Cancer Causes & Control (2022) 33:779–791
https://doi.org/10.1007/s10552-022-01565-y

ORIGINAL PAPER

Salt intake and gastric cancer: a pooled analysis within the Stomach cancer Pooling (StoP) Project

Samantha Morais[1,2,3] · Adriana Costa[1,2] · Gabriela Albuquerque[1,2] · Natália Araújo[1,2,3] · Claudio Pelucchi[4] · Charles S. Rabkin[5] · Linda M. Liao[5] · Rashmi Sinha[5] · Zuo-Feng Zhang[6] · Jinfu Hu[7] · Kenneth C. Johnson[8] · Domenico Palli[9] · Monica Ferraroni[4] · Rossella Bonzi[4] · Guo-Pei Yu[10] · Lizbeth López-Carrillo[11] · Reza Malekzadeh[12] · Shoichiro Tsugane[13] · Akihisa Hidaka[13] · Gerson Shigueaki Hamada[14] · David Zaridze[15] · Dmitry Maximovitch[15] · Jesus Vioque[16,17] · Manoli García de la Hera[16,17] · Victor Moreno[16,18,19,20] · Mercedes Vanaclocha-Espi[21] · Mary H. Ward[5] · Mohammadreza Pakseresht[12,22,23] · Raúl Ulises Hernández-Ramirez[24] · Malaquias López-Cervantes[25] · Farhad Pourfarzi[12,26] · Lina Mu[27] · Robert C. Kurtz[28] · Stefania Boccia[29,30] · Roberta Pastorino[29] · Areti Lagiou[31] · Pagona Lagiou[32,33] · Paolo Boffetta[34,35] · M. Constanza Camargo[5] · Maria Paula Curado[36] · Eva Negri[4] · Carlo La Vecchia[4] · Nuno Lunet[1,2,3]

Received: 19 December 2021 / Accepted: 22 February 2022 / Published online: 19 March 2022

Abstract

Purpose Previous studies show that consuming foods preserved by salting increases the risk of gastric cancer, while results on the association between total salt or added salt and gastric cancer are less consistent and vary with the exposure considered. This study aimed to quantify the association between dietary salt exposure and gastric cancer, using an individual participant data meta-analysis of studies participating in the Stomach cancer Pooling (StoP) Project.

Methods Data from 25 studies (10,283 cases and 24,643 controls) from the StoP Project with information on salt taste preference (tasteless, normal, salty), use of table salt (never, sometimes, always), total sodium intake (tertiles of grams/day), and high-salt and salt-preserved foods intake (tertiles of grams/day) were used. A two-stage approach based on random-effects models was used to pool study-specific adjusted (sex, age, and gastric cancer risk factors) odds ratios (aORs), and the corresponding 95% confidence intervals (95% CI).

Results Gastric cancer risk was higher for salty taste preference (aOR 1.59, 95% CI 1.25–2.03), always using table salt (aOR 1.33, 95% CI 1.16–1.54), and for the highest tertile of high-salt and salt-preserved foods intake (aOR 1.24, 95% CI 1.01–1.51) *vs.* the lowest tertile. No significant association was observed for the highest *vs.* the lowest tertile of total sodium intake (aOR 1.08, 95% CI 0.82–1.43). The results obtained were consistent across anatomic sites, strata of *Helicobacter pylori* infection, and sociodemographic, lifestyle and study characteristics.

Conclusion Salty taste preference, always using table salt, and a greater high-salt and salt-preserved foods intake increased the risk of gastric cancer, though the association was less robust with total sodium intake.

Keywords Consortium · Pooled analysis · Sodium, Dietary · Sodium chloride · Stomach neoplasms

Introduction

Gastric cancer is the fourth most common cancer worldwide and the fourth leading cause of cancer deaths [1]. Over the last several decades, there has been a steady decline in its incidence and mortality [2]. This burden reduction is mainly attributed to a decrease in the prevalence of *Helicobacter pylori* (*H. pylori*) infection [3, 4], and to improvements in food preservation practices, such as an increased use of refrigeration, which enables a greater consumption of fresh fruits and vegetables, and a decreased use of traditional methods of food preservation, such as salting [5].

The most recent World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) Report found strong evidence that consuming foods preserved by salting increases the risk of gastric cancer, while there was

✉ Nuno Lunet
nlunet@med.up.pt

Extended author information available on the last page of the article

limited evidence on the association between total salt or use of table salt and gastric cancer [6]. Most studies examining these associations have been conducted in East Asian countries, and predominantly focus on high-salt foods and salt-preserved foods, including pickled vegetables and salted or dried fish [6]. Additionally, analyses considering cancer anatomical subtype have not been possible and most studies do not take into account *H. pylori* infection status [6].

The Stomach cancer Pooling (StoP) Project, an international consortium of case–control and nested case–control within cohort studies, which uses an individual participant data approach for the evaluation of the associations between risk factors and gastric cancer [7], allows for some of these limitations to be overcome. Therefore, this study aimed to quantify the association between dietary salt exposure, defined according to different criteria (salt taste preference, use of table salt, total sodium intake, and high-salt and salt-preserved foods intake), and gastric cancer, using an individual participant data meta-analysis of studies participating in the StoP Project.

Methods

For this study, version 3.0 of the StoP Project dataset was used, which includes a total of 12,511 cases of gastric cancer and 29,964 controls from 32 case–control or nested case–control studies [8–37]. All data were collected and harmonized according to a pre-specified format at the pooling center. The participating studies were conducted in accordance with applicable laws, regulations and guidelines for the protection of human subjects, and the StoP Project was approved by the University of Milan Review Board (Reference 19/15).

The present analysis used data from 25 studies, corresponding to 10,283 cases and 24,643 controls with information on dietary salt and/or sodium intake: Brazil (two studies) [31, 32], Canada [14], China (four studies) [9, 15, 19, 20], Greece [13], Iran (two studies) [17, 18], Italy (four studies) [8, 10–12], Japan [33], Mexico (three studies) [28–30], Portugal [22], Russia [16], Spain (two studies) [25, 27], and USA (three studies) [21, 35, 37].

The quality of studies included was assessed using the Newcastle–Ottawa Scale (NOS) [38]. The scale evaluates the quality of studies based on three different categories: selection, comparability, and exposure (case-control studies)or outcome (nested case-control studies). A study can be awarded a maximum of nine stars, which indicates the highest quality.

