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ORIGINAL PAPER

Reproductive factors, hormonal interventions, and gastric cancer risk in the Stomach cancer Pooling (StoP) Project

Minkyo Song[1] · Harindra Jayasekara[2,3,4] · Claudio Pelucchi[5] · Charles S. Rabkin[1] · Kenneth C. Johnson[6] · Jinfu Hu[7] · Domenico Palli[8] · Monica Ferraroni[5] · Linda M. Liao[1] · Rossella Bonzi[5] · David Zaridze[9] · Dmitry Maximovitch[9] · Nuria Aragonés[10,11] · Vicente Martin[10,12] · Gemma Castaño-Vinyals[10,13,14,15] · Marcela Guevara[10,16,17] · Shoichiro Tsugane[18,19] · Gerson Shigueaki Hamada[20] · Akihisa Hidaka[18] · Eva Negri[21] · Mary H. Ward[1] · Rashmi Sinha[1] · Areti Lagiou[22] · Pagona Lagiou[23,24] · Paolo Boffetta[21,25] · Maria Paula Curado[26] · Nuno Lunet[27,28,29] · Jesus Vioque[10,30] · Zuo-Feng Zhang[31] · Carlo La Vecchia[5] · M. Constanza Camargo[1]

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Abstract

Background Gastric cancer incidence is higher in men, and a protective hormone-related effect in women is postulated. We aimed to investigate and quantify the relationship in the Stomach cancer Pooling (StoP) Project consortium.

Methods A total of 2,084 cases and 7,102 controls from 11 studies in seven countries were included. Summary odds ratios (ORs) and 95% confidence intervals (CIs) assessing associations of key reproductive factors and menopausal hormone therapy (MHT) with gastric cancer were estimated by pooling study-specific ORs using random-effects meta-analysis.

Results A duration of fertility of ≥ 40 years (vs. < 20), was associated with a 25% lower risk of gastric cancer (OR = 0.75; 95% CI: 0.58–0.96). Compared with never use, ever, 5–9 years and ≥ 10 years use of MHT in postmenopausal women, showed ORs of 0.73 (95% CI: 0.58–0.92), 0.53 (95% CI: 0.34–0.84) and 0.71 (95% CI: 0.50–1.00), respectively. The associations were generally similar for anatomical and histologic subtypes.

Conclusion Our results support the hypothesis that reproductive factors and MHT use may lower the risk of gastric cancer in women, regardless of anatomical or histologic subtypes. Given the variation in hormones over the lifespan, studies should address their effects in premenopausal and postmenopausal women. Furthermore, mechanistic studies may inform potential biological processes.

Keywords Estrogens · MHT · Premenopause · Postmenopause

Abbreviations

BMI	Body mass index
CI	Confidence interval
DHEA	Dehydroepiandrosterone
FFQs	Food frequency questionnaires
HR	Hazard ratio
MHT	Menopausal hormone therapy
OR	Odds ratio
StoP Project	Stomach cancer Pooling Project

Introduction

Gastric cancer is the fifth most common cancer globally with an estimated over one million cases in 2020 [1]. Despite a decline in incidence, it also remains the fourth leading cause of death from cancer with an estimated 769,000 deaths in the same year worldwide [1]. Because of the indiscriminate symptoms, gastric cancers are typically diagnosed at an advanced stage (e.g., 35% present with metastases [2]) and remain among the most lethal cancers [3], and incur high health care costs.

Over 90% of gastric cancers are adenocarcinomas, and nearly twice as many are diagnosed in men than in women, observed consistently globally regardless of geographical, racial, or cultural differences [4]. The predominance in men likely reflects differing exposure to environmental factors and/or sex hormones, as evidenced by the male-to-female

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ratio of this cancer reverses in younger age groups and increases significantly in older age groups [2, 5]. Some evidence point to the genetic influence of variants associated with estrogen and the X chromosome, showing their potential protective role gastric cancer risk [6–8]. Established risk factors for gastric cancer include chronic *Helicobacter pylori* infection, cigarette smoking, and high salt intake [9]. A protective effect from female reproductive factors including sex hormones has been proposed but is still inconclusive [10].

The present study aimed to assess the associations of female reproductive factors and menopausal hormone therapy (MHT) use with the risk of gastric cancer using a large pooled dataset.

Materials and methods

Study design

The Stomach cancer Pooling (StoP) Project is an international consortium of case–control and nested case–control studies which uses pooled individual participant data to evaluate associations between risk factors and gastric cancer risk [11]. The present analysis used data from 11 studies in version 3.0 of the StoP Project dataset, including 2,084 premenopausal and postmenopausal women with gastric cancer (cases) and 7,102 women without gastric cancer (controls) who had information on reproductive factors and MHT use [12–22]. All data were 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).

Assessment of reproductive factors

Reproductive factors were assessed by questionnaire (Supplementary Table 1). The associations were only estimated for those factors that were asked by each study in their questionnaire. We derived values from other related questions if the information was not available for certain questions. For example, if duration of MHT use was'0 years', ever MHT use was imputed as 'never use'. To calculate pooled estimates, we re-categorized and standardized some variables to match data from studies with only categorical questionnaire data, such as age at first childbirth reported using categories in study #35. Years of fertility was calculated as years between age at menarche and age at menopause for postmenopausal women, and years between age at menarche and last age at follow-up for premenopausal women. Interval from menarche to full-term pregnancy is the years between age at menarche to the first age at full-term pregnancy.

