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Cancer Epidemiology, Biomarkers & Prevention

Review

Sex Hormones, Hormonal Interventions, and Gastric Cancer Risk: A Meta-Analysis

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Abstract

Estrogens may influence gastric cancer risk, but published studies are inconclusive. We therefore carried out a meta-analysis addressing the associations of gastric cancer in women with menstrual and reproductive factors and with use of estrogen- and antiestrogen-related therapies. Searches of PubMed up to June, 2011 and review of citations yielded a total of 28 independent studies, including at least one exposure of interest. Random effects pooled estimates of relative risk (RR) and corresponding 95% CIs were calculated for eight exposures reported in at least five studies, including: age at menarche, age at menopause, years of fertility, parity, age at first birth, oral contraceptive use, hormone replacement therapy (HRT), and tamoxifen treatment. Longer years of fertility (RR = 0.74, 95% CI: 0.63–0.86) and HRT (RR = 0.77; 95% CI: 0.64–0.92) were each associated with decreased gastric cancer risk. Conversely, tamoxifen treatment was associated with increased risk (RR = 1.82; 95% CI: 1.39–2.38). The other five exposures were not significantly associated. Our analysis supports the hypothesis that longer exposure to estrogen effects of either ovarian or exogenous origin may decrease risk of gastric cancer. Additional studies are warranted to extend this finding and to identify the underlying mechanisms. *Cancer Epidemiol Biomarkers Prev; 21(1); 20–38. ©2011 AACR.*

Background

Gastric cancer represents the fourth most common cancer and the second leading cause of cancer death worldwide (1). Notably, for most populations in both high- and low-incidence regions, the overall incidence in males is approximately double that of females (2, 3). Because these sex differences cannot be totally explained by variations in sociodemographic characteristics, environmental factors, or *Helicobacter pylori* (*H. pylori*) infection (4, 5), female sex hormones have been proposed to be protective (6). This hypothesis has been previously evaluated by examining associations of gastric cancer risk in women with sex hormone–related exposures, but most individual studies have been inconclusive. To more precisely characterize the reported associations, we have done a meta-analysis of these data.

Materials and Methods

We searched for studies published in any language before June 30, 2011 evaluating the associations of sex hormone–related exposures with gastric cancer incidence or mortality, using PubMed software to search Medline (U.S. National Library of Medicine, Bethesda, MD).

To identify studies of menstrual and reproductive factors, as well as exogenous estrogens, the following search strategy was used: (gastric cancer OR stomach cancer OR stomach neoplasms) AND (reproductive factors OR menstrual factors OR age at menarche OR menarche OR menstruation OR parity OR pregnancy OR breastfeeding OR miscarriage OR abortion OR fertility OR age at menopause OR estrogens OR sex hormones OR ovariectomy OR oophorectomy OR hysterectomy OR sex differences OR male predominance OR exogenous hormones OR oral contraceptives (OC) OR hormone replacement therapy (HRT) OR menopausal hormone therapy OR climacteric OR reproductive history) AND (risk assessment OR risk OR risk factors OR epidemiology) AND (case–control studies OR case–control OR cohort studies OR cohort). Reference lists of the selected papers were also screened for other potential articles that may have been missed in the database search. If necessary, we attempted to contact the authors to request additional information.

For the search of tamoxifen studies, the following strategy was used: tamoxifen AND (gastric cancer OR stomach

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cancer OR stomach neoplasms OR gastrointestinal neoplasms) AND (case–control studies OR case–control OR cohort studies OR cohort OR longitudinal studies OR longitudinal OR retrospective studies OR retrospective OR prospective studies OR prospective OR follow-up studies OR epidemiologic studies). We also searched for data on primary gastric cancer in randomized clinical trials of tamoxifen therapy for breast cancer treatment or prevention by combining the following terms: tamoxifen AND (gastric cancer OR stomach cancer OR stomach neoplasms OR gastrointestinal neoplasms OR "second cancers" OR "second malignancies" OR neoplasms, second primary[MeSH Terms]) AND (breast cancer OR breast neoplasms OR breast malignancy) AND (randomized controlled trial[Publication Type] OR (randomized[Title/Abstract] AND controlled[Title/Abstract] AND trial[Title/Abstract]) OR random*[Title/Abstract] OR random allocation[MeSH Terms]). We also reviewed the reference lists of identified articles and of 2 previous meta-analyses addressing the associations of tamoxifen therapy with breast cancer recurrence and with adverse effects (7, 8).