Dietary salt exposure was defined according to several different criteria, as described in detail in Supplementary Table 1. First, salt taste preference was collected and defined as tasteless, normal, or salty ($n = 11$ studies). Second, the frequency of use of table salt was assessed and defined as never, sometimes, or always ($n = 11$ studies). Third, total dietary sodium intake in grams/day, as a computed nutrient, was estimated using food frequency questionnaires (FFQs). Two studies [9, 20] only provided information on the consumption of salt in grams/day as reported by participants. For analysis, total sodium intake in grams/day was categorized into study-specific tertiles according to the distribution in controls ($n = 16$ studies). Fourth, high-salt and salt-preserved foods intake in grams/day was estimated by adding up the amounts in grams of each single food item or group consumed per day obtained using FFQs. These foods included the main food items or food groups contributing to total dietary sodium intake [39], namely pickles or pickled vegetables, vegetables braised in soy sauce, preserved and/or fermented bean curd, miso soup, salty snacks (e.g., potato chips, corn chips, popcorn, crackers), cheese (e.g., cream cheese, parmesan cheese, sliced cheese), salty condiments (e.g., soy sauce, mayonnaise, ketchup), salted vegetables, fish or meat, smoked, dried or processed fish or meat (e.g., canned tuna, sausages or hot dogs, bacon, ham, cold cuts or lunch meats, croquettes), and grains, cereals and potatoes (e.g., rice, pasta, bread). For analysis, the study-specific tertiles of high-salt and salt-preserved foods intake observed in the controls were used as cut-offs to define groups of exposure ($n = 20$ studies).

Depending on the study, FFQs were used to obtain information on the dietary habits of participants for the period of one, two, or five years before diagnosis (for cases from case–control studies), onset of disease or hospital admission (for hospital-based controls) or recruitment (for population-based controls, and participants from the nested case–control study [37]; Supplementary Table 1). Most studies ($n = 21$) used face-to-face interviews by trained researchers for the administration of FFQs, while the remaining used self-administered FFQs. Fourteen of the included studies reported that the FFQ used was previously validated using 24-h recall interviews and/or dietary records. The FFQs used in the studies included between 19 and 147 individual food and beverage items.

A two-stage modeling approach was used to quantify the association between dietary salt exposure and gastric cancer [40]. First, the study-specific odds ratios (ORs) and corresponding 95% confidence intervals (95% CI) were estimated for the association between each measure of dietary salt exposure and gastric cancer using multivariable unconditional logistic regression models. Models were adjusted for sex, age (5-year age groups: < 40; 40–44; …; 70–74; ≥ 75), socioeconomic status (low, intermediate, or high, as defined in each original study based on education, income or occupation), smoking status (never, former and current smokers of < 10 cigarettes/day [low]; 10 to 20 cigarettes/day [intermediate]; > 20 cigarettes/day [high]), alcohol

drinking (never, low: < 13 g of ethanol/day, intermediate: 13 to 47 g of ethanol/day, high: > 47 g of ethanol/day), fruits and vegetables intake (study-specific tertiles), total energy intake (study-specific tertiles), study center (for multicenter studies), and race/ethnicity (White, Black/African American, Asian, Hispanic/Latino, other), when appropriate and available as described in detail in Supplementary Table 2. Second, summary (pooled) effect estimates were computed using random-effects models [41]. Heterogeneity between studies was quantified using I^2 (%) statistics [42].

Stratified analyses were also carried out to further explore the effect of dietary salt exposure across strata of sex, age (≤ 55, 56–65, > 65), geographic region, socioeconomic status, smoking status, alcohol drinking, fruits and vegetables intake, and type of study (hospital-based controls, population-based controls, nested case–control study). The difference between groups was assessed through the Q test for heterogeneity [43]. Multinomial logistic regression models were used to estimate the ORs for each cancer anatomical subsite separately (i.e., cardia, non-cardia, not accurately classifiable), and each histological type separately (i.e., intestinal, diffuse, undifferentiated).

Sensitivity analyses were carried out by defining the same categories of exposure for all studies according to the distribution of total sodium intake, and high-salt and salt-preserved foods intake in all controls. Categories of exposure for total sodium intake were also further defined considering the maximum intake amounts recommended by the World Health Organization (WHO), i.e., less than two grams of sodium/day [44]. The cut-offs that describe consumption of less than half of the recommended amount, between half and the recommended amount or more than the recommended amount were used, resulting in three categories (< 1.0, 1.0–1.9, ≥ 2.0 g of sodium/day). Additional sensitivity analyses included comparing the estimates adjusted and not adjusted for total energy intake ($n = 16$ studies), as well as stratified by seroinfection by *H. pylori*, among studies with the available information ($n = 11$ studies). Furthermore, studies that used a self-administered FFQ ($n = 4$ studies), non-validated FFQs ($n = 11$), and that scored five or less stars in the NOS ($n = 5$ studies, lower quality) were removed, and analyses were also restricted to studies evaluating participants more than one year before the gastric cancer diagnosis. Finally, the influence of each study on the pooled estimates was also examined by excluding one study at a time.

Statistical analyses were performed using STATA version 15.1 (STATA Corporation, College Station, Texas, USA). A *p*-value less than 0.05 was considered statistically significant.

Results

The main sociodemographic characteristics of the cases and controls are described in Supplementary Table 3, and the distribution of dietary salt exposure, defined according to different criteria by case–control status, is shown in Supplementary Tables 4 and 5.

The study-specific and pooled adjusted ORs for dietary salt exposure, defined according to different criteria, and gastric cancer are presented in Fig. 1. A significantly higher risk of gastric cancer was observed for a salty taste preference (OR 1.59, 95% CI 1.25–2.03, $I^2 = 66.2\%$), always using table salt