Assessment of covariates

Participants were asked about their smoking and alcohol drinking habits and findings have been published previously [23, 24]. Food frequency questionnaires (FFQs) were used to obtain information on the dietary habits of participants including total dietary sodium intake in grams/day, as a computed nutrient [25], and vegetable intake [26]. First degree family history of gastric cancer was also assessed through questionnaire. Most studies included in this analysis ($n = 8$) used face-to-face or telephone interviews conducted by trained researchers for the administration of FFQs while the remaining studies used self-administered FFQs.

Statistical analysis

A two-stage modeling approach was used to quantify the associations of reproductive factors and MHT with gastric cancer [27]. First, the study-specific odds ratios (ORs) and the corresponding 95% confidence intervals (CIs) were estimated for the association between each measure of reproductive factors and gastric cancer risk using multivariable unconditional logistic regression models. Models were adjusted for age (continuous), socioeconomic status (low, intermediate, or high, as defined in each original study based on education, income, or occupation), smoking status (never, former and current), alcohol intake (never, low: < 13 g of ethanol/day, intermediate: 13 to 47 g of ethanol/day, high: > 47 g of ethanol/day), vegetable intake (study-specific tertiles), salt intake (study-specific quantity of low, medium, high) and family history of gastric cancer (yes, no, unspecified), when appropriate and available as described in detail in Supplementary Table 1. Second, summary effect estimates were computed using random-effects meta-analysis models [28]. Heterogeneity between studies was quantified using I^2 (%) statistics [29]. A separate category was used for missing data in models. When a study did not have any information on a covariate, it was excluded from that analysis.

Stratified analyses were also carried out to further explore associations for reproductive factors across anatomical subsite (cardia, noncardia), histologic subtype (intestinal-, diffuse-type), age at onset ($< 50, \geq 50$), and type of case–control study (hospital-based, population-based, nested). Heterogeneity across each subgroup analysis was assessed by calculating the difference in p-trend based on the per-category increase in ORs using SAS macro %metadose [30]. Analyses restricted to postmenopausal women were conducted for age at menopause, MHT use, and years of MHT use; analyses were restricted to

parous women for age at first full-term pregnancy and corresponding interval from menarche. Sensitivity analyses were carried out comparing meta-analysis (analysis from the two-stage modeling approach) *vs*. pooled results (analysis as a single large dataset, adjusting for study site) for overall gastric cancer. A p-value less than 0.05 was considered statistically significant. Statistical analyses were performed using SAS version 9.4 software (SAS Inc, Cary, North Carolina, USA).

Results

The main characteristics and design of the included studies are shown in Table 1. The majority (76%) of the gastric cancer cases were from Italy, Canada, and the US. The distribution of the sociodemographic and lifestyle characteristics of the study participants is described in Table 2. Approximately 60% of both cases and controls were never smokers and slightly below 40% did not consume alcohol. A family history of gastric cancer was three times more common among cases (12.2% *vs*. 3.9%) although this information was missing for approximately half of the cases and controls. The proportion with no or elementary school education was higher in cases (29.2%) than in controls (14.4%). Similarly, low socioeconomic status was more common among cases (45.8%) as compared to controls (36.3%). The ratio between cancers of the gastric cardia and noncardia was 1:2.8 with 56.2% of the tumors classified as overlapping or unspecified lesions. There were slightly more intestinal (18.3%) than diffuse (15.9%) type cancers with approximately two-thirds of cases classified as other or unspecified for histology.

Associations for overall gastric cancer

Figure 1 shows associations between reproductive factors and gastric cancer. A duration of fertility of ≥ 40 years, compared with < 20 years, was associated with a 25% lower risk of gastric cancer (OR = 0.75; 95% CI: 0.58–0.96). The age at menarche and at first full-term pregnancy, the length of the interval between menarche and first full-term pregnancy, and parity were not associated with the risk of gastric cancer. The null findings for age at first full-term pregnancy and the length of the interval between menarche and first full-term pregnancy with gastric cancer risk did not change substantially when we limited the analysis to parous women. Related to MHT use among postmenopausal women, ever, 5–9 years and ≥ 10 years use of MHT, compared with never use, showed ORs of 0.73 (95% CI: 0.58–0.92), 0.53 (95% CI: 0.34–0.84) and 0.71 (95% CI: 0.50–1.00).

Stratified associations for various subgroups

There was no evidence of heterogeneity for MHT use and duration of MHT across anatomical subsites (Fig. 2), histologic subtypes (Fig. 3), and by type of study (Supplementary Table 2). The inverse association was only calculable for late-onset gastric cancer (Fig. 4).

Sensitivity analysis

The associations between reproductive factors and gastric cancer overall estimated using pooled individual-level data did not differ appreciably from those estimated using meta-analysis (Supplementary Fig. 2).