Two investigators in our team independently reviewed the articles and extracted the data; any disagreement was resolved by consulting a third reviewer. For inclusion in this reanalysis, the studies had to present adjusted estimates of relative risk (or similar measures of association including odds ratios; RR), and corresponding 95% CIs. If anatomical subsite–specific RRs were reported, we extracted data on noncardia gastric cancer only. Although gastric cancer risk was purportedly increased with tamoxifen exposure presumed from date of diagnosis in 2 cancer registry studies (9, 10), we only included data for known exposure status.

The following information was recorded for each study: first author, journal, country in which conducted, year of publication, study design, studied outcome, exposure variables and categories, number of gastric cancer cases, number of controls, cohort size (if applicable), age range, menopausal status of the participants, duration of follow-up (if applicable), total person-years of observation (if applicable), treatment regimen (if applicable), adjusted-RR estimates and 95% CI for incident gastric cancer, and confounding variables controlled.

Pooled risk estimates were calculated for exposure variables that were reported in at least 5 studies, which included age at menarche, age at menopause, years of fertility (defined as years between menarche and menopause in all but one study, which also omitted periods of pregnancy; ref. 11), parity, age at first birth, OC use, HRT, and tamoxifen treatment.

Other sex hormone–related variables reported in fewer than 5 studies included menstrual regularity, number of pregnancies, age at first pregnancy, breastfeeding of offspring, spontaneous abortion, induced abortion, oophorectomy, hysterectomy, menopausal status, intrauterine device use, parenteral contraceptive use, tubal sterilization, duration of OC use, duration of HRT, and history of endometriosis or vaginosis.

Exposures to exogenous estrogens and tamoxifen therapy were analyzed as dichotomous variables. Because some studies reported associations for varying durations of OC use, as compared with never use, we pooled those risk estimates using random effects meta-analysis to estimate the overall effect for ever versus never use. Because the categories of other exposure measures varied across studies, we conducted a meta-analysis of the comparison of the highest versus the lowest category (or the inverse of the comparison of the lowest vs. the highest category, as applicable) in each study. For 2 instances, in which an adjusted RR for this comparison was unavailable, we calculated a crude RR (with Fisher exact 95% CI) from the reported data. On the basis of 95% CI, we calculated the standard error (se) for the ln(RR) by the formula: $se = (\ln(\text{upper limit}) - \ln(\text{lower limit}))/(2^{*}Z_{1-\alpha/2})$, in which for a 95% CI, $Z_{1-\alpha/2}$ equal to 1.96 (12). Pooled RRs with corresponding 95% CI were then obtained using the random effects method of DerSimonian and Laird, with inverse variance weights (13). Between-study heterogeneity was assessed for statistical significance using the Q statistic and quantified with the I^2 metric, classified as low (<25%), moderate (25%–50%), and high (>50%) following Higgins and colleagues (14, 15). If moderate or high heterogeneity was identified for a given variable, meta-regression techniques were used to examine the extent to which 1 or more of the following covariates might be explanatory: study design (cohort, case–control, or randomized clinical trial), continent in which conducted (Asia, Europe, or North America), studied outcome (incidence or mortality), menopausal status of the participants (all postmenopausal or both pre- and postmenopausal), and whether or not the study adjusted for a proxy variable related to socioeconomic status (SES) such as education, income, or occupation. Galbraith plots were used to identify studies which were major contributors to heterogeneity (16). Given that SES is inversely associated with gastric cancer risk (17) and is also an important predictor of HRT use (18), we tried to minimize confounding with an alternative meta-analysis which excluded 3 studies that did not adjust for any SES-related variables.

