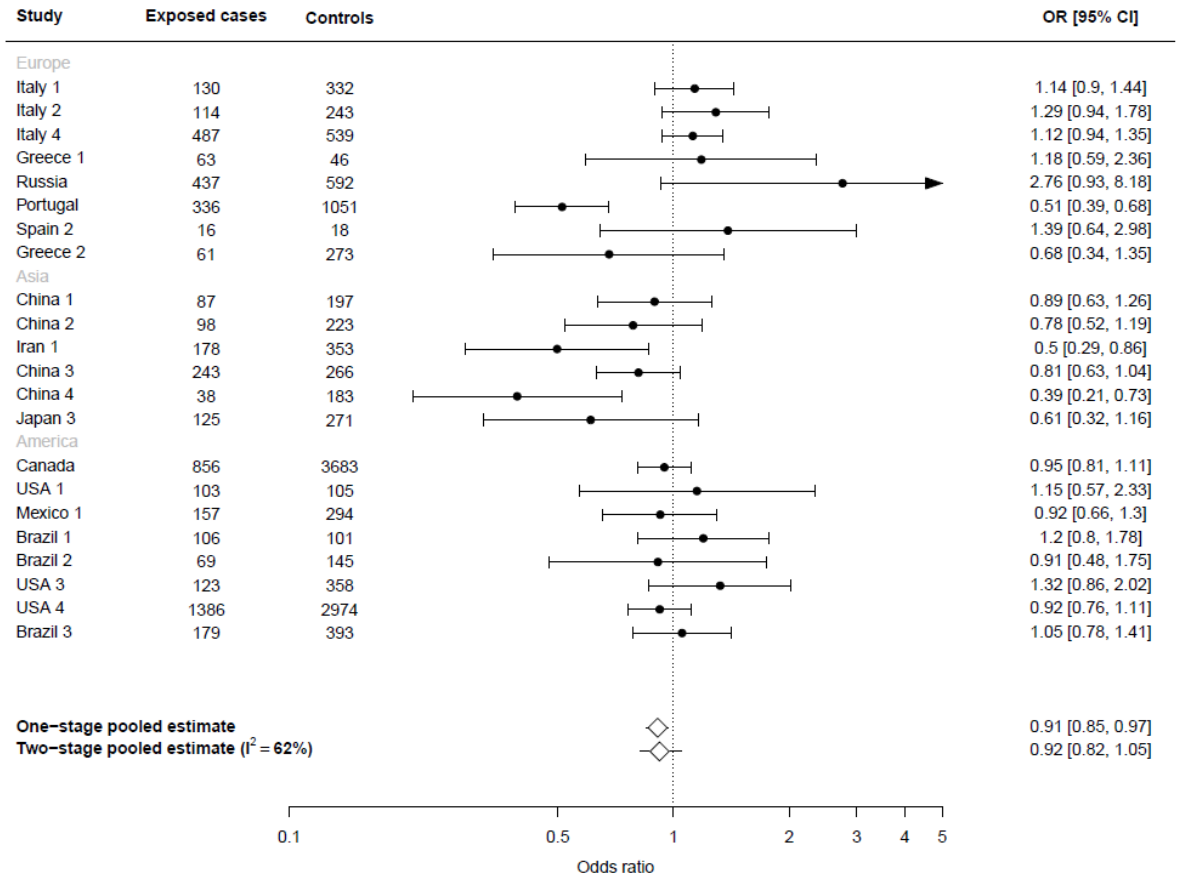


Table II-2 Number and percentage of gastric cancer cases and controls† by tea consumption levels, and adjusted pooled ORs and 95% CIs of gastric cancer.

	Cases		Controls		OR (95% CI)[a]
	N	%	N	%	
Tea drinking status[b]					
Non-regular drinkers	3,921	42.4	7,271	37.0	1 [Reference]
Regular drinkers	5,331	57.6	12,362	63.0	0.91 (0.85, 0.97)
Tea drinking intensity[c]					
Non-regular drinkers	5,804	73.8	12,303	69.4	1 [Reference]
1 cup/day	920	11.7	2,198	12.4	1.03 (0.94, 1.12)
2 cups/day	557	7.1	1,725	9.7	0.98 (0.88, 1.10)
≥3 cups/day	586	7.4	1,507	8.5	0.91 (0.80, 1.03)
p-trend					0.27
Study-specific tea drinking intensity[c]					
Non-regular drinkers	3,529	45.8	7,850	45.1	1 [Reference]
Low	2,417	31.4	5,246	30.1	0.92 (0.85, 0.99)
Moderate	979	12.7	2,432	14.0	0.98 (0.89, 1.07)
High	776	10.1	1,879	10.8	0.90 (0.80, 1.01)
p-trend					0.10
Temperature of tea drinking[d]					
Non-tea drinkers	797	40.8	1,132	36.5	1 [Reference]
Cold/warm	372	19.0	929	30.0	0.65 (0.53, 0.79)
Hot/very hot	786	40.2	1,041	33.6	1.04 (0.88, 1.23)
How strong tea is					
Non-tea drinkers	573	35.5	648	28.4	1 [Reference]
Regular or light	383	23.7	719	31.6	0.77 (0.63, 0.93)
Strong or very strong	572	35.5	717	31.5	1.11 (0.89, 1.39)

† For some variables, the sum does not add to the total because of missing values in tea drinking status (104 cases,408 controls), tea drinking intensity (218 cases, 886 controls), study-specific tea drinking intensity (94 cases, 211 controls), and tea drinking temperature (85 cases, 195 controls).

[a] One-stage pooled ORs were estimated using a mixed-effects model adjusted for sex, age category, social class, smoking status, salt intake, vegetable and fruit intake, alcohol intake, and family history of gastric cancer.

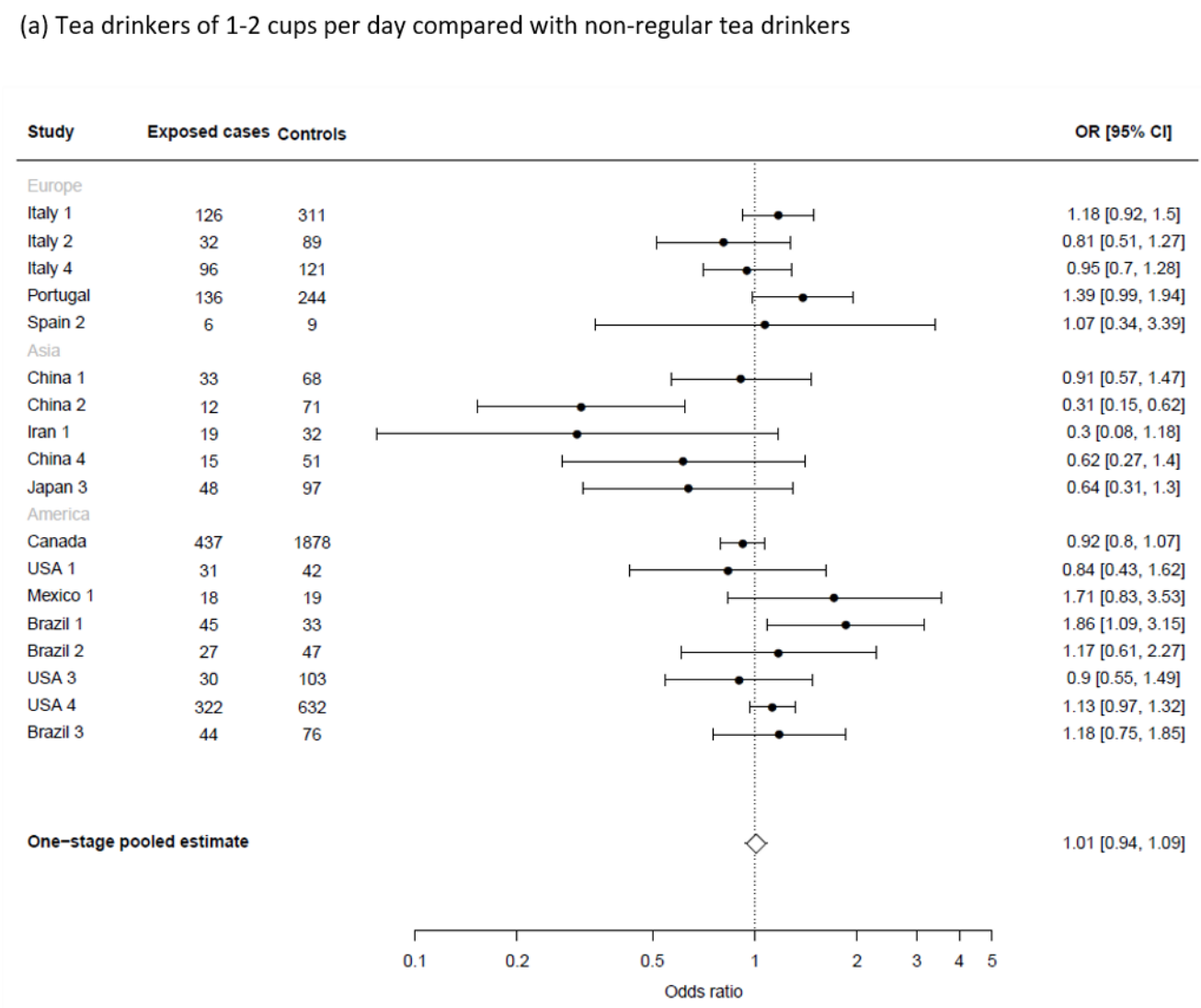
[b] The study Greece 2 (29) only provided locally computed estimates and thus was not included in one-stage analyses.