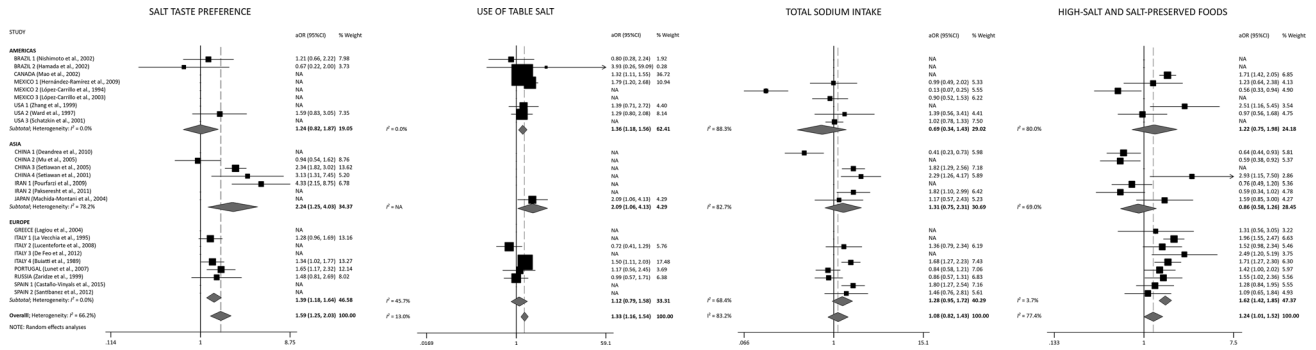

Fig. 1 Forest plots describing the association between salt taste preference (salty *vs.* tasteless), use of table salt (always *vs.* never), total sodium intake (grams/day—study-specific 3rd tertile *vs.* 1st tertile), and high-salt and salt-preserved foods intake (grams/day—study-specific 3rd tertile *vs.* 1st tertile), and gastric cancer using estimates from the Stomach cancer Pooling (StoP) Project database. *95% CI* 95% confidence interval, *aOR* adjusted odds ratio, *NA* not available. [a]Pooled ORs were computed using random-effects models. Study-specific ORs were adjusted, when available and applicable, for sex, age (5-year age groups: < 40; 40–44; …; 70–74; ≥ 75), socioeconomic status (low, intermediate, or high, as defined in each original study based on education, income or occupation), smoking status (never, former and current smokers of < 10 cigarettes/day [low]; 10–20 cigarettes/day [intermediate]; > 20 cigarettes/day [high]), alcohol drinking (never, low: < 13 g of ethanol/day, intermediate: 13 to 47 g of ethanol/day, high: > 47 g of ethanol/day), fruit and vegetables intake (study-specific tertiles), total energy intake (study-specific tertiles), study center (for multicenter studies), and race/ethnicity (White, Black/African American, Asian, Hispanic/Latino, other)

(OR 1.33, 95% CI 1.16–1.54, $I^2 = 13.0\%$), and a higher high-salt and salt-preserved foods intake (grams/day; OR highest *vs.* lowest tertile: 1.24, 95% CI 1.01–1.51, $I^2 = 77.4\%$). No significant association was observed for a greater total sodium intake (grams/day; OR highest *vs.* lowest tertile: 1.08, 95% CI 0.82–1.43, $I^2 = 83.2\%$). Using the same cut-off for all studies, defined either by the overall distribution in all controls or taking the total sodium intake amounts recommended by the WHO into account, led to estimates of the same magnitude, with slightly lower heterogeneity (Table 1).

The effect of dietary salt exposure was consistent across most strata of sociodemographic and lifestyle characteristics, and similar when considering each cancer anatomical subsite and histological type (Table 2). Although the difference was not statistically significant, studies with population-based controls presented a higher risk of gastric cancer for salty taste preference (OR 1.83, 95% CI 1.33–2.52, $I^2 = 72.6\%$) compared to studies with hospital-based controls (OR 1.27, 95% CI 0.98–1.64, $I^2 = 0.0\%$; p for interaction = 0.081). For high-salt and salt-preserved foods intake, there were significant differences according to geographic region (p for interaction = 0.007), with a significant association being observed among studies conducted in Europe (OR 1.62, 95% CI 1.42–1.85, $I^2 = 3.7\%$) but not in studies conducted in the Americas (OR 1.22, 95% CI 0.75–1.98, $I^2 = 80.0\%$) or Asia (OR 0.86, 95% CI 0.58–1.26, $I^2 = 69.0\%$). Differences were also observed considering socioeconomic status (p for interaction = 0.024), though no consistent pattern was observed, a stronger and significant association was found among those with a higher socioeconomic status (OR 1.71, 95% CI 1.32–2.22, $I^2 = 1.2\%$). Further sensitivity analyses did not result in major changes in the direction or magnitude of the associations when considering OR estimates adjusted for total energy intake.

Additional stratified analyses according to study characteristics generally yielded similar and consistent results throughout (Supplementary Table 6). The magnitude of estimates remained essentially unchanged when considering the validity of the FFQ and method of administration. Regarding the period of assessment, the results did not materially differ from those of the main analysis, except for a stronger and statistically significant association between high total sodium intake and gastric cancer being observed when considering studies evaluating dietary intake more than one year before diagnosis (OR 1.60, 95% CI 1.33–1.93, $I^2 = 0.0\%$). Finally, applying the NOS to the included studies and removing those with five stars or less (lower quality) also did not change the associations observed in the overall analyses.

Discussion

In this study within the StoP consortium, a higher risk of gastric cancer was observed for a salty taste preference, always using table salt, and a greater intake of high-salt and salt-preserved foods, which was consistent across sociodemographic, lifestyle, and tumor characteristics. No significant association was found for the highest tertile intake of sodium compared to the lowest tertile.

Several systematic reviews reported that excessive salt intake is associated with the risk of gastric cancer [45–47] and the WCRF/AICR has classified salt as an important risk factor for gastric cancer [6]. In particular, strong evidence was observed for the association between consuming foods preserved by salting or high-salt foods and a greater risk of gastric cancer [6, 47]. However, the majority of studies examining this association were conducted in Asian countries [6]. In the current study, which includes participants from 11 countries in America, Asia and Europe, we observed an association between high-salt and salt-preserved foods intake and gastric cancer risk. However, a statistically significant association was not found when considering studies conducted in the Americas and Asia. This may have occurred due to the diversity of items included in each study, ranging from pickles or pickled vegetables, salty snacks, salted vegetables or fish to salty condiments, which likely also contributed to the heterogeneity observed. Furthermore, although several systematic reviews found that the risk of gastric cancer was higher among individuals with high salt intake than in those with low levels of consumption [45–47], the WCRF/AICR reported limited evidence regarding the association between total salt or added salt and gastric cancer risk [6]. In the current study, we observed an association between always using table salt and gastric cancer, though our findings were less robust when considering total sodium intake.

