The global gastric cancer consortium: an update from the Stomach cancer Pooling (StoP) project

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We updated to December 2023 the main findings of the stomach cancer pooling (StoP) project including about 13 000 cases and 31 000 controls from 29 case–control and 5 nested studies. The StoP project quantified more precisely than previously available the positive associations of tobacco smoking, high alcohol consumption, meat intake, selected occupations (e.g. agricultural and miners), gastric ulcer and family history with gastric cancer and the inverse associations with socioeconomic status and selected aspects of diet (fruits, including citrus fruits, vegetables, including allium and mushrooms, and polyphenols). No consistent associations were found with coffee, yoghurt and leisure-time physical activity, metformin or proton pump inhibitors use. *European Journal of Cancer Prevention* 33: 433–437 Copyright © 2024 The Author(s). Published by Wolters Kluwer Health, Inc.

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Despite substantial falls in mortality over the last century and despite being largely neglected, gastric cancer (GC) remains the fourth cause of cancer death worldwide (Sung *et al.*, 2021; Collatuzzo *et al.*, 2023a).

In 2012, we established a global consortium of epidemiological studies of GC, the 'stomach cancer pooling (StoP) project' (Pelucchi *et al.*, 2015). Its main aim is to examine the role of several lifestyles and genetic determinants and their interaction in the etiology of GC, through pooled analyses of individual participant data, after central collection and validation of the original datasets. The third version of the StoP database (v. 3.3) was released in March 2022, and includes original data from 34 studies (+1 with genetic data only), mostly case–control, but including also case–control studies nested within cohorts: 15 from Europe, 11 from America, 9 from Asia,

with a total of about 13 000 cases and over 31 000 controls (Table 1). To date, the StoP project contributed a detailed quantification of the risk of GC associated with several factors (selected aspects of diet, socioeconomic and lifestyle factors) and a total of 33 scientific papers have been published (or are currently in press) in international peer-reviewed journals, most of them being released over the last 3 years.

Selected major findings published from the StoP dataset in relation to nondietary factors are summarized in Table 2 and shortly described hereafter.

Helicobacter pylori is the key risk factor for noncardia GC. The StoP pooled analysis showed an independent effect of sex on the seroprevalence of *H. pylori* infection. Men had higher prevalences [odds ratio (OR), 1.33; 95% confidence interval (CI), 1.04–1.70) of infection as compared to women (Ferro *et al.*, 2019). Cigarette smoking also plays a role in GC risk. In the overall StoP dataset, there was an about 40% excess risk in smokers vs. nonsmokers (Praud

Table 1   Studies included in the StoP project (2023) – release version 3.3 – the StoP project study group