Table 1 Characteristics and design of the Stomach cancer Pooling (StoP) Project

StoP Study ID	Study Area(s), Country	Period	Study Type	Cases		Controls		References
				N	%	*N*	%	
1	Milan, Italy	1985–1997	CC, hospital-based	300	14.4	861	12.1	La Vecchia et al. [13]
3	Milan, Italy	1997–2007	CC, hospital-based	87	4.2	261	3.7	Foschi et al. [20]
5	Four areas, Italy	1985–1987	CC, population-based	376	18.0	454	6.4	Palli et al. [12]
6	Athens, Greece	1981–1984	CC, hospital-based	53	2.5	51	0.7	Lagiou et al. [14]
7	Eight provinces, Canada	1994–1997	CC, population-based	379	18.2	2,490	35.1	Mao et al. [15]
9	Moscow, Russia	1996–1997	CC, hospital-based	202	9.7	318	4.5	Zaridze et al. [16]
21	Ten provinces, Spain	2008–2013	CC, population-based	151	7.3	1,548	21.8	Castaño-Vinyals et al. [17]
28	Brazilian origin, Brazil	1991–1994	CC, hospital-based	63	3.0	63	0.9	Nishimoto et al. [18]
29	Japanese origin, Brazil	1991–1994	CC, hospital-based	35	1.7	70	1.0	Hamada et al. [19]
32	Nebraska, USA	1988–1993	CC, population-based	73	3.5	216	3.0	Ward et al. [21]
35	6 states, USA	1995–1996	Cohort, nested case–control	365	17.5	770	10.8	Shatzkin et al. [22]
	Total			2,084	100	7,102	100	

Table 2 Distribution of gastric cancer cases and controls according to selected covariates in the Stomach cancer Pooling (StoP) Project

Characteristics	Cases		Controls	
	N	%	*N*	%
Age at Recruitment				
< 40	67	3.2	466	6.6
40–49	185	8.9	1,167	16.4
50–59	344	16.5	1,524	21.4
60–69	710	34.1	2,100	29.6
≥ 70	778	37.3	1,845	26.0
Smoking				
Never	1,329	63.8	4,226	59.5
Past	365	17.5	1,497	21.1
Current	288	13.8	1,228	17.3
Missing	102	4.9	151	2.1
Alcohol Drinking				
Never	827	39.7	2,490	35.0
Low	554	26.6	2,650	37.3
Intermediate	530	25.4	1,141	16.1
High	53	2.5	171	2.4
Missing	120	5.8	650	9.1
Vegetable/Fruit Consumption				
Low	563	27.0	1,811	25.5
Intermediate	657	31.5	2,320	32.6
High	809	38.8	2,662	37.5
Missing	55	2.6	309	4.3
Salt Consumption				
Low	623	29.9	2,506	35.3
Medium	653	31.3	2,306	32.5
High	323	15.5	1,501	21.1
Missing	485	23.3	789	11.1
Family history of gastric cancer				
No	833	40.0	3,324	46.8
Yes	255	12.2	276	3.9
Missing	996	47.8	3,502	49.3
Socioeconomic Status				
Low	954	45.8	2,578	36.3
Medium	824	39.5	2,817	39.6
High	255	12.2	1,623	22.8
Missing	51	2.4	84	1.2
Anatomical Subsite				
Cardia	240	11.5		
Noncardia	672	32.2		
Overlapping/unspecified	1,172	56.2		
Histological Subtype				
Intestinal	382	18.3		
Diffuse	332	15.9		
Other	932	44.7		
Unspecified	438	21.0		

Discussion

We conducted a pooled data analysis of 11 case–control and nested case–control studies from seven countries to ascertain whether female reproductive factors and MHT use were associated with gastric cancer. In line with prior studies [10, 31], the evidence was suggestive of a lower risk of gastric cancer with a long duration of fertility (≥ 40 years compared with < 20 years) and MHT use among post-menopausal women (≥ 5 years compared with never use). There was no evidence of differential associations by anatomical or histologic subtype.

The nature of the relationship between female reproductive factors including the length of potential exposure to endogenous or exogenous hormones and the risk of gastric cancer is complex and inconclusive. We believe that female reproductive factors including the interval between menarche and menopause and MHT use represent proxies for exposure to endogenous and exogenous hormone concentrations, respectively. An analysis of the European Prospective Investigation into Cancer and Nutrition (EPIC) data found an increased risk of gastric cancer in women who had ovariectomy (25 gastric cancer cases with ovariectomy), compared with women who did not (hazard ratio, HR = 1.79; 95% CI: 1.15–2.78) [32]. The authors also reported an inverse association with gastric cancer risk for the total cumulative years of menstrual cycling (HR = 0.55 for the fifth *vs*. the first quintile; 95% CI: 0.31–0.98). Neither the age at menopause nor other reproductive factors including the duration of oral contraceptive use, MHT use, parity, and age at first full-term pregnancy were associated with gastric cancer risk. An updated analysis of the EPIC study confirmed an increased risk of gastric noncardia cancer in women who had a bilateral ovariectomy (only 13 noncardia cases with bilateral ovariectomy) and reported an inverse association for noncardia cancer with older age at first pregnancy (HR = 0.54 for > 26 years compared with < 22 years; 95% CI: 0.32–0.91) [33]. Our meta-analysis of observational studies published until 2011 also found that longer years of fertility had an inverse association with gastric cancer risk (pooled RR = 0.74; 95% CI = 0.63–0.86), further supporting the hypothesis that longer exposure to estrogen effects of ovarian origin may decrease the risk of gastric cancer. We reported a similar inverse association between gastric cancer risk and exposure to exogenous estrogen [10]. A lower risk of gastric cancer with ever use of MHT, compared with never use, has also been reported by others [31, 34, 35]. The underlying proposed biological mechanisms for the apparent protective effect on gastric cancer from MHT use are still being elucidated.