Because some studies of tamoxifen reported no gastric cancers in one of the treatment groups, we could not compute individual RR estimates. We therefore summed the gastric cancers and corresponding person-time for tamoxifen-treated and tamoxifen-untreated groups, separately for randomized trials and observational studies. Summary RRs (with Fisher exact 95% CI) were derived for the 2 marginal analyses and then pooled using a random effects meta-analysis.

Publication bias was investigated by visual inspection of Begg's funnel plots and formally tested using Egger's regression asymmetry method (19, 20). The influence of individual studies on the overall meta-analysis RR was assessed by sequentially dropping each one before pooling study-specific RRs. A priori, we considered an

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influential study to be one for which its exclusion altered the overall pooled RR by more than 10%.

Statistical analyses were done with Stata version 11 (StataCorp) using a combination of published macros for meta-analysis, including metan, metainf, metareg, galbr, and metabias (21). A P value ≤ 0.05 was considered statistically significant for all tests, except the heterogeneity and Egger regression tests for which $P < 0.1$ was considered significant. All statistical tests were 2-sided.

Results

Literature search for menstrual and reproductive factors and exogenous estrogens

The literature search identified 336 publications, for which the titles and abstracts were scanned to determine potential eligibility for inclusion. Of the 336, 19 were retrieved for further evaluation that also led to identification of 5 more citations from their collective references (Fig. 1A). Thus, 24 articles (23 written in English and 1 in Japanese) reported associations of at least 1 sex hormone–related variable with gastric cancer risk (11, 22–44). However, we excluded the articles by Miller and colleagues (22), Plesko and colleagues (23), Tsukuma and colleagues (24), La Vecchia and colleagues (25), and Kvale and colleagues (28) because only point estimates were reported without 95% CI. Two articles reported partially overlapping data from the Japanese Collaborative Cohort Study (31, 37); we extracted data from Sakauchi and colleagues (37), the more recent reference, for all sex-related variables except years of fertility, which was only available from Kaneko and colleagues (31). Two articles from the Shanghai Women's Health Study reported overlapping results on OC use (36, 40), so those results were extracted from the more recent reference (40); other sex-related variables were extracted from Freedman and colleagues (36). Two articles reported risk estimates based on the same Italian hospital based case–control study, so data from the larger sample of Fernandez and colleagues (32) were used for HRT, whereas other sex-related variables were only available from La Vecchia and colleagues (26). Two reports based on the U.K. General Practice Research Database overlapped (34, 44), so data from the more recent reference were used (44). Exogenous estrogen exposure in the Japan Public Health Center–based Prospective Study reported by Persson and colleagues (38) was excluded because OC use and HRT were not distinguished. Therefore, a total of 18 articles, representing 14 independent studies, were included in the meta-analysis (Table 1). All but 2 articles reported on gastric cancer incidence as the outcome; the exceptions being 2 articles on gastric cancer mortality by Sakauchi and colleagues (37) and Chang and colleagues (43). Six studies had been carried out in Europe, 6 in Asia, and 2 in North America. Seven studies reported case–control comparisons and 7 were analyses of cohorts. Five studies were restricted to postmenopausal women (26, 27, 30, 37, 44), and the remaining 9 studies included both pre- and postmenopausal women. Studies differed with respect to the risk factors controlled in the original analyses: all studies adjusted for age, 7 controlled for SES-related variables (11, 26, 27, 35, 36, 39, 43), 6 controlled for body mass index