Country	Period	Study design	Cases	Control	PI/Referent
Italy	1985–1997	Case–control, hospital-based	769	2081	C. La Vecchia
China	1987–1989	Case–control, hospital-based	266	533	J. Hu
Italy	1997–2007	Case–control, hospital-based	230	547	E. Negri, C. La Vecchia
Italy	2006–ongoing	Case–control, hospital-based	164	444	S. Boccia
Italy	1985–1987	Case–control, population-based	1016	1159	M. Ferraroni, D. Palli
Greece	1981–1984	Case–control, population-based	110	100	P. Lagiou
Canada	1994-1997	Case–control, population-based	1182	5039	K. C. Johnson
China	2000	Case–control, population-based	206	415	L. Mu, Z. F. Zhang
Russia	1996–1997	Case–control, hospital-based	448	610	D. Zaridze, D. Maximovich
Iran	2004–2005	Case–control, population-based	217	394	R. Malekzadeh, F. Pourfarzi
Iran	2005–2007	Case–control, population-based	286	304	R. Malekzadeh, M. Pakseresht
China	1991–1993	Case–control, population-based	951	951	G. P. Yu, Z. F. Zhang
China	1995	Case–control, population-based	133	433	G. P. Yu, Z. F. Zhang
USA	1992–1994	Case–control, hospital-based	134	132	Z. F. Zhang
USA	1980–1990	Case–control, hospital-based	700	2082	J. Muscat
Portugal	1999–2006	Case–control, population-based	692	1667	N. Lunet
Sweden	1998–2010	Cohort, nested case–control (SMC study)	88	352	A. Wolk, N. Håkansson
Iran	2001–2004	Case–control, hospital-based	119	119	R. Malekzadeh, M. Derakhshan
Sweden	1998–2010	Cohort, nested case–control (COSM study)	161	644	A. Wolk, N. Håkansson
Spain	2008–2012	Case–control, population-based	441	3441	N. Aragonés, G. Castano Vinyals
Sweden	1989–1995	Case–control, population-based	514	1164	W. Ye
Spain	1995–1999	Case–control, hospital-based	434	455	J. Vioque
Mexico	2004–2005	Case–control, population-based	248	478	L. López-Carrillo
Mexico	1989–1990	Case–control, population-based	220	752	L. López-Carrillo, M. Ward
Mexico	1994–1996	Case–control, hospital-based	234	468	L. López-Carrillo
Brazil	1991–1994	Case–control, hospital-based (Brazilian residents)	236	236	S. Tsugane, G. S. Hamada
Brazil	1991–1994	Case–control, hospital-based (Japanese residents)	96	192	S. Tsugane, G. S. Hamada
Japan	1998–2002	Case–control, hospital-based	153	301	S. Tsugane
Latvia	2007–ongoing	Case–control, hospital-based	215	430	M. Leja
USA (NE)	1988–1993	Case–control, population-based	170	502	M. H. Ward, C. S. Rabkin
Greece	1994–1999	Cohort, nested case–control (EPIC study)	85	425	A. Trichopoulou
Finland	1985–1988	Cohort, nested case–control (ATBC study)	462	462	D. Albanes, C. S. Rabkin
USA (6 states)	1995–1996	Cohort, nested case–control (AARP study)	1583	3331	L. M. Liao, C. S. Rabkin
Brazil	2016–2020	Case–control, population-based	368	738	M. P. Curado, E. Dias-Neto
Lithuania	2005–2017	Case–control, genetic data only			J. Kupcinskas

Table 2   Synthesis of the identified associations between nondietary-related risk factors and gastric cancer

Nondietary-related factors	Evidence of association/ risk evaluation
Cigarette smoking	POS ↑
Socioeconomic indicators level of education: highest vs. lowest	NEG ↓
Aromatic amines/coal derivatives	POS ↑
Height	NE ↔
Leisure-time physical activity	NE ↔
Sleep-stress	POS ↑
Gastric ulcer	POS ↑
Duodenal ulcer	NE ↔
Diabetes (gastric cardia cancer only)	POS ↑
Metformin	NE ↔
Proton pump inhibitors	POS↑[a]
Family history of GC	POS ↑

NE, no evidence/evidence of no association; NEG, negative association (decreased risk); POS, positive association (increased risk).
[a]Might be mainly due to reverse causality.

et al., 2018). The StoP dataset showed a strong inverse relationship between socioeconomic indicators and GC risk: the pooled OR for the highest compared to the lowest level of education was 0.60 (95% Cl, 0.44–0.84) and that for the relative index of inequality was 0.45 (95% Cl, 0.29–0.69) (Rota *et al.*, 2020). Selected occupations including agricultural and animal husbandry workers (OR, 1.33; 95% CI, 1.06–1.68); miners, quarrymen, well-drillers and related workers (OR, 1.70; 95% CI, 1.01–2.88); bricklayers, carpenters and construction workers (OR, 1.30; 95% CI, 1.06–1.60) and related exposures to wood-dust, aromatic amine and coal derivatives were related to GC risk (Shah *et al.*, 2020). There was no consistent association between adult height and GC risk (Giraldi *et al.*, 2023). No consistent association was observed with leisure-time physical activity, but there was a suggestion of decreased risk with increasing physical activity in individuals below age 55 (Mariani *et al.*, 2023). Long sleep and psychological stress levels were also moderately associated with GC risk, particularly noncardia GC (Collatuzzo *et al.*, 2023b). There was a strong association between a history of gastric ulcer (OR, 3.04; 95% CI, 2.07–4.49), but not duodenal ulcer, and GC cancer risk (Paragomi *et al.*, 2022). Diabetes was associated to gastric cardia, but not to corpus/pylorus GC (Dabo *et al.*, 2022).