Some studies have measured circulating hormone levels. A pooled nested case–control analysis for men from

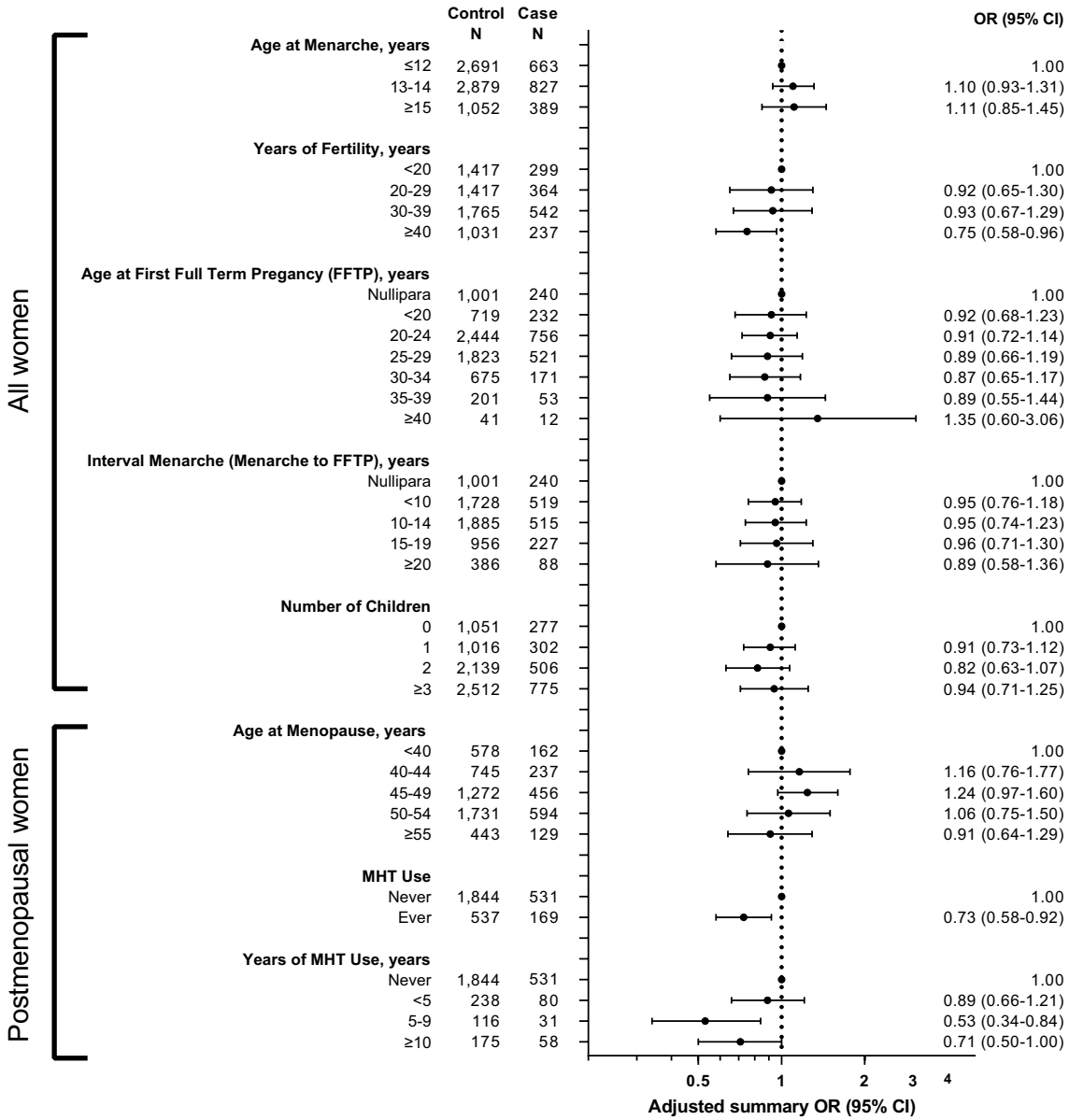

Fig. 1 Associations between selected reproductive factors and overall gastric cancer in the Stomach cancer Pooling (StoP) Project. Study-specific models adjusted for age, smoking, alcohol use, vegetable intake, salt intake, family history of gastric cancer, and socioeconomic status. OR, odds ratio, 95% CI, confidence interval, MHT, menopausal hormone therapy

three cohort studies reported a markedly lower risk of gastric cardia adenocarcinoma with increasing concentrations of dehydroepiandrosterone (DHEA) (OR = 0.62 per unit increase in $\log_2$ DHEA; 95% CI: 0.47–0.82) and estradiol (OR = 0.66; 95% CI: 0.45–0.98) [36]. In our case–control study of gastric cancer in men and women, we found a significant inverse association with DHEA, but null associations with estradiol and testosterone [37]. While DHEA concentrations seem to be similar in both sexes [38–40], estradiol concentrations are higher in women until they reach menopause after which they are roughly equivalent to men [41]. Even large individual cohort studies in regions with low gastric cancer incidences such as North America and Europe are limited by the low case load in conducting analyses for circulating hormones (e.g., $n = 0$ gastric cancer cases with estradiol level ≥ 175.0 pmol/L, compared with $n = 67$ with estradiol level < 175 pmol/L, in the UK Biobank) [42]. In our recent multi-center study including postmenopausal women from high-risk East Asian countries, we found that levels of urinary estrogen metabolites were not associated with gastric cancer risk [43].