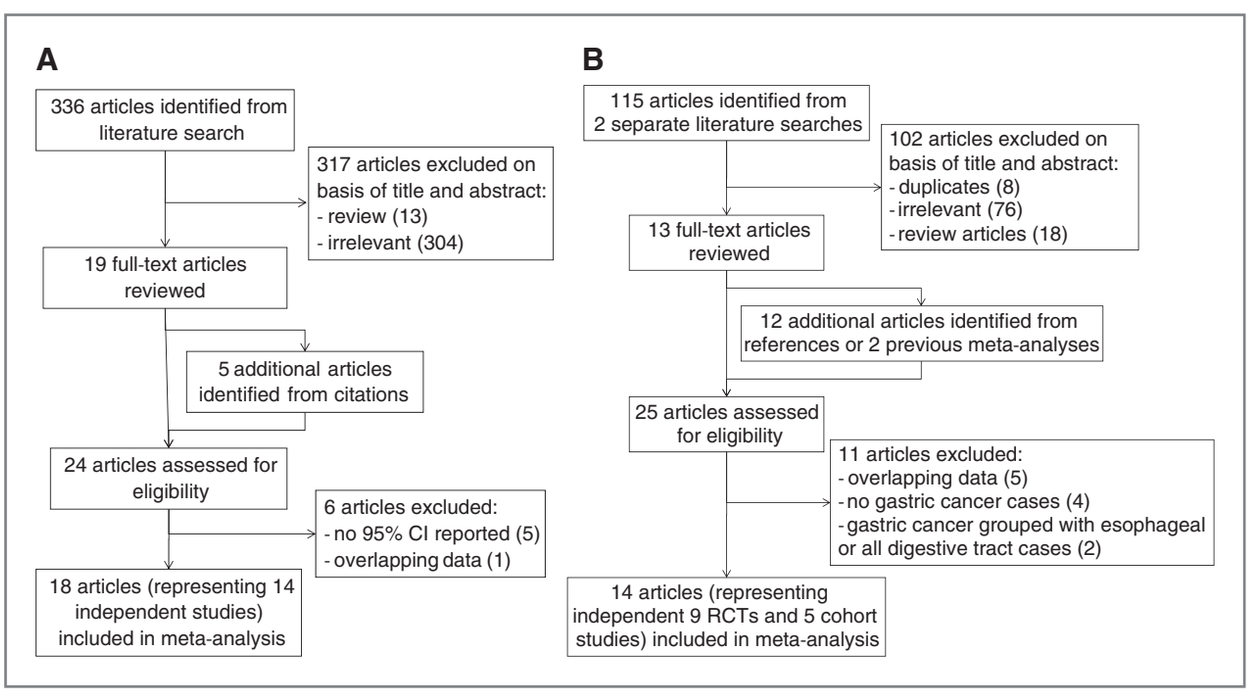

Figure 1. Flow diagram of the literature search for studies of (A) menstrual and reproductive factors and exogenous hormones and (B) tamoxifen.

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Table 1. Characteristics of observational studies addressing the association of gastric cancer with menstrual and reproductive factors, and with use of estrogen-related therapies

Authors, year (reference)	Country in which conducted	Exposure(s) studied	Type of study	Cases/ controls (overall follow-up time)	Comparison group	Age range (menopausal status)	Histologic type of cases	Anatomic site of cases	Confounders controlled
La Vecchia and colleagues 1994 (26)	Italy	Age at menopause, age at menarche, years of fertility, parity, age at first birth, OC use, HRT use, history of spontaneous and induced abortions.	Case–control	229/614	Hospital-based controls	35–79 (all postmenopausal)	No data	No data	Age, education, area of residence, family history of gastric cancer, total calories, beta-carotene and vitamin C intake, and other hormone-related exposure variables
Palli and colleagues 1994 (27)	Italy	Age at menopause[a], age at menarche, years of fertility[a], parity, age at first birth, number of spontaneous/ induced abortions.	Case–control	339/515	Population-based controls	<75 (all postmenopausal)	No data	No data	Age, geographic area, place of residence, migration from the south, SES, family history of gastric cancer, BMI, total caloric intake and protein and ascorbic acid intake.
Heuch and colleagues 2000 (29) and Heuch and colleagues 2003 (33)	Norway	Age at menopause, age at menarche, parity, age at first birth, number of abortions and duration of breastfeeding.	Cohort	572/∼ 62,518 (1,442,514 p-y)	Participants in a screening program for breast cancer (1956–1959)	32–79 (pre and postmenopausal)	No data	Cardia and fundus:58; corpus: 58; antrum and pylorus: 180; unspecified: 276	Age, birth cohort, area of residency and county. Parity and age at delivery were included in some models.
Inoue and colleagues 2002 (30)	Japan	Age at menopause, age at menarche, menstrual irregularity, years of fertility, pregnancy, parity, age at first birth, number of children breastfed and duration of breastfeeding[a].	Case–control	365/1,825	Hospital-based controls	39–82 (all post-menopausal)	Differentiated: 133; undifferentiated: 232.	Upper third: 72; middle third: 155; lower third: 127.	Age, year and season of interview, family history of gastric cancer, smoking status and raw vegetable and cooked fish intake.