A concern in assessing total dietary sodium intake is the fact that it is a natural component present in most foods, and it may also be added during the cooking process or at the table in amounts that individuals usually ignore or are unable to accurately report [48]. Although excretion of sodium in urine over a 24-h period is widely regarded as the gold standard method for the assessment of sodium ingested from different sources [49] it cannot be retrospectively used in case–control studies. As such, several different approaches, including salt taste preference, adding salt at the table, total sodium intake, and high-salt and salt-preserved foods intake were considered in the present pooled analyses. In fact, a salty taste preference and the use of salt at the table may result in an increase in overall salt consumption, and may be a more comprehensive measure of dietary salt intake since it considers more than the intrinsic sodium content of foods,

Table 1 Pooled odds ratios and 95% confidence intervals for gastric cancer according to salt taste preference (tasteless, normal, salty), use of table salt (no, sometimes, always), total sodium intake (grams/day—study specific, overall distribution and recommended amounts), and high-salt and salt-preserved foods intake (grams/day—study specific, overall distribution)

	Cases		Controls		Adjusted OR (95% CI)[a]	I^2 (%)
	N	%	N	%		
Total	10,283		24,643			
Salt taste preference[b]						
Tasteless	1,057	23.1	1,817	25.1	1	
Normal	1,935	42.3	3,578	49.4	1.09 (0.89–1.34)	59.2
Salty	1,581	34.6	1,845	25.5	**1.59 (1.25–2.03)**	66.2
Missing	78		1,082			
Not available	5,632		16,321			
Use of table salt[c]						
Never	2,564	55.5	5,672	52.6	1	
Sometimes	1,136	24.6	2,744	25.4	1.11 (0.95–1.30)	42.4
Always	920	19.9	2,373	22.0	**1.33 (1.16–1.54)**	13.0
Missing	93		4,39			
Not available	5,570		13,415			
Total sodium intake[d]						
According to the study-specific distribution in controls						
1st tertile	2,156	30.7	5,085	33.5	1	
2nd tertile	2,290	32.7	5,038	33.2	1.03 (0.86–1.24)	70.7
3rd tertile	2,587	36.8	5,040	33.2	1.08 (0.82–1.43)	83.2
Missing	166		468			
Not available	3,084		9,012			
According to the overall distribution in controls						
1st tertile	2,587	36.8	5,067	33.4	1	
2nd tertile	2,179	31.0	5,057	33.4	0.93 (0.77–1.13)	63.0
3rd tertile	2,267	32.2	5,039	33.2	1.05 (0.77–1.43)	75.0
Missing	166		468			
Not available	3,084		9,012			
According to the recommended sodium amounts (2 g/day)						
< 1.0	827	11.8	1,018	6.7	1	
1.0–1.9	1,573	22.4	3,610	23.8	1.18 (0.86–1.61)	42.7
≥ 2.0	4,633	65.9	10,535	69.5	1.12 (0.72–1.76)	56.4
Missing	166		468			
Not available	3,084		9,012			
High-salt and salt-preserved foods intake[e]						
According to the study-specific distribution in controls						
1st tertile	2,052	27.9	6,393	32.8	1	
2nd tertile	2,399	32.6	6,605	33.9	1.12 (0.98–1.27)	51.4
3rd tertile	2,905	39.5	6,505	33.3	**1.24 (1.01–1.51)**	77.4
Missing	80		219			
Not available	2,847		4,921			
According to the overall distribution in controls						
1st tertile	2,229	30.3	6,491	33.3	1	
2nd tertile	1,912	26.0	6,511	33.4	1.12 (0.90–1.40)	64.2
3rd tertile	3,215	43.7	6,501	33.3	1.27 (0.94–1.72)	68.2
Missing	80		219			
Not available	2,847		4,921			

95% CI 95% confidence interval, *OR* odds ratio

Percentages may not add to 100% due to rounding

Table 1 (continued)

[a]Pooled ORs were computed using random-effects models. Study-specific ORs were adjusted, when available and applicable, for sex, age (5-year age groups: < 40; 40–44; …; 70–74; ≥ 75), socioeconomic status (low, intermediate, or high, as defined in each original study based on education, income or occupation), smoking status (never, former and current smokers of < 10 cigarettes/day [low]; 10–20 cigarettes/day [intermediate]; > 20 cigarettes/day [high]), alcohol drinking (never, low: < 13 g of ethanol/day, intermediate: 13 to 47 g of ethanol/day, high: > 47 g of ethanol/day), fruit and vegetables intake (study-specific tertiles), total energy intake (study-specific tertiles), study center (for multicenter studies), and race/ethnicity (White, Black/African American, Asian, Hispanic/Latino, other)

[b]No information for studies: CANADA [14]; CHINA 1 [9] and 3 [19]; GREECE [13]; IRAN 2 [18]; ITALY 2 [10] and 3 [11]; JAPAN [33]; MEXICO 1 [28], 2 [29] and 3 [30]; SPAIN 1 [25] and 2 [27]; USA 1 [21] and 3 [37]

[c]No information for studies: CHINA 1 [9], 2 [15] and 4 [20]; GREECE [13]; IRAN 1 [17] and 2 [18]; ITALY 1 [8]; MEXICO 2 [29] and 3 [30]; SPAIN 1 [25] and 2 [27]; USA 3[37]

[d]No information for studies: BRAZIL 1 [31] and 2 [32]; CANADA [14]; CHINA 2 [15]; GREECE [13]; IRAN 1 [17]; ITALY 1 [8] and 3 [11]; USA 1 [21]. Two studies [9, 20] only provided information on the consumption of salt in grams/day as reported by participants, which was converted into total sodium intake in grams/day by dividing by 2.5 [44]

[e]No information for studies: BRAZIL 1 [31] and 2 [32]; CHINA 3 [19]; MEXICO 3 [30]; USA 3 [37]

which may underestimate intake. In fact, previous studies found that preference for salty foods was moderately associated with daily salt intake [50, 51]. Furthermore, the measurement of total sodium intake in diet is subject to methodological difficulties. In particular, diet records or diet recall often underestimate total sodium intake due to underreporting by participants and due to difficulties in quantifying the concentration of sodium in food items or food groups, as well as discretionary salt intake [49].