Several potential biological pathways that may regulate estrogen's protective effect against gastric cancer have been

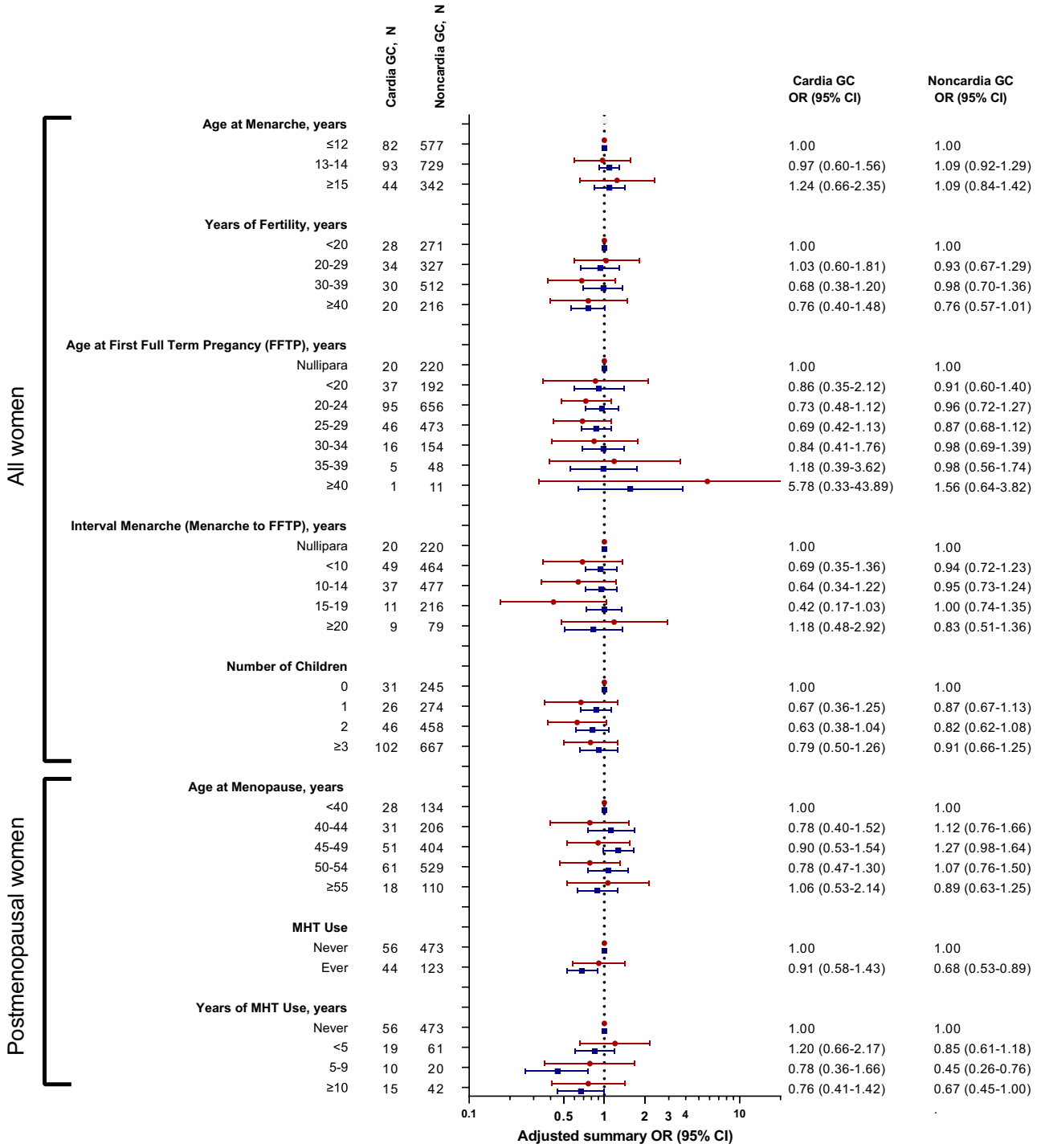

Fig. 2 Association between selected reproductive factors and anatomical subsite gastric cancer (circle: cardia, square: noncardia) in the Stomach cancer Pooling (StoP) Project. Study-specific models adjusted for age, smoking, alcohol use, vegetable intake, salt intake, family history of gastric cancer, and socioeconomic status. All *p*-values for heterogeneity (cardia *vs.* noncardia) > 0.05. GC, gastric cancer, OR, odds ratio, 95% CI, confidence interval, MHT, menopausal hormone therapy. (Color figure online)

postulated including via interactions with cellular receptors in gastric mucosa [44, 45], by increasing expression of trefoil factor family genes which encode products that protect gastric mucosa from endogenous and exogenous insults [46], through enhanced apoptosis in human gastric cancer cells seen in vitro [47] and due to strengthening of the immune response to bacterial pathogens by directly blocking expression of caspase-12 [48]. Related to how genetics