[c] Information on tea drinking intensity was not available for the studies Greece 1 (30), Russia (35), China 3 (85), and Greece 2 (29).

[d] Information on the temperature of tea drinking was available for the studies China 1 (66), China 2 (83), Russia (35), Iran 1 (82), USA 3 (38), and China 3 (85).

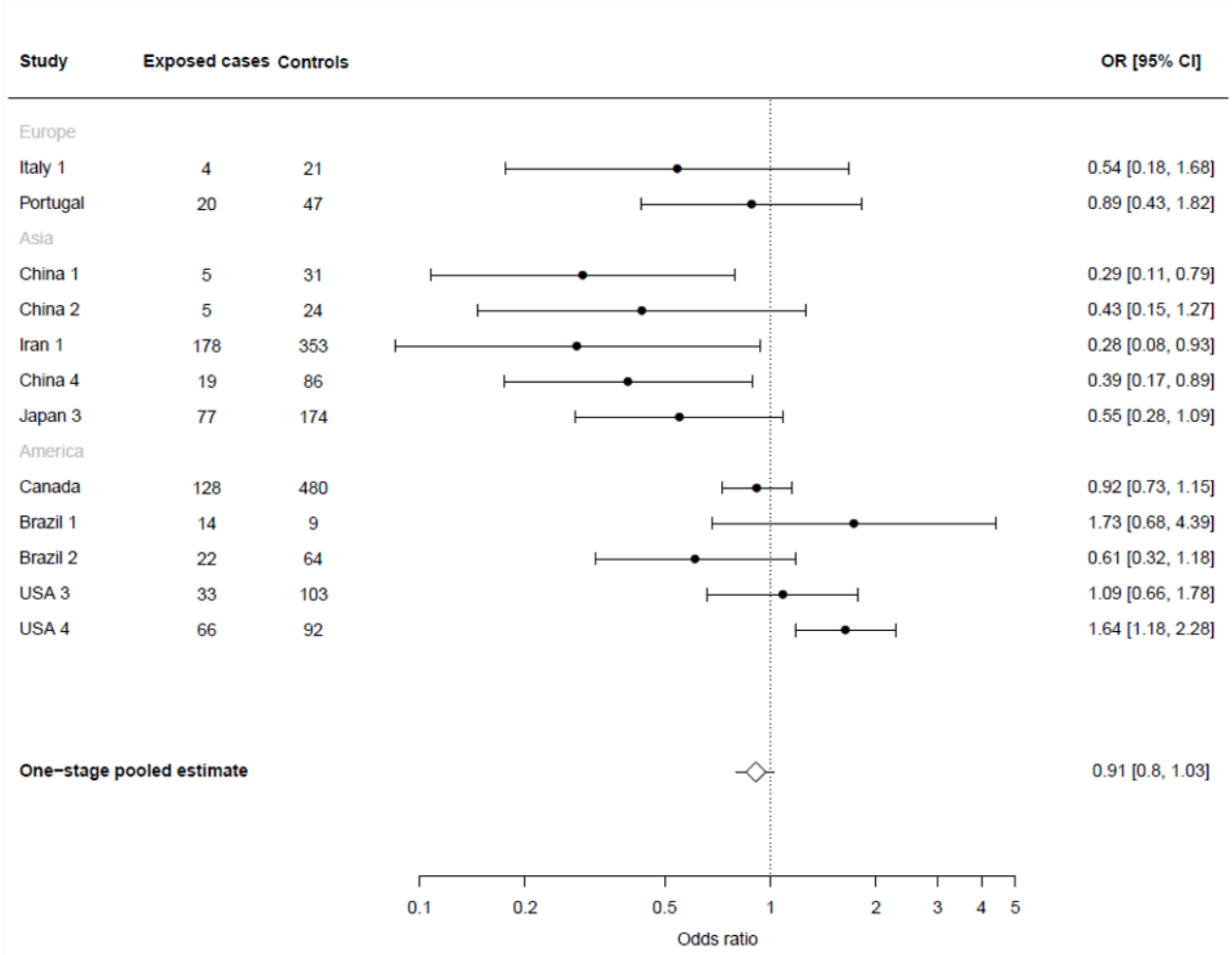
The forest plots of one-stage adjusted pooled ORs between tea drinking of 1-2 cups of tea per day (**Panel a**) and 3 or more cups per day (**Panel b**) and gastric cancer are shown in **Figure II-2**. Comparing tea drinkers to non-tea or non-regular tea drinkers, no association between tea drinking levels and gastric cancer was observed. The adjusted pooled ORs were 1.01 (95 % CI: 0.94-1.09) for participants who consumed 1-2 cups of tea per day (**Panel a**) and 0.91 (95 % CI: 0.80-1.03) for those who consumed 3 or more cups per day (**Panel b**).

Figure II-2 Study-specific and adjusted pooled ORs and 95% CIs of gastric cancer for tea drinkers of 1-2 cups per day (a)† and ≥3 cups per day (b)† compared with non-regular tea drinkers.



† Studies with more than five subjects in exposed cases or controls are shown.

(b) Tea drinkers of ≥3 cups per day compared with non-regular tea drinkers



† Studies with more than five subjects in exposed cases or controls are shown

The dose-response relationship between the amount of tea consumed and gastric cancer is presented in **Figure II-3**. As is shown from the consumption of three cups of tea per day to higher levels of intake, the risk gradually decreased.

The **Figure II-4** shows the findings of the stratified analysis among tea drinkers. In studies conducted in Asia (OR: 0.62, 95% CI: 0.48-0.81), in subjects with intermediate vegetable and fruit intake (OR: 0.87, 95% CI: 0.78-0.97), and in subjects with low salt intake (OR: 0.87, 95% CI: 0.78-0.97), significant inverse relationships for tea consumption were found. Similar results were seen in those who tested positive for *H. pylori* (OR: 0.68, 95% CI: 0.58-0.80) but not in non-infected subjects (OR: 0.96, 95% CI: 0.76-1.22). When the analysis was restricted to studies in China and Japan, where green tea is usually consumed, a strong inverse association was found (OR: 0.67, 95% CI: 0.49-0.91). Heterogeneity was evident only across the strata of the geographic area of the studies, diagnosis of *H. pylori* infection (Q=10.7, P=0.001 and Q=5.7, P=0.017, respectively) and type of controls (Q=8.5, P=0.003). The studies with population-based controls were the only ones with a lowered risk (OR: 0.86, 95% CI: 0.80-0.92). While no heterogeneity was significant by cancer subsite and histological type strata, there was a negative association for tea drinkers for cardia cancer (OR: 0.64, 95% CI: 0.49-0.84), and non-cardia cancer (OR: 0.77, 95% CI: 0.66-0.90), and intestinal histological type (OR: 0.76, 95 % CI: 0.63-0.92). The results for the CC (OR: 0.91, 95% CI: 0.85-0.97) and NCC (OR: 0.92, 95% CI: 0.76-1.11) studies were similar.

Figure II-3 Dose-response relationship between tea consumption and gastric cancer.