High sodium intake is reported to act as a gastric mucosa stimulant, leading to atrophic gastritis, increased DNA synthesis, and cell proliferation, thereby providing the basis for gastric cancer development [47]. Furthermore, high sodium intake may weaken the protective effect of the mucous barrier and promote the carcinogenic effect of *H. pylori* infection serostatus, which is a known primary risk factor for gastric cancer [52]. This could translate into a stronger association among *H. pylori* positive individuals; however, we did not observe significant differences in the risk of gastric cancer when stratifying according to *H. pylori* seroinfection. Nevertheless, these results should be interpreted cautiously since infection status was evaluated using serum samples in case–control studies, which may lead to false negative results in the presence of advanced infection [53]. Additionally, there are potential aetiological differences between gastric cancer anatomical subsites and histological types, with previous studies suggesting a greater influence of lifestyle factors among intestinal type gastric cancers compared to those of the diffuse type [22, 54]. We conducted various analyses considering cancer anatomical subsite and histological type, with consistent results being generally observed.

Low socioeconomic status is a well-recognized risk factor for gastric cancer [55–57] partly because of an unfavorable distribution of risk factors including selected dietary and lifestyle habits, which were included in the models as covariates. Individuals with a low socioeconomic status may have a diet high in salt, which may increase the negative effects of other lifestyle risk factors related to a low socioeconomic status, potentially leading to a higher gastric cancer risk. Additionally, in some countries refrigerator use was likely initially restricted to higher socioeconomic status groups, which enabled the consumption of fresh foods including seasonal vegetables and fruits year round, as well as fresh meat, and reduced the need for salting, smoking, curing, and pickling to preserve food [58, 59]. As such, we could hypothesize that lower socioeconomic status groups may have been more exposed to salt-preserved foods due to lack of alternatives rather than a preference for these foods. Indeed, previous studies have found that the consumption of processed or ultra-processed foods increases with education and income level [60, 61], and these foods are major contributors to an individual's dietary salt intake [62, 63]. In the present individual participant data meta-analysis, although differences according to socioeconomic status were observed for high-salt and salt-preserved foods intake, there was substantial heterogeneity among the studies included and there was an absence of a consistent trend. In general, no convincing evidence was observed for differences in the association between dietary salt intake and gastric cancer according to socioeconomic status, despite several criteria being used to evaluate dietary salt exposure.

Significant geographical differences were observed when considering high-salt and salt-preserved foods, with lower estimates among studies conducted in Asia, and higher ORs for studies from Europe and the Americas. Although not significantly different, higher estimates were observed among studies from Asia for salt taste preference and total sodium intake. The geographical differences observed may reflect the different diets, with higher sodium intakes being generally reported in Asia [64], but also the detail of the FFQs applied regarding the number and types of food items included, which likely contributed to the observed heterogeneity. Nevertheless, the concentration of salt in many processed foods consumed in Europe and North America approaches that of salt-preserved foods [6].

Table 2 Pooled odds ratio and 95% confidence interval of gastric cancer for the highest *vs.* lowest salt taste preference (salt *vs.* tasteless), use of table salt (always *vs.* never), total sodium intake (grams/day—study-specific 3rd tertile *vs.* 1st tertile), and high-salt and salt-preserved foods intake (grams/day—study-specific 3rd tertile *vs.* 1st tertile) according to strata of selected variables

	Salt taste preference		Use of table salt		Total sodium intake		High-salt and salt-preserved foods intake	
	Adjusted OR (95% CI)[a]	I^2 (%)	Adjusted OR (95% CI)[a]	I^2 (%)	Adjusted OR (95% CI)[a]	I^2 (%)	Adjusted OR (95% CI)[a]	I^2 (%)
Overall	1.59 (1.25–2.03)	66.2	1.33 (1.16–1.54)	13.0	1.08 (0.82–1.43)	83.2	1.24 (1.01–1.51)	77.4
Sex								
Males	1.52 (1.16–1.99)	51.2	1.20 (0.98–1.47)	23.7	1.02 (0.76–1.38)	74.4	1.14 (0.89–1.46)	72.2
Females	1.78 (1.44–2.21)	6.8	1.59 (1.14–2.22)	35.9	1.28 (0.87–1.87)	71.0	1.40 (1.12–1.75)	44.3
p for interaction	0.371		0.157		0.359		0.227	
Age (years)								
≤ 55	1.63 (1.27–2.10)	0.0	1.29 (1.01–1.64)	0.0	0.92 (0.65–1.31)	44.9	1.21 (0.94–1.55)	36.9
56–65	1.53 (1.14–2.05)	23.5	1.43 (1.14–1.79)	0.0	1.21 (0.83–1.75)	61.1	1.25 (0.91–1.70)	59.8
> 65	1.63 (1.17–2.28)	53.1	1.32 (1.02–1.71)	21.1	1.19 (0.91–1.54)	51.6	1.22 (0.96–1.55)	53.0
p for interaction	0.941		0.813		0.455		0.987	
Geographic region								
Americas	1.24 (0.82–1.87)	0.0	1.36 (1.18–1.56)	0.0	0.69 (0.34–1.43)	88.3	1.22 (0.75–1.98)	80.0
Asia	2.24 (1.25–4.03)	78.2	–	–	1.31 (0.75–2.31)	82.7	0.86 (0.58–1.26)	69.0
Europe	1.39 (1.18–1.64)	0.0	1.12 (0.79–1.58)	45.7	1.28 (0.95–1.72)	68.4	1.62 (1.42–1.85)	3.7
p for interaction	0.246		0.258		0.292		**0.007**	
Socioeconomic status[b]								
Low	1.80 (1.28–2.52)	62.8	1.46 (1.21–1.76)	0.0	1.33 (1.00–1.76)	54.4	1.30 (0.99–1.71)	68.8
Intermediate	1.58 (1.21–2.06)	14.6	1.21 (0.94–1.57)	20.3	0.91 (0.63–1.31)	65.9	0.98 (0.72–1.33)	61.8
High	1.00 (0.63–1.61)	0.0	1.24 (0.74–2.08)	40.7	1.07 (0.78–1.48)	0.0	1.71 (1.32–2.22)	1.2
p for interaction	0.129		0.479		0.255		**0.024**	
Smoking status								
Never	1.68 (1.31–2.15)	37.0	1.52 (1.23–1.88)	0.0	1.05 (0.74–1.47)	72.9	1.24 (0.96–1.61)	66.0
Former	1.57 (1.09–2.25)	20.4	1.28 (1.06–1.54)	0.0	1.03 (0.81–1.31)	10.3	1.18 (0.83–1.68)	60.8
Current	1.44 (1.00–2.09)	41.8	1.31 (0.79–2.16)	46.1	1.32 (0.76–2.30)	77.2	1.18 (0.93–1.50)	27.7
p for interaction	0.790		0.482		0.720		0.956	
< 10 cigarettes/day	2.54 (0.88–7.33)	60.7	0.93 (0.45–1.93)	0.0	1.84 (0.67–5.05)	65.2	1.12 (0.74–1.71)	3.8
10–20 cigarettes/day	1.29 (0.67–2.48)	45.1	1.65 (1.00–2.72)	0.0	1.19 (0.50–2.81)	66.2	1.09 (0.70–1.70)	29.7
> 20 cigarettes/day	0.83 (0.44–1.58)	8.6	0.98 (0.43–2.24)	36.8	1.78 (1.02–3.10)	12.2	1.20 (0.84–1.71)	0.0
p for interaction	0.266		0.451		0.377		0.988	
Alcohol drinking[c]								
Never	1.31 (0.87–1.97)	53.6	1.55 (1.07–2.23)	29.0	0.88 (0.58–1.33)	58.4	1.10 (0.83–1.47)	56.3
Ever drinker	1.47 (1.12–1.95)	41.2	1.32 (1.11–1.56)	8.6	0.92 (0.66–1.29)	77.2	1.32 (1.04–1.66)	69.1
p for interaction	0.647		0.437		0.870		0.333	
< 13 g/day	1.59 (1.06–2.38)	0.0	1.44 (1.13–1.84)	0.0	0.82 (0.47–1.41)	72.8	1.25 (0.89–1.75)	54.4
13–47 g/day	1.36 (1.06–1.74)	0.0	1.59 (1.08–2.34)	44.3	1.34 (1.03–1.73)	7.9	1.50 (1.13–2.00)	37.6
> 47 g/day	1.61 (1.08–2.39)	0.0	0.90 (0.52–1.55)	30.4	1.11 (0.66–1.86)	36.5	1.47 (1.02–2.10)	23.6
p for interaction	0.816		0.356		0.546		0.429	
Fruit and vegetable intake[d]								
Low	1.26 (0.70–2.27)	77.1	1.30 (0.95–1.78)	22.4	1.13 (0.70–1.80)	71.2	1.37 (0.98–1.93)	64.6
Intermediate	1.45 (1.12–1.89)	15.4	1.33 (1.08–1.64)	0.0	1.04 (0.75–1.43)	53.1	1.22 (0.95–1.57)	49.0
High	1.74 (1.27–2.37)	49.8	1.36 (0.97–1.91)	42.8	1.09 (0.74–1.61)	65.7	1.14 (0.86–1.52)	57.5
p for interaction	0.540		0.982		0.957		0.717	
Type of study								
Hospital-based controls[e]	1.27 (0.98–1.64)	0.0	1.16 (0.69–1.94)	52.1	1.18 (0.88–1.60)	0.0	1.46 (1.02–2.10)	76.6