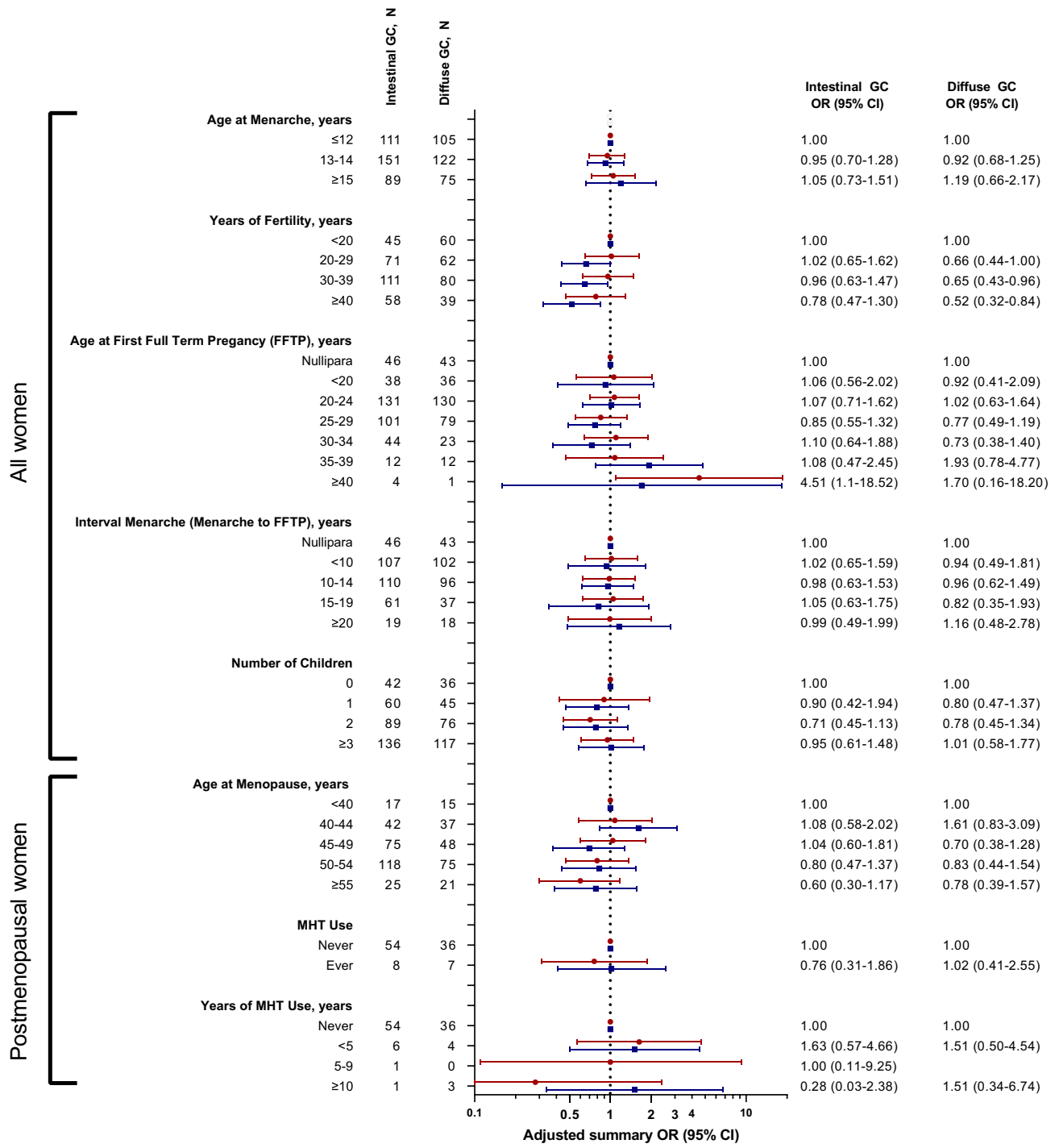

Fig. 3 Association between selected reproductive factors and histologic subtype gastric cancer (circle: intestinal, square: diffuse) in the Stomach cancer Pooling (StoP) Project. Study-specific models adjusted for age, smoking, drinking, vegetable intake, salt intake, family history of gastric cancer, and socioeconomic status. All *p*-values for heterogeneity (intestinal *vs*. diffuse) > 0.05. GC, gastric cancer, OR, odds ratio, 95% CI, confidence interval, MHT, menopausal hormone therapy. (Color figure online)

would explain sex differences in gastric cancer, variants in genes involved in estrogen synthesis and metabolisms have been associated with gastric cancer risk [7]. More recently, genome-wide association studies have also documented the variants in the X chromosome with a protective effect for this malignancy [8, 49].