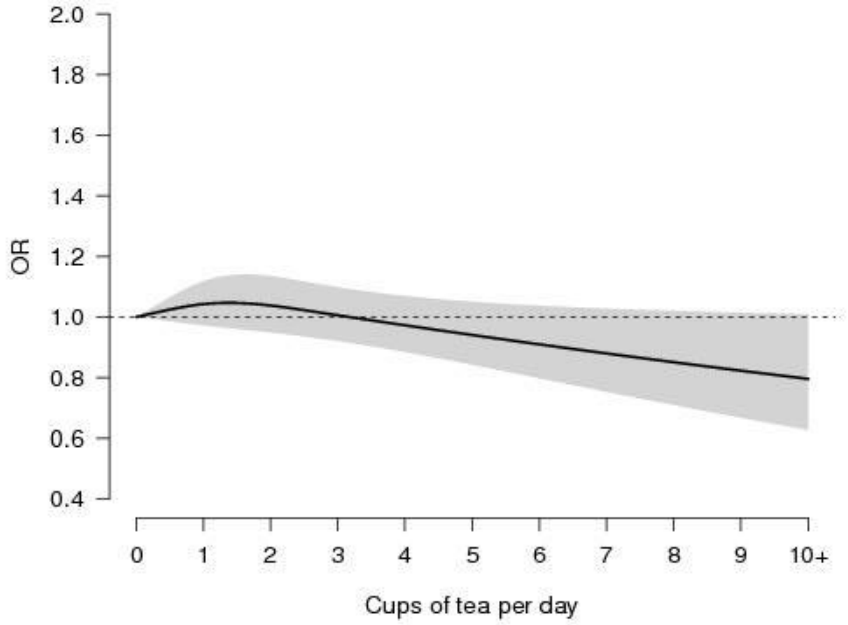
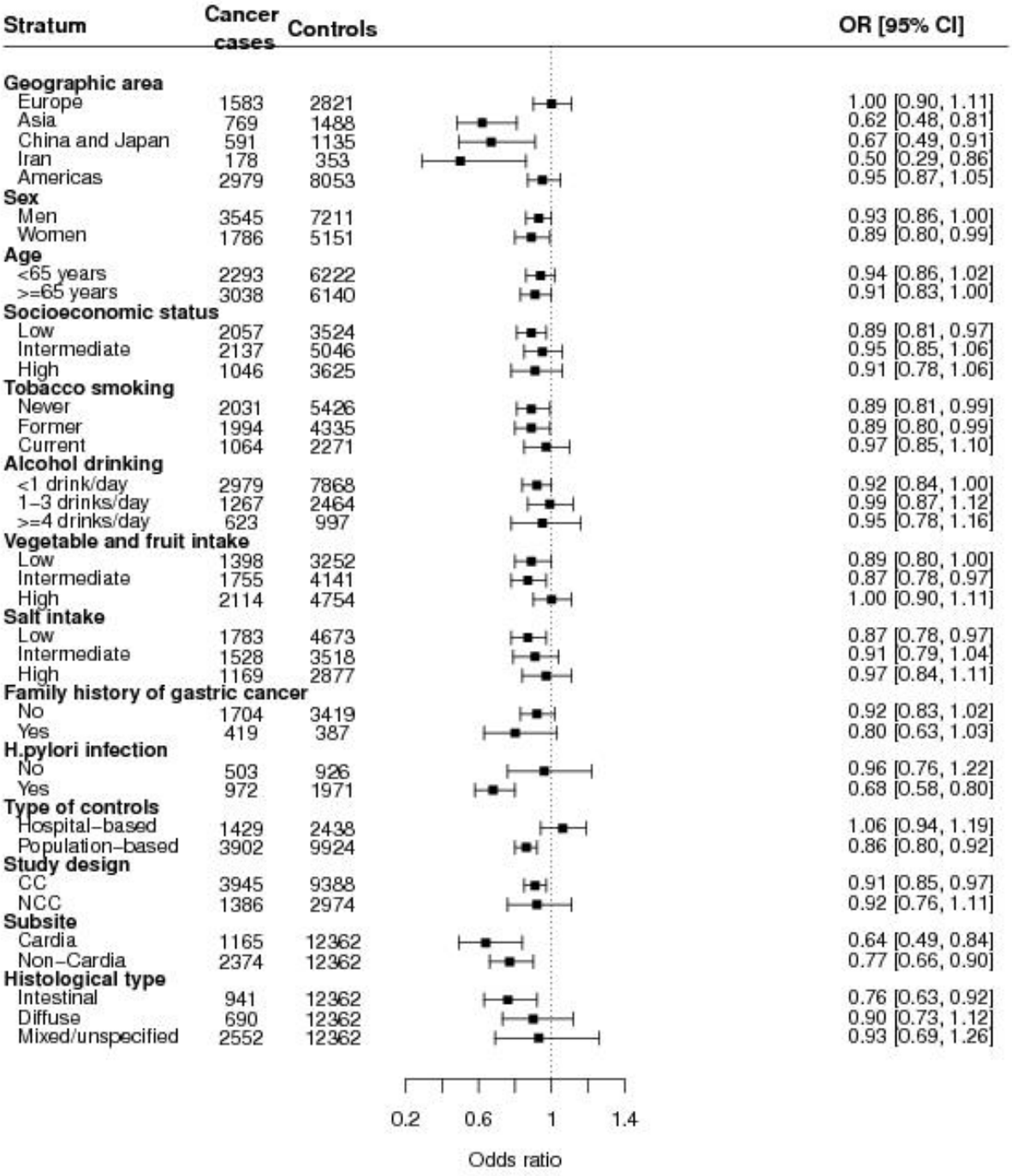


Figure II-4 Adjusted pooled ORs and 95% CIs for regular tea drinkers compared to non-regular tea drinkers, by strata of selected risk factors of gastric cancer.



Discussion

Based on data from a global consortium of gastric cancer studies, this study (90) found a small inverse relationship between tea consumption and gastric cancer. Regular tea drinkers were associated with a 9% lower risk than non-regular tea drinkers. Asian studies, *H. pylori* infected patients, and subjects with gastric cardia cancer all showed stronger inverse relationships. In studies from Asia, a 38% significantly lower risk of gastric cancer, supported by an OR of 0.67 in studies from China and Japan only and an OR of 0.50 observed in the Iranian study was found. These results could be explained by increased tea consumption rates as well as differences in tea types in those countries, such as black tea consumption in Iran and green tea in China and Japan (55, 75, 91, 92).

Few studies have examined the association between tea consumption and gastric cancer according to anatomic site or histological subtype of cancer. The inverse associations found in the current analysis for cancer subsites are consistent with those showed by the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort study (80) which suggested a risk reduction for cardia cancers than non-cardia cancers, however non-significantly. Similarly, the EPIC study revealed lower, non-significant, risks for diffuse and intestinal cancers with higher tea drinking levels. Drinking hot or very hot tea was not related to an increased risk of gastric cancer in the current study while drinking warm or cold tea was associated with a reduced risk of gastric cancer. A cohort study that included 231 cardia patients and 224 non-cardia patients in the USA found that hot tea drinking was not related to either gastric cardia or non-cardia cancers (78).

Only those who were infected with *H. pylori* had an inverse association when considering regular tea consumption. This result can be explained by the potential protection against *H. pylori* infection that tea drinking may provide. Studies on animal models have revealed that green tea polyphenols may be a useful method for preventing the growth of bacteria, including *H. pylori*, as well as disorders linked to *H. pylori* such as atrophic gastritis and gastric carcinogenesis (93, 94). Additionally, a study of 150 individuals with dyspepsia discovered that drinking green or black tea was related to a lower prevalence of *H. pylori* infection (OR: 0.45, 95% CI: 0.21-0.95) (95).

The current findings on tea drinking temperature are consistent with those of a case-control study conducted in a Chinese population (266 gastric cancer cases and 533 controls), which found that green tea drinkers had a lower risk of developing gastric cancer when the beverage was served at cold to warm temperatures (OR: 0.61 95% CI: 0.45-0.82), but not at hot temperatures (66).

However, other studies suggested that drinking hot tea was related to a significant risk of gastric cancer, with ORs ranging from 1.82 to 2.85 (86, 96), and from 3.07 to 7.60) d for drinking it at very hot temperatures (55–60 °) (86, 96). The amount of time between pouring and drinking the tea, which was not taken into account in this study, may have at least partially masked this association (97). Furthermore, four of the six studies reporting data on drinking temperature were Asian studies and it is therefore challenging to determine if the observed association may be directly attributed to drinking temperature or if it is instead due to the geographic location.

The study's key strength is the large data set including over 9,000 patients and 19,000 controls with individual-level data information on tea consumption together with significant confounders. Extensive multivariate analyses adjusted for a number of potential sociodemographic and lifestyle confounding variables, including five-year age groups, smoking, alcohol intake, salt intake, vegetable and fruit intake, and family history of stomach cancer carried using patient-level methods Furthermore, information on the anatomical location and histological type of cancer were available.

The fact that the majority of the findings are based on retrospective studies means that information on tea drinking and other dietary intakes may be subject to recall bias. However, the results were comparable to those of the case-control and nested case-control studies results separately. The inclusion of hospital-based controls in some studies may have impacted the reported prevalence of dietary variables, but it was seen that an inverse relationship between tea consumption and gastric cancer was revealed primarily among those with population-based controls. Differences in types of tea questions used across the included studies may be a source of heterogeneity and probably explain some of the inconsistent outcomes for high levels of intake found in different studies. Regular tea drinkers were found to have a slight advantage over non-regular tea drinkers, which may have been influenced by bias or a lack of confounding control in some of the included studies.