Table 2 (continued)

	Salt taste preference		Use of table salt		Total sodium intake		High-salt and salt-preserved foods intake	
	Adjusted OR (95% CI)[a]	I^2 (%)	Adjusted OR (95% CI)[a]	I^2 (%)	Adjusted OR (95% CI)[a]	I^2 (%)	Adjusted OR (95% CI)[a]	I^2 (%)
Population-based controls[f]	1.83 (1.33–2.52)	72.6	1.38 (1.22–1.58)	0.0	1.18 (0.76–1.83)	88.1	1.08 (0.81–1.44)	80.6
p for interaction	0.081		0.523		1.00		0.201	
Nested case–control study[g]	–		–		1.02 (0.78–1.33)	–	–	
p for interaction	–		–		0.735		–	
Cancer anatomical subsite[h]								
Non-cardia	1.40 (1.06–1.85)	27.1	1.30 (1.00–1.69)	43.5	1.24 (0.97–1.59)	58.2	1.46 (1.21–1.76)	38.0
Cardia	2.00 (1.08–3.69)	41.3	1.34 (1.04–1.72)	0.0	1.36 (1.05–1.75)	0.0	1.25 (0.80–1.95)	63.4
Not accurately classifiable	1.73 (1.16–2.57)	22.6	1.42 (1.15–1.75)	0.0	0.74 (0.38–1.43)	79.6	1.17 (0.84–1.63)	64.1
Histological type[i]								
Intestinal	1.65 (1.11–2.47)	50.5	1.47 (1.15–1.87)	0.0	1.23 (0.92–1.64)	44.0	1.34 (1.00–1.79)	53.0
Diffuse	1.62 (1.20–2.19)	0.0	1.31 (0.99–1.73)	0.0	1.22 (0.95–1.56)	7.5	1.30 (1.00–1.70)	22.8
Undifferentiated	1.60 (1.06–2.43)	30.3	1.29 (1.11–1.51)	0.0	1.17 (0.97–1.42)	0.0	1.63 (1.34–1.97)	8.1
Studies with information on *H. pylori* infection serostatus[j]								
H. pylori positive	1.52 (0.93–2.48)	50.5	1.64 (0.98–2.74)	44.3	1.39 (0.95–2.01)	65.7	1.14 (0.75–1.74)	70.1
H. pylori negative	1.61 (0.60–4.35)	54.8	1.18 (0.65–2.14)	0.0	0.93 (0.54–1.63)	11.9	0.97 (0.66–1.43)	6.8
p for interaction	0.919		0.412		0.238		0.580	
Studies with information on energy intake[k]								
Adjusting for energy intake	–		–		1.10 (0.83–1.46)	82.0	1.24 (0.99–1.54)	60.1
Not adjusting for energy intake	–		–		1.38 (1.09–1.73)	83.9	1.35 (1.10–1.66)	82.3

95% CI 95% confidence interval, *OR* odds ratio

[a]Pooled ORs were computed using random-effects models. Study-specific ORs were adjusted, when available and applicable, for sex, age (5-year age groups: < 40; 40–44; …; 70–74; ≥ 75), socioeconomic status (low, intermediate, or high, as defined in each original study based on education, income or occupation), smoking status (never, former and current smokers of < 10 cigarettes/day [low]; 10–20 cigarettes/day [intermediate]; > 20 cigarettes/day [high]), alcohol drinking (never, low: < 13 g of ethanol/day, intermediate: 13 to 47 g of ethanol/day, high: > 47 g of ethanol/day), fruit and vegetables intake (study-specific tertiles), total energy intake (study-specific tertiles), study center (for multicenter studies), and race/ethnicity (White, Black/African American, Asian, Hispanic/Latino, other)