Strengths of our pooled study are the availability of information on a range of female reproductive factors and MHT

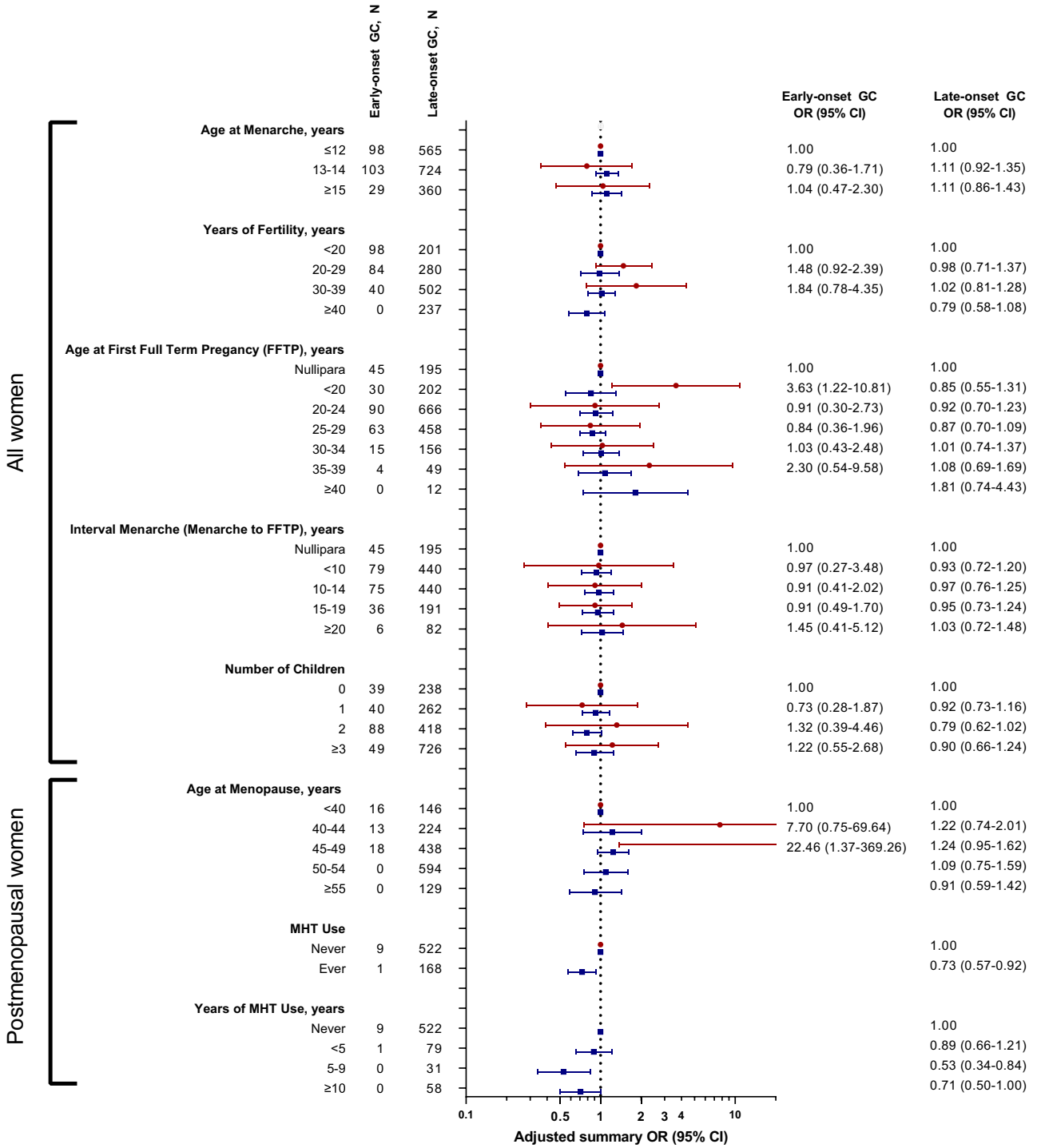

Fig. 4 Association between selected reproductive factors and early *vs*. late-onset gastric cancer (circle: early [< 50 years], square: late [≥ 50 years]) in the Stomach cancer Pooling (StoP) Project. Study-specific models adjusted for age, smoking, drinking, vegetable intake, salt intake, family history of gastric cancer, and socioeconomic status. All *p*-values for heterogeneity (< 50 *vs.* ≥ 50 years) > 0.05. GC, gastric cancer, OR, odds ratio, 95% CI, confidence interval, MHT, menopausal hormone therapy. (Color figure online)

use as well as on potential confounders, such as alcohol use, smoking, salt intake, vegetable intake, and family history of gastric cancer; and the relatively large sample size for the analyses on overall gastric cancer risk. Notably, our results were based on both premenopausal and postmenopausal women. Nonetheless, our study has limitations. First, we were unable to assess associations directly for estrogen including oral contraceptive use but used proxy female

hormonal indicators instead. Similarly, the cumulative years exposed to endogenous hormones may not be complete due to the lack of information on oral contraceptive use or breast feeding duration. Second, there may still be residual confounding in the models due to incomplete adjustment and/or unmeasured factors, such as history of ovariectomy. Third, we could not investigate the effect modification by *H. pylori* infection status. However, we would not expect *H. pylori* infection status to confound our findings because the likelihood of *H. pylori* infection is not plausibly linked directly to (i.e., not a cause of) female reproductive factors or MHT use. Nonetheless, some animal studies suggest that exogenous E2 treatment can protect against *H. pylori*-induced gastritis and premalignant lesions in male INS-GAS mice. If confirmed in humans, this finding may indicate a stronger protective effect of HRT against gastric cancer in women with prior *H. pylori* infections [50]. Fourth, case–control studies may be prone to selection bias. It is possible that hospital-based controls include individuals with gynecological conditions that could potentially be related to reproductive factors or MHT use, while population-based controls are considered to be more representative of the population under study, however, the latter may be healthier. Nevertheless, the results of our stratified analysis by type of study indicated negligible differences. Another limitation inherent to case–control studies, in general, is recall bias. It is also to be noted that we did not have information on the MHT formulation in the present study (e.g., whether it comprised unopposed estrogen or estrogen plus progesterone). Finally, our findings might not be generalizable to all populations.