Reverse causality is possible if tea or strong tea consumption causes heartburn in patients, though this is still unclear. Only four studies, which showed no heterogeneity, reported information on how strong a cup of tea was. This might possibly be related to the higher prevalence of *H. pylori* in Asian nations, and our study revealed that the inverse correlation was stronger among participants who were *H. pylori* positive. Twelve studies from 8 countries (98) in the same consortium, the StoP Project, showed that 80.3% of cases overall, 82.1% of cases in Japan, and around 88% of cases on average in the three Iranian studies were *H. pylori* positive. Therefore, a higher *H. pylori* positivity in Asian studies cannot largely or entirely explain the stronger inverse association with tea in Asia.

In conclusion, in this study (90) between tea drinking and gastric cancer, by analyzing a unique global pool of epidemiological studies on gastric cancer, a slightly inverse association with overall gastric cancer was found. A stronger inverse association was found in studies from Asia and in participants infected with *H. pylori*, indicating that tea drinking may protect against the bacteria.

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Chapter III gives a brief overview of two more studies conducted as part of the Stomach Cancer Pooling Project and I was a co-author. The two studies below examine the associations between allium vegetable consumption and sleep duration, and stress levels and gastric cancer.

Chapter III. Other collaborative studies from the Stomach cancer Pooling (StoP) Project consortium

A. Allium vegetables intake and the risk of gastric cancer in the Stomach cancer Pooling (StoP) Project (99).

Allium vegetables including garlic, onions, leeks, chives, and scallions are high in flavonoids and organosulfur compounds with preventive effects against gastrointestinal tract malignancies (100, 101). In the literature, only case-control studies reported a significant inverse association compared to the null association that appeared for the cohort studies (102). A pooled analysis by investigators of the StoP project study was carried out to examine whether high consumption of total allium vegetables, garlic, and onions, separately is related to a reduced risk of gastric.

Seventeen studies out of the thirty-five in the StoP Project had information on the consumption of total allium vegetables, accounting for a total of 6.097 gastric cancer cases and 13,017 controls. The following studies were included in the current analysis: three from China, two from Greece, two from Italy, two from Spain, two from Mexico, two from Iran, and one from Portugal, Russia, Japan and Brazil, respectively. Total intake of allium vegetables was calculated by adding the available intakes of onions, garlic, chives, leeks, and scallions for each study. The total consumption of allium vegetables was expressed in grams per day either by accounting for portion size and frequency of consumption or by converting the average weight for each food item into grams (150 g for leeks, 40 g for onions, and 15 g for scallions). The consumption of total allium vegetables was then classified into tertiles specific to each study and the distribution of each study's controls. Consumption of onions and garlic was divided into two groups above and below the study-specific median intake since, in some studies, the computation of tertiles was not supported by the distribution of their intake.

A two-stage meta-analysis including multivariable unconditional logistic regression models for each study in the first phase and a random-effects model for the summary pooled estimate in the second phase was used to estimate the relationship between consumption of total allium vegetables and onions, and garlic intakes separately, and gastric cancer. Cochran’s Q test was used to examine heterogeneity across studies and the I2 test to quantify it. The missing values on confounding covariates were either included as a separate category in the corresponding variables or included in the lowest category when the proportion of missing was less than five percent. The dose-response

relationships between grams of total allium vegetables per week and gastric cancer were modeled by multivariable one- and two-order fractional polynomial models, adjusted for the main recognized risk factors of gastric cancer. In addition, stratified analyses by strata of several selected dietary and lifestyle covariates were carried out. Sensitivity analyses included a one-stage approach analysis between total allium vegetables, onion, and garlic intakes, and gastric cancer, metaregression models, and excluding studies with non-consumers of more than 10%.

The results showed that compared to the lowest category of intake the OR for the highest intake category of intake was 0.71 (95% CI: 0.56–0.90, I2:82.2%) for total allium vegetables intake, 0.69 (95% CI: 0.55–0.86; I2 =86.6%) for onions and 0.83 (95% CI, 0.75–0.93; I2:0%) for garlic. The dose-response relationships showed a decreasing risk of gastric cancer for a higher consumption of total allium vegetables, onions, and garlic. Only for garlic, the estimated effect for an intake greater than 50–60 g per day reached a steady rate. The stratified analysis revealed a stronger inverse association among studies in Asian countries (OR: 0.50, 95% CI: 0.29–0.86, I2:89.5%). No heterogeneity was significant among the other strata such as alcohol drinking, and family history of gastric cancer. Results did not differ by cancer subtype (cardia vs non-cardia) and histotype (intestinal versus diffuse and unspecified site). Sensitivity analyses including one-stage models found similar results as the two-stage ones.

This study (99) revealed an inverse association between the intake of total allium vegetables, onion, and garlic intakes and the risk of gastric cancer. These findings are consistent with the results of other case-control studies (103-106) but not with those of prospective design (107-112). In the current analysis, only a nested case-control study within a cohort was included and showed an OR of 0.94 (95% CI: 0.43-2.08) for high versus low total allium vegetable intake. This inverse association seen in case-control studies may be partially explained by reverse causation as there is the possibility that the presence of symptoms in the stomach may have caused cases to consume fewer allium vegetables. In addition, significant heterogeneity was found between allium vegetable consumption and gastric cancer among the geographic areas, with a greater reduced risk of gastric cancer in Asian countries. This could be attributed to the diverse amounts and patterns of consumption such as the preparation and processing methods of allium vegetables observed across the countries. For example, both cooked and raw onions are usually consumed in Mediterranean countries and Iran, while onions in China are preferred cooked in contrast to garlic which is consumed mostly raw.

B. Sleep duration and stress level in the risk of gastric cancer: A pooled analysis of case-control studies of the StoP Consortium (113).

Psychological stress and sleep duration have been rarely studied in relation to gastric cancer risk. This study aimed to investigate the role of psychological stress and sleep duration on gastric cancer risk through a pooled analysis of five studies from the StoP project consortium.

Sleep duration data were available in one study from the USA, two studies from Spain, and two studies from Brazil, for a total of 1,293 gastric cancer cases and 4,439 controls. Information on stress levels was available in one study from the USA, one study from Spain, and two studies from Brazil accounting for a total of 843 gastric cancer cases and 976 controls. The self-reported hours of sleep during nighttime were used to calculate sleep length, which was further categorized into the following four categories: 6 or fewer hours, 7 hours, 8 hours, and 9 or more hours of sleep. Psychological stress was based on two questions regarding how much stress participants experienced on a daily basis and how frequently it caused them to worry or to experience physical symptoms like back or stomach aches. Stress was categorized into three levels: low, moderate, and high.

A one-stage pooled analysis of the individual-data of studies using a multivariable logistic regression model adjusted for study, sex, five-year age groups, socioeconomic status, and other known dietary and lifestyle risk factors was carried out. The odds ratios (ORs) and the corresponding 95% confidence intervals (CIs) of gastric cancer were estimated for levels of stress, and sleep duration separately, as well as included together in the models to calculate the marginal impact after accounting for each other. An interaction between sleep and stress was also examined. The reference category for sleep duration was eight hours of sleep per night and for the stress variable was the lower level. A stratified analysis to investigate the effect of each exposure by strata of selected variables and by anatomical subsite (cardia versus. non-cardia) and histological type (intestinal versus diffuse) was performed. For sensitivity analysis, the pooled analysis was repeated excluding one study at a time.

Compared to eight hours of sleep, nine or more hours of sleep per night were associated with an increased risk of gastric cancer (OR:1.57, 95% CI:1.25-2.01). The effect of sleep duration did not change when stress levels were also encountered in the model. When race or ethnicity and family history of gastric cancer were accounted the estimates did not change. An increased stronger risk for non-cardia gastric cancer (OR: 1.59, 95% CI: 1.22-2.07) and gastric cardia cancer (OR: 1.67, 95% CI: 1.00-2.80) was found for nine or more hours of sleep per night. Similarly, the ORs for the

histological types of gastric cancer for nine or more hours of sleep per night were 1.80 (95% CI: 1.21-2.66) for diffuse and 1.44 (95% CI: 1.05-1.98) for intestinal types. No heterogeneity was found between other strata groups. Compared to a low-stress level, a high-stress level was associated with an increased risk of gastric cancer (OR: 1.78, 95% CI: 1.40-2.27). The association was similar when the exposure was assessed as continuous variables of one level of increase in stress (OR: 1.34, 95% CI: 1.18-1.51) levels. High levels of stress were associated with non-cardia gastric cancer (OR: 1.28, 95% CI: 1.12-1.47), but not with gastric cardia cancer. In addition, high levels of stress compared to low levels were significantly associated with both diffuse and intestinal types of gastric cancer (OR: 2.23, 95% CI: 1.53-3.26 and OR: 1.80, 95% CI: 1.34-2.41, respectively). The stratified analysis also revealed an increased risk between stress and gastric cancer among current smokers (OR: 1.86, 95% CI: 1.43-2.41).