[b]As defined in each original study based on education, income, or occupation

[c]Excluding studies: CHINA 3 [19] and 4 [20]; IRAN 2 [18]

[d]Excluding studies: CHINA 4 [20]; MEXICO 3 [30]

[e]Including studies: BRAZIL 1 [31]; CHINA 1 [9]; GREECE [13]; ITALY 1 [8], 2 [10] and 3 [11]; JAPAN [33]; MEXICO 3 [30]; SPAIN 2 [27]; USA 1 [21]. Excluding studies: BRAZIL 2 [32] and RUSSIA [16] as they include both hospital- and population-based controls

[f]Including studies: CANADA [14]; CHINA 2 [15], 3 [19] and 4 [20]; IRAN 1 [17] and 2 [18]; ITALY 4 [12]; MEXICO 1 [28] and 2 [29]; PORTUGAL [22]; SPAIN 1 [25]; USA 2 [35]. Excluding studies: BRAZIL 2 [32] and RUSSIA [16] as they include both hospital- and population-based controls

[g]One study: USA 3 [37]

[h]Excluding studies: CHINA 1 [9], 2 [15], 3 [19] and 4 [20]; MEXICO 2 [29] and 3 [30]; USA 2 [35]

[i]Excluding studies: CHINA 1 [9], 2 [15], 3 [19] and 4 [20]; GREECE [13]; JAPAN [33]; MEXICO 2 [29]; USA 2 [35]

[j]No information for studies: CANADA [14]; CHINA 1 [9] and 3 [19]; GREECE [13]; ITALY 1 [8], 2 [10] and 3 [12]; MEXICO 2 [29]; USA 1 [21], 2 [35] and 3 [37]

[k]No information for studies: BRAZIL 1 [31] and 2 [32]; CANADA [14]; CHINA 1 [9], 2 [15] and 4 [20]; IRAN 1 [17]; ITALY 1 [8] and 3 [11]

Substantial heterogeneity was observed, particularly when considering salt taste preference, total sodium intake, and high-salt and salt-preserved foods intake. This is mainly due to the different methods used to collect dietary data, particularly the period of dietary assessment, the number and the items included in each FFQ. Within the StoP consortium, most studies used FFQ designed not only to be representative of the diet of each country but also to consider the seasonality of the items included. However, the diversity of food items in each questionnaire, particularly high-salt and salt-preserved foods, likely contributed to the heterogeneity observed. Nevertheless, 12 studies included in the present analysis used previously validated FFQs, and 21 studies collected data using trained interviewers, which have an acceptable validity when compared to reference measures [65, 66]. Overall, our sensitivity analyses considering study characteristics showed no significant differences, providing further support to the robustness of our findings.

Dietary habits were reported by participants that may have led to recall bias, particularly among patients, since changes in lifestyle may occur as cancer develops and becomes symptomatic [67]. Nevertheless, studies recruited incident, histologically confirmed gastric cancer cases, and most obtained dietary information regarding at least the year before diagnosis or the period before changes in dietary habits. We conducted sensitivity analyses considering studies evaluating dietary intake more than one year before diagnosis, and in general, the magnitude and directions of the associations did not change meaningfully, except for the association between high total sodium intake and gastric cancer that became stronger and reached statistical significance among these studies. Furthermore, no significant differences in the results obtained were observed between hospital- or population-based control studies and the prospective cohort study included. Additionally, case–control studies may be prone to selection bias. It is possible that hospital-based controls include individuals with conditions that could potentially be related to dietary salt intake, while population-based controls are more likely to be representative of the study base. Nevertheless, the results of our stratified analysis by type of controls showed that the overall conclusions are not driven by the studies with hospital- *vs.* population-based controls.

Although substantial heterogeneity was observed, the harmonization of the definition of exposure and control of confounding used in studies of the StoP consortium, contributes to the validity of our estimates. Additionally, the significant effect of salty taste preference, use of table salt, and high-salt and salt-preserved foods intake detected in the main analysis was consistently observed among strata of different sociodemographic, lifestyle, and clinical variables, as well as study characteristics. Sensitivity analyses, either removing one study at a time or considering the same cut-off for all studies, yielded estimates similar to those observed in the main analyses, albeit with less heterogeneity.

In conclusion, our uniquely large individual participant data meta-analysis of studies participating in the StoP Project showed salty taste preference, always using table salt, and a greater intake of high-salt and salt-preserved foods were associated with a risk of gastric cancer. The association was less robust with total sodium intake, which may be due to the high heterogeneity of the food assessment methods used in each study. In particular, this study adds to previous evidence, allowing for analyses considering *H. pylori* infection status, as well as cancer anatomical subsite and histological type.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10552-022-01565-y.

Author Contributions SM harmonized the data, performed the statistical analysis and interpreted the data, drafted and revised the manuscript. GA harmonized and interpreted the data. SM, AC, GA, NA, CP, CSR, LML, RS, ZFZ, JH, KCJ, DP, MF, RB, GPY, LLC, RM, ST, AH, GSH, DZ, DM, JV, MGH, VM, MVE, MHW, MP, RUHR, MLC, FP, LM, RCK, SB, RP, AL, PL, PB, MCC, MPP, EN, CLV, NL supplied the data, as part of the StoP Project. NL supervised the analysis and interpretation of data, and reviewed the manuscript. SM and NL defined the study hypotheses and designed the investigation. All authors contributed to the discussion of the results. All authors read and approved the final version of the manuscript.

Funding This study was funded by national funds from the Foundation for Science and Technology—FCT (Portuguese Ministry of Science, Technology and Higher Education), under the Unidade de Investigação em Epidemiologia—Instituto de Saúde Pública da Universidade do Porto (EPIUnit; UIDB/04750/2020), by the Associazione Italiana per la Ricerca sul Cancro (AIRC), Project no. 21378 (Investigator Grant), and the Agency for Management of University and Research Grants (AGAUR) of the Catalan Government (Grant 2017SGR723). AC and SM were funded under the scope of the project "NEON-PC—Neuro-oncological complications of prostate cancer: longitudinal study of cognitive decline" (POCI-01-0145-FEDER-032358; ref. PTDC/SAU-EPI/32358/2017). SM was also funded under EPIUnit—Junior Research—Prog Financing (UIDP/04750/2020). An individual grant attributed to NA (SFRH/BD/119390/2016) was funded by FCT and the 'Programa Operacional Capital Humano' (POCH/FSE). The authors thank the European Cancer Prevention (ECP) Organization for providing support for the project meetings, all MCC-Spain study collaborators (CIBERESP, ISCIII, ISGlobal, ICO, University of Huelva, University of Oviedo, University of Cantabria, University of León, ibs. Granada, Instituto Salud Pública de Navarra, FISABIO, Murcia Regional Health Authority and cols). The funding sources had no role in the study design; collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the article for publication.