With reference to selected medications, no consistent association was observed with metformin (Sassano *et al.*, 2022), while a positive association between proton pump inhibitors and GC appeared to be largely explained by reverse causation (Sassano *et al.*, 2023). Besides quantification of environmental factors related to GC risk, the StoP project includes information on family history and biological material to analyze genetic polymorphisms related to excess risk. The pooled OR of GC was 1.84 (95% CI, 1.64–2.04)

Table 3 Synthesis of the identified associations between selected dietary-related risk factors and gastric cancer

Dietary-related factors	Evidence of association/risk evaluation
Heavy alcohol drinking	POS ↑
Total meat intake	POS ↑
Red meat	POS ↑
Processed meat	POS ↑
White meat	NE ↔
Fruits	NEG ↓
Fruits (other than citrus)	NEG ↓
Citrus fruit	NEG ↓
Total vegetables	NEG ↓
Allium vegetables	NEG ↓
Mushrooms	NEG ↓
(Green) tea	NEG ↓
Coffee	NE ↔
Yoghurt	NE ↔
Salt	POS ↑
Polyphenols	NEG ↓

NE, no evidence/evidence of no association; NEG, negative association (decreased risk); POS, positive association (increased risk).

in individuals with vs. those without first-degree relatives with a history of GC (Vitelli-Storelli *et al.*, 2021).

With reference to selected dietary factors, key results are summarized in Table 3.

There was no association for light or moderate drinkers, but a 50% increased risk was found for heavy drinkers (>4 drinks per day) compared to never-drinkers (Rota *et al.*, 2017). As for tobacco smoking, the uniquely large dataset available allowed a more precise quantification of the risks related to these habits, including results for the type of alcoholic beverage, amount, duration, cessation of exposure as well as for specific subgroups or characteristics of disease (e.g. cardia vs. noncardia). Comparing the highest vs. the lowest tertiles of meats, the OR was higher for red meat: OR, 1.24 (95% Cl, 1.00−1.53), processed meat: OR, 1.23 (95% Cl, 1.06-1.43) and total meat intake: OR, 1.30 (95% Cl, 1.09-1.55). There were modest associations for moderate meat intake and for white meat. Thus, adherence to dietary recommendations to reduce red and processed meat consumption may contribute to a reduction in the burden of GC (Ferro *et al.*, 2020a). A reduced risk of GC was observed for the highest vs. lowest tertiles of fruits: OR, 0.76 (95% Cl, 0.64−0.90), fruits other than citrus: OR, 0.86 (95% Cl, 0.73−1.02) and total vegetables: OR, 0.68 (95% Cl, 0.56−0.84) (Ferro *et al.*, 2020b). With reference to citrus fruit, compared to the first tertile of the distribution, the adjusted pooled OR for the highest tertile was 0.80 (95% Cl, 0.73−0.87). The favorable effect of citrus fruits increased up to three servings/week and leveled off thereafter (Bertuccio *et al.*, 2019). Inverse associations were also observed for allium vegetables (Dalmartello *et al.*, 2022) and mushroom consumption (Ba *et al.*, 2023). Moderate (green) tea consumption in Asia (Martimianaki *et al.*, 2022b) also showed a moderate inverse association. In contrast, no association was observed between coffee or yoghurt consumption

and GC (Martimianaki *et al.*, 2022a; Collatuzzo *et al.*, 2023c). Salt intake was directly related to GC risk (Morais *et al.*, 2022). Thus, data from the StoP project confirmed an inverse association between vegetables, fruits (particularly citrus fruits) and a direct one between salt and GC. Among phenolic compounds, total polyphenols (OR, 0.67; 95% CI, 0.54−0.81), total flavonoids (OR, 0.73; 95% CI, 0.55−0.90) and anthocyanidins (OR, 0.74; 95% CI, 0.56−0.92) were inversely related to GC risk (Vitelli-Storelli *et al.*, 2020).

Over 20 additional analyses are now at various stages of completion with the involvement of an international network of multidisciplinary cancer researchers (many of whom are young leading investigators in several specific subprojects) focusing on GC epidemiology.

Thus, the StoP project remains a unique resource for etiological research, and to focus priority on genetic and mainly environmental factors to optimize GC control.

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Conflicts of interest
There are no conflicts of interest.

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Appendix: The StoP Project Working Group

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