In conclusion, this study (113) found an increased risk of gastric cancer among subjects with nine or more hours of sleep per night compared to eight hours of sleep, and an increased risk of gastric cancer for high-stress levels than low-stress levels. The findings are consistent with those of another previous study which described a U-shaped curve between sleep duration and gastric cancer risk (1). Non-cardia gastric cancer and diffuse histological type of cancer were greater associated with both longer sleep duration and high-stress levels. Studies have shown that long sleep duration changes metabolism and raises carcinogenic levels (114, 115). Long-term stress makes the body more susceptible to a pro-inflammatory environment, affecting gastrointestinal functions such as altering the microbiota in the gut that can contribute to carcinogenesis and the spread of cancer (116, 117). No other studies to date have analyzed the effect of stress on the risk of gastric cancer. Reverse causality may impact the results since gastric cancer patients may experience problems with poor quality of sleep and high levels of stress compared to controls, though patients seem to be affected by shorter duration of sleep than longer duration, and the current results showed an increased risk for extended hours of sleep.

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Chapter IV summarizes the research activities conducted in the context of the collaboration with the Hellenic Health Foundation during the three years of the Ph.D. program. The three studies below examine the usual diet and adherence to the Mediterranean diet of the adult population in Greece, the relationship between oral factors and adherence to the Mediterranean diet in an older Greek population, and the methods used to evaluate dietary supplement use in the National Health and Nutrition Survey - HYDRIA.

Chapter IV. Assessment of the usual diet of the adult population in Greece – the National Health and Nutrition Survey HYDRIA.

A. Today's Mediterranean Diet in Greece: Findings from the National Health and Nutrition Survey—HYDRIA (2013–2014) (118).

This study assessed the population's food and macronutrient intake as well as its adherence to the traditional Mediterranean diet using data from the HYDRIA survey, the National Health and Nutrition Survey of the adult population in Greece. The HYDRIA survey was created to fill the knowledge gap in national representative data on food, macronutrient, and micronutrient intakes and health indicators in Greece that are comparable to data from national surveys of other European countries and to give insights on the population's nutritional and health status.

In the HYDRIA study, which took place between June 2013 and December 2014, 1,873 men and 2,138 women between the ages of 18 and 94 who had a fixed residence in Greece were included. Participants were drawn from all 51 prefectures in the country's 13 regions, and on the day of the interview, they completed questionnaires about their sociodemographic characteristics, lifestyle, and medical history. The same day they also undertook blood pressure, anthropometric, and blood test examinations (119). Additionally, participants provided information about all the food and beverages consumed, their preparation method, the type of each food, and the quantity consumed over the time of the preceding twenty-four hours through a face-to-face interview. About fifteen to thirty days after the initial 24-hour recall, a second one was repeated by phone. A food propensity questionnaire, or a non-quantitative food frequency questionnaire, was also used to supplement the dietary collection, asking about the usual frequency of consumption of eighty-eight items and dietary supplements over the previous twelve months.

Protein, glycaemic carbohydrates, dietary fiber, total fat, saturated fatty acids (SFA), monounsaturated fatty acids (MUFA), polyunsaturated fatty acids (PUFA), and alcohol intake were all calculated using the HYDRIA Food Composition Table (H-FCT) (120, 121). Using the National Cancer Institute statistical method (122-124), which corrects for measurement errors that occur during the collection of food intakes consumed episodically (123, 125). Then the distribution of the usual intake of energy, macronutrients, thirteen food groups, and several subgroups was calculated. The

population's diet was also evaluated using a nine-point scale, which was incorporated in the NCI models mentioned before, that included consumption of vegetables, legumes, fruit, nuts, cereal, fish, meat, dairy, alcohol, and the proportion of monounsaturated to saturated lipids (126, 127). Participants were given a value of 0 for intake of vegetables, legumes, fruits, nuts, cereals, and fish that was below the sex-specific median consumption, and a value of 0 for above-median consumption of meat and dairy products. Men who consumed 10–50 g of alcohol daily and women who consume 5–25 g were assigned a value of 1. A total score of 0 to 3 points, 4-5 points, and 6-9 points, respectively, were used to identify low, intermediate, and high adherence to the Mediterranean diet (126). All models were weighted and adjusted for age, education level, geographic location, and the frequency of dietary variables from the food propensity questionnaire. The analysis was carried out separately for men and women.

Compared to older participants who were less educated, lived in rural areas, and followed a diet that included the consumption of fruit, vegetables, legumes, olive oil, seafood, and whole grains, the results of this nationally representative survey (118) showed that younger individuals with higher education and in urban areas were more adherent to a Western diet pattern characterized by the consumption of red meat, and animal fats. Younger participants had a lower (25.5%) percentage of adherence to the Mediterranean diet than older adults (39.7%). Significant decreases in fruit and vegetable consumption were seen when compared to AICR/WRCF and WHO dietary recommendations (128, 129), i.e., less than one-third of the population consumed more than 400 g. However, more than half of the younger individuals consumed more than 50 g of red meat per day. The results discussed above may indicate unfavorable effects on morbidity and mortality among younger people. Numerous epidemiological studies have shown that following a diet more in line with the Mediterranean dietary pattern, which is characterized by little consumption of animal products and a greater intake of plant-based foods, not only extends life expectancy and improves the quality of life for individuals but also has long-term and ecological advantages for the environment (130).

B. Oral factors and adherence to Mediterranean diet in an older Greek population (131).

Few studies have looked at the relationship between oral factors and Mediterranean diet adherence in an older population with potential dental issues. The current study involved a total of 130 participants, 33 men and 91 women with an average age of 74 years. People over 60 who had no cognitive impairments, no trouble speaking or understanding the language, and no dental issues that would have impaired their ability to chew and who were residents in the Greek metropolis of Athens between June 2019 and March 2020 were included. Data on the subject's somatometric measurements, smoking, medical history, and drug use were collected. In terms of dental status, participants were asked to self-evaluate their own oral health, chewing ability, denture dislocation during speech or mastication, pain from wearing dentures, dental visitation habits, oral hygiene habits, and xerostomia.

The MDI BNC4H index, which has a range of zero to fourteen, was used to measure how closely people adhered to the Mediterranean diet (132) and included pre-determined cut-offs for the consumption of olive oil, fruits, vegetables, legumes, nuts and seeds, low-salted or regular olives, cereals, dairy products, red meat, white meat, fish and shellfish, and wine. The Modified Kapur Scale was used in the oral examination to assess the number of removable dental prostheses, including partial and complete dentures, that were either natural or artificial, as well as the degree of tooth mobility (133). To measure their ability to masticate, participants were given two-color chewing gum. Higher degrees of color mixing indicated poorer masticatory function (134).

Using univariate linear regression analyses and Kruskal-Wallis one-way analysis of variance on ranks, participants' oral health indicators, dental status indicators, and masticatory performance were examined in relation to their adherence to the Mediterranean diet score after being adjusted for age, sex, medical conditions, medications, BMI, and other covariates. The masticatory and dental indicators that were significantly associated with adherence to the Mediterranean diet score were further investigated by multivariable linear regression models excluding non-significant predictors following a backward selection deleting covariates with $p>0.10$.

The results (131) showed no statistically significant relationships between oral health parameters and Mediterranean diet adherence. Older participants who adhered to the Mediterranean

diet more consistently also adhered to higher masticatory performance (β=− 1.12, p=0.050). The Mediterranean diet was not shown to be associated with other dental characteristics. The above results showed the importance to strengthen masticatory function for the optimization of factors suggested being related to it such as better nutritional quality and the prevention of frailty and sarcopenia in older communities (135, 136).

C. Dietary Supplement use in Greece: Methodology and Findings from the National Health and Nutrition Survey – HYDRIA (2013-2014) (137).

The purpose of the current study was to describe dietary supplement use among 4,011 adults, 1,873 men, and 2,138 women, in a nationally representative sample in Greece.

This study used data from the HYDRIA survey where its methodology and data collection have been described in detail previously (119). Information on the use of dietary supplements was collected using three different assessment techniques: 24-hour dietary recalls, the food propensity questionnaire, and a questionnaire assessed during the blood sample collection examination. Trained interviewers conducted all three dietary assessment methods. Participants in the two dietary recall provided information on the type and brand of any dietary supplements they had used the day before each interview. Anyone who reported using at least one dietary supplement in at least one of the two recall interviews was considered to be a dietary supplement user. In addition, participants answered a food propensity questionnaire (i.e. non-quantitative food frequency questionnaire) reporting information on the frequency of consumption of fourteen specific dietary supplements over the previous twelve months. These supplements included a variety of vitamins and minerals, multivitamins with or without minerals, supplements based on fatty acids or herbs, and those for maintaining weight and muscle mass. Participants also had the chance to report any dietary supplements that were not covered by the previously mentioned categories at the end of the questionnaire. The Food Propensity Questionnaire defined a user of dietary supplements as someone who indicated frequent usage of any supplement at least once. The last assessment method included a questionnaire that was administered together with the blood test, and participants were required to bring any drugs or dietary supplements they had been taking the previous day, the previous week, or on a regular basis. With the exception of homeopathic medications and foodstuffs, the reported items that corresponded to vitamins, minerals, or other comparable substances were classified into the same groups defined in the food propensity questionnaire.