Data availability The data that support the findings of this study are available from the StoP Project but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of the StoP Project.

Declarations

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval The participating studies were conducted in accordance with applicable laws, regulations, and guidelines for the protection of human subjects, and the StoP Project was approved by the University of Milan Review Board (Reference 19/15).

Consent to participate Not applicable.

Consent to publish Not applicable.

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Authors and Affiliations

Samantha Morais[1,2,3] · Adriana Costa[1,2] · Gabriela Albuquerque[1,2] · Natália Araújo[1,2,3] · Claudio Pelucchi[4] · Charles S. Rabkin[5] · Linda M. Liao[5] · Rashmi Sinha[5] · Zuo-Feng Zhang[6] · Jinfu Hu[7] · Kenneth C. Johnson[8] · Domenico Palli[9] · Monica Ferraroni[4] · Rossella Bonzi[4] · Guo-Pei Yu[10] · Lizbeth López-Carrillo[11] · Reza Malekzadeh[12] · Shoichiro Tsugane[13] · Akihisa Hidaka[13] · Gerson Shigueaki Hamada[14] · David Zaridze[15] · Dmitry Maximovitch[15] · Jesus Vioque[16,17] · Manoli García de la Hera[16,17] · Victor Moreno[16,18,19,20] · Mercedes Vanaclocha-Espi[21] · Mary H. Ward[5] · Mohammadreza Pakseresht[12,22,23] · Raúl Ulises Hernández-Ramirez[24] · Malaquias López-Cervantes[25] · Farhad Pourfarzi[12,26] · Lina Mu[27] · Robert C. Kurtz[28] · Stefania Boccia[29,30] · Roberta Pastorino[29] · Areti Lagiou[31] · Pagona Lagiou[32,33] · Paolo Boffetta[34,35] · M. Constanza Camargo[5] · Maria Paula Curado[36] · Eva Negri[4] · Carlo La Vecchia[4] · Nuno Lunet[1,2,3]

[1] EPIUnit, Instituto de Saúde Pública, Universidade do Porto, Porto, Portugal

[2] Laboratório para a Investigação Integrativa e Translacional em Saúde Populacional (ITR), Porto, Portugal

[3] Departamento de Ciências da Saúde Pública e Forenses e Educação Médica, Faculdade de Medicina, Universidade do Porto, Alameda Prof. Hernâni Monteiro, 4200-319 Porto, Portugal

[4] Department of Clinical Sciences and Community Health, University of Milan, Milan, Italy

[5] Division of Cancer Epidemiology and Genetics, National Cancer Institute, Rockville, MD, USA

[6] Department of Epidemiology, UCLA Fielding School of Public Health and Jonsson Comprehensive Cancer Center, Los Angeles, CA, USA

[7] Harbin Medical University, Harbin, China

[8] School of Epidemiology and Public Health, Department of Medicine, University of Ottawa, Ottawa, ON, Canada

[9] Cancer Risk Factors and Life-Style Epidemiology Unit, Institute for Cancer Research, Prevention and Clinical Network, ISPRO, Florence, Italy

[10] Medical Informatics Center, Peking University, Peking, China

[11] Mexico National Institute of Public Health, Morelos, Mexico

[12] Digestive Oncology Research Center, Digestive Disease Research Institute, Tehran University of Medical Sciences, Tehran, Iran

[13] Epidemiology and Prevention Group, Center for Public Health Sciences, National Cancer Center, Tokyo, Japan

[14] Nikkei Disease Prevention Center, São Paulo, Brazil

[15] Department of Epidemiology and Prevention, Russian N.N. Blokhin Cancer Research Center, Moscow, Russia

[16] Consortium for Biomedical Research in Epidemiology and Public Health (CIBERESP), Madrid, Spain

[17] Instituto de Investigación Sanitaria y Biomédica de Alicante, ISABIAL-UMH, Alicante, Spain

[18] Oncology Data Analytics Program, Catalan Institute of Oncology (ICO), Barcelona, Spain

[19] Colorectal Cancer Group, ONCOBELL Program, Institut de Recerca Biomedica de Bellvitge (IDIBELL), Barcelona, Spain

[20] Department of Clinical Sciences, Faculty of Medicine, University of Barcelona, Barcelona, Spain

[21] Cancer and Public Health Area, FISABIO – Public Health, Valencia, Spain

[22] Department of Agricultural, Food and Nutritional Sciences, University of Alberta, Edmonton, AB, Canada

[23] Nutritional Epidemiology Group, Centre for Epidemiology and Biostatistics, University of Leeds, Leeds, UK

[24] Department of Biostatistics, Yale School of Public Health, Yale School of Medicine, New Haven, CT, USA

[25] Facultad de Medicina, UNAM, Coyoacán, Mexico

[26] Digestive Disease Research Center, Ardabil University of Medical Sciences, Ardabil, Iran

[27] Department of Epidemiology and Environmental Health, School of Public Health and Health Professions, University at Buffalo, Buffalo, NY, USA

[28] Department of Medicine, Memorial Sloan Kettering Cancer Centre, New York, NY, USA

[29] Section of Hygiene, University Department of Life Sciences and Public Health, Università Cattolica del Sacro Cuore, Rome, Italy

[30] Department of Woman and Child Health and Public Health - Public Health Area, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy

[31] Department of Public and Community Health, School of Health Sciences, University of West Attica, Egaleo, Greece

[32] Department of Hygiene, Epidemiology and Medical Statistics, School of Medicine, National and Kapodistrian University of Athens, Athens, Greece

[33] Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, MA, USA

[34] Stony Brook Cancer Center, Stony Brook University, Stony Brook, NY, USA

[35] Department of Medical and Surgical Sciences, University of Bologna, Bologna, Italy

[36] Centro Internacional de Pesquisa, A. C. Camargo Cancer Center, São Paulo, Brazil