In conclusion, this study adds a pooled analysis to the previously published literature, allowing to perform subtype analyses namely by anatomical location and histologic type of gastric cancer, assessing the associations between reproductive factors and MHT use and gastric cancer. The main finding of the present study is a reduction in overall gastric cancer risk with a long duration of fertility and MHT use among post-menopausal women. Given the complexity of the metabolism of sex hormones, future epidemiologic and non-human studies are needed to evaluate sex hormone pathways other than estrogens.

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Author contributions MS and MCC led study conceptualization and design. CSR, KCJ, JH, DP, MF, LML, RB, DZ, DM, NA, VM, GC-V, MG, ST, GSH, AH, EN, MHW, RS, AL, PL, and CLV collected the original data and provided them to StoP. CP, RB and EN, members of the StoP coordinating center harmonized core variables and contributed to database management. MS harmonized the data on reproductive factors and performed the statistical analysis. MS and HJ drafted the manuscript. All authors contributed to data interpretation and critical revision of the manuscript for important intellectual content. All authors read and approved the final version of the manuscript. MCC was responsible for study supervision.

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Data availability The data underlying this article are subject to restrictions, as they were used under license for this study and so are not publicly available. However, they will be shared on reasonable request to the authors and after permission of the Steering Committee of the StoP Project.

Declarations

Conflict of interest The authors have no conflicts of interest to declare.

Ethical approval All participating studies previously received ethical approval from their local Institutional Review Boards (IRBs).

Consent to participate Written informed consent was obtained from all participants in this study.

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Authors and Affiliations

Minkyo Song[1] · Harindra Jayasekara[2,3,4] · Claudio Pelucchi[5] · Charles S. Rabkin[1] · Kenneth C. Johnson[6] · Jinfu Hu[7] · Domenico Palli[8] · Monica Ferraroni[5] · Linda M. Liao[1] · Rossella Bonzi[5] · David Zaridze[9] · Dmitry Maximovitch[9] · Nuria Aragonés[10,11] · Vicente Martin[10,12] · Gemma Castaño-Vinyals[10,13,14,15] · Marcela Guevara[10,16,17] · Shoichiro Tsugane[18,19] · Gerson Shigueaki Hamada[20] · Akihisa Hidaka[18] · Eva Negri[21] · Mary H. Ward[1] · Rashmi Sinha[1] · Areti Lagiou[22] · Pagona Lagiou[23,24] · Paolo Boffetta[21,25] · Maria Paula Curado[26] · Nuno Lunet[27,28,29] · Jesus Vioque[10,30] · Zuo-Feng Zhang[31] · Carlo La Vecchia[5] · M. Constanza Camargo[1]

✉ M. Constanza Camargo
camargomc@mail.nih.gov

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

[2] Cancer Epidemiology Division, Cancer Council Victoria, Melbourne, VIC, Australia

[3] School of Public Health and Preventive Medicine, Faculty of Medicine, Nursing and Health Sciences, Monash University, Clayton, VIC, Australia

[4] Centre for Epidemiology and Biostatistics, Melbourne School of Population and Global Health, The University of Melbourne, Melbourne, VIC, Australia

[5] Branch of Medical Statistics, Biometry, and Epidemiology "G. A. Maccacaro", Department of Clinical Sciences and Community Health, University of Milan, Milan, Italy

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

[7] Harbin Medical University, Harbin, China

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

[9] Department of Clinical Epidemiology, N.N. Blokhin National Medical Research Center for Oncology, Moscow, Russia

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

[11] Cancer Registration and Surveillance Unit, Public Health Division, Department of Health of Madrid, Madrid, Spain

[12] Instituto de Biomedicina (IBIOMED), Universidad de León, León, Spain

[13] Barcelona Institute for Global Health—ISGlobal, Barcelona, Spain

[14] IMIM (Hospital del Mar Medical Research Institute), Barcelona, Spain

[15] Universitat Pompeu Fabra (UPF), Barcelona, Spain

[16] Instituto de Salud Pública y Laboral de Navarra, 31003 Pamplona, Spain

[17] Navarra Institute for Health Research (IdiSNA), 31008 Pamplona, Spain

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

[19] National Institute of Health and Nutrition, National Institutes of Biomedical Innovation, Health and Nutrition, Tokyo, Japan

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

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

[22] Department of Public and Community Health, School of Public Health, University of West Attica, Athens, Greece

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

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

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

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

[27] EPIUnit – Instituto de Saúde Pública da Universidade do Porto, Porto, Portugal

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

[29] Departamento de Ciências da Saúde Pública e Forenses e Educação Médica, Faculdade de Medicina da Universidade do Porto, Porto, Portugal

[30] Instituto de Investigación Sanitaria y Biomédica de Alicante, Universidad Miguel Hernandez (ISABIAL-UMH), Alicante, Spain

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