Anyone who reported using supplements in at least one of the three aforementioned assessment methods was defined in this study as a user of dietary supplements. Statistical analyses were conducted separately for men and women. The socioeconomic, lifestyle, and health variables that were evaluated on the day of the face-to-face examination were divided into groups, and the percentages of dietary supplement use were compared between these groups using chi-square tests.

Additionally, categories of usual intakes of fruits, vegetables, and alcohol were used to evaluate differences in dietary supplement use. These categories were determined by the corresponding median values computed using the National Cancer Institute (NCI) method (125). The analyses taken into account weighting factors to produce nationally representative estimates.

The use of dietary supplements has been observed to be rising in Greece, which was placed 22nd out of other countries in Europe (138). According to the results of the current analyses (137), 31% of Greek individuals reported using dietary supplements overall, with consumption rates nearly doubling for women (39.9%, $p < 0.01$) and those in urban areas. About 8% of the participants reported using at least one dietary supplement in all three assessment methods, compared to 69% who did not. Employed men with an intermediate level of education who were obese and had a higher waist circumference or waist-to-hip ratio stated to use dietary supplements more frequently. Women who consumed more than 109 g of fruit daily had a greater percentage of supplements (51%). Calcium (5.3%), iron (4.6%), and multivitamins with or without minerals (5.4%) were the three most popular forms of supplements. Younger people up to the age of 34 used dietary supplements more frequently for weight loss (30% in women) and muscle growth (59% in men), whereas people over the age of 55 years used more frequently calcium (in women) and iron (in men) supplements.

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Chapter V describes the project I undertook during my six-month visiting research period as a PhD student at the Department of Nutrition at Harvard T.H. Chan School of Public Health. The following pages outline the methodology and the preliminary results for the association between olive oil consumption and prostate cancer risk using data from two large follow-up prospective cohorts conducted in the United States and Greece.

Chapter V. Olive oil consumption and risk of prostate cancer.

Olive oil is considered the core of the Mediterranean diet, and Mediterranean basin populations have long used it as their primary cooking and dressing fat, consuming large amounts of it. In a number of epidemiological studies, olive oil consumption has been linked to a lower risk of cancer, cardiovascular diseases, total and specific-cause mortality (139-144). In a recent review and meta-analysis, including 37 case-control studies and 8 cohort studies, high levels of olive oil consumption were found to be protective against cancer risk in both the Mediterranean and non-Mediterranean populations (RR: 0.69, 95%CI: 0.60-0.79, and RR: 0.49, 95% CI: 0.34-0.71, respectively) (145). In terms of research for prostate cancer and olive oil consumption, only four case-control studies examined its association with the disease suggesting a 54% decreased risk of prostate cancer (RR: 0.61, 95% CI: 0.40-0.92) (145).

The objective of the following study was to examine the relationship between olive oil intake and prostate cancer in two diverse populations using data from the Health Professionals Follow-up Study (HPFS) and the Greek part of the European Investigation into Nutrition and Cancer (EPIC-Greece) study.

Health Professionals Follow-up Study (HPFS)

The HPFS began in 1986 and it recruited 51,529 male health professionals in the United States between the ages of 40 and 75 years. Participants were asked to fill out a baseline questionnaire and to report every 2 years their medical history, medications, height, weight, ethnicity, and lifestyle characteristics. At baseline and every four years, the participants' dietary intake was also evaluated using a validated semi-quantitative food-frequency questionnaire (FFQ) assessing over 130 food items. Specific foods, types of fats, brands of oils, and types of oils added to meals during the year prior were all recorded.

Olive oil consumption was first included in the FFQ in 1990. Three questions on olive oil intake—olive oil for salad dressing, olive oil added to food or bread, and olive oil used for baking and frying at home—were summed to calculate olive oil’s total consumption. Then four categories of olive oil intake were calculated: (1) never or less than once per month, (2) more than 0 to 1 teaspoon (>0 to 4.5 g per day), (3) more than 1 teaspoon to 1/2 tablespoon (>4.5-7 g per day), and (4) more

than 1/2 tablespoon (>7 g per day). 13.5 g of olive oil was equivalent to one tablespoon. Consumption of olive oil was also calculated per 5 g per day increase in its consumption.

In the same study, questionnaires on disease diagnoses were administered every two years to collect information on new cancer diagnoses, the medical history of the cases, the progression of the disease, and the appearance of any metastases. Then, trained personnel who were ignorant of the patient's exposure status and clinical symptoms reviewed the medical records and pathology reports. When medical records were not available the cancer diagnoses were validated by linkage to state tumor registries. Family reports and the National Death Index verified the patients' deaths. According to the level of metastasis, prostate cancer cases were defined as localized (stage T1/T2 and N0, M0 at diagnosis), advanced (stage T3b/T4/N1/M1 at diagnosis), lethal (distant metastasis or death from prostate cancer), and fatal (death from prostate cancer). Stage T1a cases were excluded from the analyses.

In HPFS, a prospective cohort analysis with follow-up from 1990 to 2016 was carried out to examine the relationship of olive oil intake with prostate cancer risk.

EPIC-Greece

The European Prospective Investigation into Cancer and Nutrition (EPIC) study is a prospective, longitudinal cohort study that examined how diet and lifestyle choices affect the development of cancer and other chronic diseases. The Greek part of the EPIC cohort study recruited 28,572 volunteers in good health condition, including 11,954 males, between 1994 and 1997, from around Greece, aged from 25 to 82 years old. A validated food frequency questionnaire (FFQ) that included 150 of the most popular foods in Greece was used to calculate usual food and beverage consumption at baseline in EPIC-Greece. Then, the daily food, nutrient, and energy intake in grams for each participant were computed. Information on smoking status, alcohol intake, education, occupation, family history, anthropometric measures, medical history, surgical procedures, and physical activity was gathered using a separate questionnaire on lifestyle factors. Following the baseline intake, the diet was evaluated every three to four years, between 1997 and 2016, and through four follow-up telephone interviews using a qualitative food frequency questionnaire (FFQ) with the following even pre-specified responses: none, much less, less, the same, more, much more, and do not remember.

Olive oil intake, in terms of quantity, was assessed only at baseline through an interviewer-administered food frequency questionnaire (FFQ). In EPIC-Greece's FFQ, olive oil intake was collected in grams per day. For the purposes of the current analysis, olive oil intake was converted into categories of consumption in tablespoons based on a diet of 2,000 kcal per day, considering that 1 tablespoon equals to 13.5 g.

Prostate cancer incidence cases were recorded through the participants' active follow-up and verified by hospital records. The diagnosis and date of diagnosis, behavioral tumor code, and morphology code were verified by medical and pathology records. Mortality registries or, if necessary, family members were identifying deaths. Prostate cancer cases were categorised according to ICD-O-2 behavioral codes as benign, uncertain whether benign or malignant, carcinoma in situ, malignant primary, malignant metastatic, and malignant uncertain whether primary or metastatic site.

In EPIC-Greece, a prospective cohort analysis with follow-up from 1994 to 2016 was carried out to examine the relationship of olive oil intake with prostate cancer risk.

The relationship between olive oil consumption and risk of incident prostate cancer was investigated using Cox proportional hazards models overall and for clinical subgroups, in both the HPFS and EPIC-Greece study. Person-time was computed using the age at baseline as the entry time and the age at first prostate cancer diagnosis for incident cases, while the age at death or the last full follow-up for non-cases, depending on which occurred first. Cox proportional hazards regression models were adjusted, where variables were available for the two studies, for age, time period, ethnicity (white, non-white), Southern European/Mediterranean ancestry (yes, no), height (inches; ≤68, >68 to 70, >70 to 72, >72 or in cm as continuous for EPIC-Greece), BMI at age 21 (kg/m^2; ≤20, 21 to <23, 23 to <25, ≥25), smoking status (never, former, current), BMI (kg/m^2; ≤18.5, 18.5 to<25, 25 to <30, ≥30), red meat, fruits and vegetables, and nuts intake (continuous or in quintiles), physical activity (as measured by metabolic equivalents, <35 MET-h, ≥35 MET-h), family history of prostate cancer (yes, no), Prostate-specific antigen (PSA) testing in >50% of previous cycles (yes, no), total energy intake (kilocalories per day), alcohol intake (quintiles or in categories in g per day), and other risk factors who have previously been linked to the incidence of prostate risk such as multivitamin use (yes, no), vitamin E supplement use (yes/no), aspirin use (yes, no), anti-cholesterol medication (yes, no), and diabetes (yes, no).

In HPFS, the cumulative method was used to update the time-varying exposure using the information from all FFQs administered throughout the course of follow-up cycles in order to better represent long-term diet and reduce within-person variation. In case of missing values, overexposure data from the previous questionnaire cycle were used. A linear trend was calculated by a Wald test, considering olive oil intake as a continuous variable using the median olive oil intake value of each category. As a reference group in models, the category of zero or less than once per month was used for HPFS, while the category of a low olive oil consumption (less or equal to 2 tablespoons per day) was assessed for EPIC-Greece study. The SAS 9.4 (SAS Institute Inc, Cary, NC) and Stata 11 (StataCorp. 2011) software were used to perform the statistical analyses. Statistical tests were two-estimated and those with $P<0.05$ were considered statistically significant.

For both studies, men with a history of cancer other than non-melanoma skin cancer at baseline or those with missing values in olive oil consumption were excluded from the analyses. In HPFS, those who reported a consumption of less than 800 kcal per day or more than 4200 kcal per day of energy intake were excluded, whereas in EPIC-Greece, those with a consumption of less than 1036 kcal per day or more than 4442 kcal per day (the top and bottom 1% of total energy intake) were excluded.

In HPFS, during an average of 20 years of follow-up, 6,650 cases of prostate cancer were identified, including 4,573 localised cases, 515 advanced cases, 956 lethal cases, and 806 fatal cases. In EPIC-Greece during a mean of a 15-year follow-up 131 cases of prostate cancer were found, where among them 31 were identified as localised, 21 as advanced, and 10 as fatal cases. The mean olive oil intake for the HPFS in the highest category (>1/2 tablespoon per day) was about 12 g per day (**Table V-1**). Men with higher intakes of olive oil were less likely to smoke and have diabetes, more likely to have more PSA screenings, and also tended to have a higher energy intake and higher intakes of fruits and vegetables than men in the lowest intake category. They were also more likely to use multivitamins and anti-cholesterol drugs (**Table V-1**). None of the male participants in the EPIC-Greece study reported zero consumption of olive oil at baseline. The majority (37.9%) of them reported a consumption between 3 and less than or equal to 4 tablespoons per day, 21.7% a consumption between 4 and less than or equal to 5 tablespoons per day, and 7.1% a consumption of more than 5 tablespoons per day of olive oil (**Table V-2**). Among them, those with the highest intake of olive oil were more likely to have a low education level, be less physically active, have a BMI between 25 and 30 kg/m^2, be former smokers, and drink less alcohol. Furthermore, they were found

to have higher intakes of vegetables, legumes, and fish and lower intakes of meat and dairy (**Table V-2**).

Multivariable analysis revealed that there was a significant association between olive oil intake and total prostate cancer (Ptrend=0.01) or localized disease (Ptrend=0.03) in HPFS. Compared with those who consumed olive oil never or less than once per month, those with > 7 g/d or ½ tablespoon intake of olive oil had 29% lower risk of total prostate cancer (HR: 0.71, 95% CI: 0.63-0.80, Ptrend=0.01). A lower risk of advanced, lethal, and fatal prostate cancer was found among men with higher olive oil intake, although the results were not linear (**Table V-3**). Per each 5 g per d increase in olive oil intake there was a marginally lower risk of total or localised prostate cancer (HR: 0.96, 95% CI: 0.93-0.99) in the overall population (**Table V-3**).

The multivariate hazards ratios for total prostate cancer risk in the EPIC-Greece study by comparing the lowest category of olive oil intake (more than 0 and less or equal to 2 tablespoons) versus higher consumptions of olive oil intake showed no associations. No associations were observed between olive oil and prostate cancer among those with a BMI of 30 kg/m2 or less and ages below or above 65 years old (**Table V-4**).

Table V-1 Characteristics of men participants† according to categories of olive oil intake in the Health Professionals Follow-up Study.

	Olive oil intake			
	Never/ < 1/month	>0–≤4.5 g/d (>0 to ≤1 teaspoon)	>4.5–≤7 g/d (>1 teaspoon to ≤1/2 TBS)	>7 g/d (>1/2 TBS)
Number of participants	3,474	24,995	5,120	7,570
Total olive oil, g/d	0.0 (0.0)	1.6 (1.3)	5.7 (0.7)	12.0 (5.3)
Ethnicity, white, %	90.4	91.9	93.4	93.3
Southern European or Mediterranean ancestry, %	19.6	19.9	22.8	31.9
Height, inches	70.0 (2.6)	70.2 (2.6)	70.2 (3.7)	70.3 (2.6)
BMI at age 21, kg/m2	21.4 (5.9)	22.1 (4.9)	22.2 (5.0)	22.4 (4.7)
Never smoker, %	88.4	75.3	64.6	67.2
Former smoker, %	10.9	24.1	34.7	32.5
Family history of prostate cancer, %	18.4	18.6	18.4	19.6
PSA screening in 1993-1994, %	45.3	46.9	44.0	41.8
Multivitamin supplement use, %	47.0	66.5	70.5	68.4
Physical activity, METs-h/week	35.6 (0.0)	35.6 (0.0)	35.6 (0.0)	35.6 (0.0)
Aspirin use, %	28.3	20.7	18.5	20.1
Anti-cholesterol drugs, %	12.1	36.3	44.5	41.7
Diabetes, %	19.5	15.9	15.3	13.9
Alcohol intake, g/d	7.1 (13.1)	10.5 (14.1)	14.7 (16.3)	16.5 (17.0)
Total energy intake, kcal/d	1897.5 (644.6)	1995.3 (652.5)	2125.0 (644.9)	2204.1 (667.0)
Red meat, serving/d	1.0 (0.7)	0.9 (0.6)	0.9 (0.6)	0.9 (0.6)
Fish, servings/d	0.3 (0.3)	0.3 (0.2)	0.4 (0.2)	0.4 (0.3)
Nuts, servings/d	0.2 (0.3)	0.3 (0.3)	0.3 (0.3)	0.3 (0.3)
Fruit, servings/d	2.4 (1.4)	2.5 (1.3)	2.6 (1.3)	2.8 (1.4)
Vegetables, servings/d	2.9 (1.4)	3.1 (1.4)	3.6 (1.4)	4.0 (1.6)

† Values are means (SD) for continuous variables; percentages for categorical variables, and are standardized to the age distribution of the study population. TBS, tablespoons; BMI, body mass index; MET, metabolic equivalent task.

Table V-2 Characteristics of men participants† according to categories of olive oil intake in the Greek segment of European Investigation into Nutrition and Cancer (EPIC-Greece) study.

	Olive oil intake				
	>0-≤2 TBS	>2-≤3 TBS	>3-≤4 TBS	>4-≤5 TBS	>5 TBS
Number of participants	1,510	2,077	4,088	2,343	769
Age <45 years, %	21	36	35	33	30
45-54 years	19	25	24	24	26
55-64 years	29	20	20	20	21
≥65 years	30	19	21	22	22
Education, Low, %	77	53	52	50	46
Intermediate,	15	26	27	26	25
High	8	21	20	24	28
Physical activity,	53	54	57	59	58
<35 MET-h, %					
≥35 MET-h	47	46	43	41	41
BMI, ≤25 kg/m^2, %	18	22	20	18	17
>25-<30 kg/m^2	50	51	53	54	54
≥30 kg/m^2	32	27	27	28	28
Height, cm	168 (7)	170 (7)	170 (7)	170 (7)	170 (7)
Smoking status, Never, %	26	21	25	26	27
Former	35	31	33	35	39
Current	39	48	42	39	33
Alcohol, 0 g/d, %	0.7	0.3	0.1	0.3	1
1-12 g/d	49	42	50	59	68
>12-≤47 g/d	37	39	40	36	29
>47 g/d	13	18	10	4	2
Energy, kcal/d	2374 (672)	2431(678)	2533 (617)	2202 (608)	2120 (670)
Vegetables, g/d	523 (197)	490 (184)	551 (182)	648 (214)	814 (303)
Legumes, g/d	8 (5)	9 (6)	10 (6)	11 (7)	14 (12)
Fruit, g/d	332 (183)	367 (200)	375 (194)	370 (208)	343 (221)
Dairy, g/d	256 (155)	248 (168)	225 (138)	187 (120)	150 (118)
Cereals, g/d	202 (77)	207 (89)	195 (74)	162 (61)	132 (54)
Meat, g/d	136 (59)	131 (61)	129 (57)	117 (56)	98 (51)
Fish, g/d	20 (14)	24 (15)	26 (17)	29 (19)	36 (40)

† Values are means (SD) for continuous variables; percentages for categorical variables, and are standardized to a diet of 2000 kcal/d. TBS, tablespoons; BMI, body mass index; MET, metabolic equivalent task.

Table V-3 Hazard ratios† and 95% confidence intervals for the association between olive oil intake and prostate cancer risk in the Health Professionals Follow-up Study (1990-2016).

	Olive oil intake					
	Never or <1/month	>0–≤4.5 g/d (>0 to ≤1 teaspoon)	>4.5–≤ 7 g/d (>1 teaspoon to ≤1/2 TBS)	>7 g/d (>1/2 TBS)	Ptrend	Per 5g increase
Total prostate cancer						
Cases	796	3934	725	1066		
Multivariable-adjusted	1 [Reference]	0.75 (0.68, 0.88)	0.76 (0.67, 0.86)	0.71 (0.63, 0.80)	0.01	0.96 (0.93,0.99)
Localized prostate cancer						
Cases	533	3037	565	854		
Multivariable-adjusted	1 [Reference]	0.84 (0.75, 0.94)	0.82 (0.71, 0.95)	0.79 (0.69, 0.90)	0.03	0.96 (0.92, 0.99)
Advanced prostate cancer						
Cases	77	270	52	54		
Multivariable-adjusted	1 [Reference]	0.74 (0.53, 1.00)	0.84 (0.54, 1.29)	0.61 (0.39, 0.94)	0.21	0.94 (0.81, 1.09)
Lethal						
Cases	164	539	81	91		
Multivariable-adjusted	1 [Reference]	0.80 (0.64, 0.99)	0.88 (0.65, 1.23)	0.65 (0.47, 0.91)	0.07	0.93 (0.84, 1.03)
Fatal						
Cases	149	436	59	75		
Multivariable-adjusted	1 [Reference]	0.75 (0.58, 0.96)	0.74 (0.50, 1.08)	0.63 (0.49, 0.91)	0.08	0.91 (0.81, 1.02)

Localized prostate cancer, stage T1/T2 and N0, M0 at diagnosis; advanced prostate cancer, stage T3b/T4/N1/M1 at diagnosis; lethal prostate cancer, prostate cancer death or distant metastasis; fatal prostate cancer, prostate cancer death.

† Multivariable-adjusted models adjusted for age, time period, ethnicity (white, non-white), Southern European/Mediterranean ancestry (yes, no), height (in; ≤68, >68 to 70, >70 to 72, >72), BMI at age 21 (kg/m2; ≤20, 21 to <23, 23 to <25, ≥25), smoking status (never, former, current), family history of prostate cancer (yes, no), PSA testing in >50% of previous cycles (yes, no), total energy intake (kilocalories per day), multivitamin use (yes, no), vitamin E supplement use (yes/no), alcohol intake (g/d; quintiles), aspirin use (yes, no), anti-cholesterol medication (yes, no), diabetes (yes, no), BMI (kg/m2; ≤18.5, 18.5 to<25, 25 to <30, ≥30), red meat, fruits and vegetables, and nuts intake (in quintiles).

Table V-4 Hazard ratios† and 95% confidence intervals for the association between olive oil intake and prostate cancer risk in the Greek segment of European Investigation into Nutrition and Cancer (EPIC-Greece) study (1994-2016).

	Olive oil intake				
	>0-≤2 TBS	>2-≤3 TBS	>3-≤4 TBS	>4-≤5 TBS	>5 TBS
Total prostate cancer					
Cases	17	17	50	35	12
Multivariable-adjusted	1 [Reference]	0.89 (0.44-1.78)	1.15(0.64-2.06)	1.31 (0.69-2.49)	1.26 (0.51-3.10)
BMI, <30 kg/m^2					
Cases	11	13	32	19	6
Multivariable-adjusted	1 [Reference]	0.95 (0.2-2.16)	1.04 (0.51-2.10)	0.96 (0.43-2.17)	0.71 (0.22-2.32)
BMI, ≥30 kg/m2	5	4	17	16	6
Cases	1 [Reference]	0.67 (0.17-2.59)	1.42 (0.51-3.98)	2.33 (0.78-6.99)	3.12 (0.73-13.4)
Multivariable-adjusted					
Age, <65 years					
Cases	11	10	32	19	9
Multivariable-adjusted	1 [Reference]	0.68 (0.28-1.68)	1.00 (0.48-2.09)	0.85 (0.37-1.95)	0.93 (0.31-2.76)
Age, ≥65 years					
Cases	6	7	18	16	3
Multivariable-adjusted	1 [Reference]	1.07 (0.35-3.3)	1.25 (0.48-3.2)	2.15 (0.77-6.05)	1.85 (0.35-9.7)

† Multivariable-adjusted model for age at recruitment, educational level, BMI, height, physical activity, smoking status, alcohol consumption, energy intake, vegetables, fruit, legumes, meat, dairy, cereals, and fish intake. TBS, tablespoons.

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Supplemental Tables

Supplemental Table I-1 Characteristics of the case-control studies with coffee information in the Stomach cancer Pooling (StoP) Project consortium.

STUDY ID	COUNTRY	PERIOD	STUDY DESIGN	CAFFEINATED	DECAFFEINATED	MEASUREMENT UNIT
1	Italy	1985-1997	CC	x	x	cups per day
3	Italy	1997-2007	Matched, CC	x	x	cups per week
5	Italy	1985-1987	Matched, CC	x		cups per month
6	Greece	1981-1984	Matched, CC	x		never; rarely; at least once a month; once a week; at least twice a week; daily
7	Canada	1994-1997	Matched, CC	x		cups per week
9	Russia	1996-1997	CC	x	x	times per week or month
14	USA	1992-1994	CC	x	x	cups per day or week or month or year
16	Portugal	1999-2006	Matched, CC	x		cups per week
20	Spain	2008-2012	Matched, CC	x	x	times per day
22	Spain	1995-1999	Matched, CC	x	x	never or less than once per month; 1-2 per month; 2-3 per month; 1-2 per week; 3-4 per week; 5-6 per week; 1 per day; 2 or more per day
24	Mexico	2004-2005	Matched, CC	x		cups per week
25	Mexico	1989-1990	Matched, CC	x		cups per week
26	Brazil	1991-1994	CC	x		cups per day
27	Brazil	1991-1994	CC	x		cups per day
28	Japan	1998-2002	Matched, CC	x		cups per day
30	USA	1998-1993	Matched, CC	x		never or less than once per month; 1 per month; 2-3 per month; 1 per week; 2 per week; 3-4 per week; 5-6 per week; every day
31	Greece	1994-1999	Matched, Cohort, nested CC	x	x	g per day
33	USA	1995-1996	Cohort, nested CC	x	x	never or less than once per month; 1 per month; 2-3 per month; 1 per week; 2 per week; 3-4 per week; 5-6 per week; every day

Supplemental Table II-1 Characteristics of the case-control studies with tea information in the Stomach cancer Pooling (StoP) Project consortium.

STUDY ID	COUNTRY	PERIOD	STUDY DESIGN	TEA	TEA AMOUNT	TEMPERATURE OF TEA DRINKING	HOW STRONG TEA IS	MEASUREMENT UNIT
1	Italy	1985-1997	CC	X	X			cups per day
2	China	1987-1989	CC	X	X	x	x	Liang (1 Liang=50 g) /year
3	Italy	1997-2007	Matched, CC	X	X			cups per week
5	Italy	1985-1987	Matched, CC	X	X			cups per month
6	Greece	1981-1984	Matched, CC	X				never; rarely; at least once a month; once a week; at least twice a week; daily
7	Canada	1994-1997	Matched, CC	X	X			cups per week
9	Russia	1996-1997	CC	X		x	x	times per week or month
10	Iran	2004-2005	Matched, CC	X	X	x	x	Cups per day
12	China	1991-1993	CC	X	X	x	x	Frequency categories
13	China	1995	CC	X		x	x	Frequency categories
14	USA	1992-1994	CC	X	X			cups per day or week or month or year
16	Portugal	1999-2006	Matched, CC	X	X			cups per week
22	Spain	1995-1999	Matched, CC	X	X			never or less than once per month; 1-2 per month; 2-3 per month; 1-2 per week; 3-4 per week; 5-6 per week; 1 per day; 2 or more per day
23	Mexico	2004-2005	Matched, CC	X	X			cups per week
26	Brazil	1991-1994	CC	X	X			cups per day
27	Brazil	1991-1994	CC	X	X			cups per day
28	Japan	1998-2002	Matched, CC	X	X			cups per day
30	USA	1998-1993	Matched, CC	X	X	x		never or less than once per month; 1 per month; 2-3 per month; 1 per week; 2 per week; 3-4 per week; 5-6 per week; every day
31	Greece	1994-1999	Matched, Cohort, nested CC	X				g per day
33	USA	1995-1996	Cohort, nested CC	X	X			never or less than once per month; 1 per month; 2-3 per month; 1 per week; 2 per week; 3-4 per week; 5-6 per week; every day
34	Brazil	2016-ongoing	CC	X	X			Cups per day