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Table 1. Characteristics of observational studies addressing the association of gastric cancer with menstrual and reproductive factors, and with use of estrogen-related therapies (Cont'd)

Authors, year (reference)	Country in which conducted	Exposure(s) studied	Type of study	Cases/ controls (overall follow-up time)	Comparison group	Age range (menopausal status)	Histologic type of cases	Anatomic site of cases	Confounders controlled
Kaneko and colleagues 2003 (31)	Japan	Age at menopause, age at menarche, years of fertility, parity, age at first pregnancy, HRT use.	Cohort	156/∼ 40,379 (330,786 p-y)	Participants in the JACC	40–79 (all postmenopausal)	No data	No data	Age.
Fernandez and colleagues 2003 (32)	Italy	HRT use.	Case–control	258/6,976	Hospital-based controls	45–79	No data	No data	Age, study center, year of interview, education, smoking, drinking, type of menopause, age at menopause and BMI.
Frise and colleagues 2006 (35)	Canada	Age at menopause, menopausal status, age at menarche[a], years of fertility, parity, age at first pregnancy, OC use, use and duration of HRT, history of hysterectomy or oophorectomy.	Case–control	326/326	Population-based controls	20–74 (pre and postmenopausal)	Intestinal: 55; diffuse: 106; mixed: 15; unknown: 150.	Proximal: 49; distal: 176; overlapping: 13; unknown: 88.	Age, education, meat consumption, and other hormone-related exposure variables.
Freedman and colleagues 2007 (36)	China	Age at menopause[a], menopausal status, age at menarche, years of fertility[a], years since menopause, pregnancies, parity, age at first pregnancy, oral and injectable contraceptives use, IUD use[a], HRT use, history of hysterectomy[a] or ovariectomy[a], duration of breastfeeding.	Cohort	154/∼73,288 (419,260 p-y)	Participants in the Shanghai Women's Health Study	40–70 (pre and postmenopausal)	No data	No data	Age, BMI, education, income, cigarette smoking status, and smoking dose.

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Table 1. Characteristics of observational studies addressing the association of gastric cancer with menstrual and reproductive factors, and with use of estrogen-related therapies (Cont'd)

Authors, year (reference)	Country in which conducted	Exposure(s) studied	Type of study	Cases/ controls (overall follow-up time)	Comparison group	Age range (menopausal status)	Histologic type of cases	Anatomic site of cases	Confounders controlled
Sakauchi, 2007 (37)	Japan	Age at menopause, age at menarche, type of menopause, years of fertility, pregnancies, parity, age at first delivery, use and duration of HRT.	Cohort	386/no data (~750,619 p-y)	Participants in the JACC	all postmenopausal	No data	No data	Age and area of study.
Persson and colleagues 2008 (38)	Japan	Age at menopause, age at menarche, years of fertility, menstruation status menopause status, regularity of menstruation, age at first delivery, age at first pregnancy, pregnancies, number of deliveries, any hormone intake, breast-feeding, history of endometritis or vaginitis.	Cohort	368/~ 44,085 (541,862 p-y)	Participants in the JPHC	40–69 (pre and postmenopausal)	Differentiated: 97; undifferentiated: 242, unclassified: 29.	Proximal: 26, distal: 265, overlapping: 11, unspecified: 66.	Age, family history of gastric cancer, and study area.
Bahmanyar and colleagues 2008 (39)	Sweden	Age at first birth and parity.	Nested case–control	2,498/ 12,490	Participants in a cohort of women born in 1925 or later	≥30 (pre and postmenopausal)	No data	Noncardia: 2,498	Year of birth, occupational class, education level, age at first birth and parity.

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Table 1. Characteristics of observational studies addressing the association of gastric cancer with menstrual and reproductive factors, and with use of estrogen-related therapies (Cont'd)

Authors, year (reference)	Country in which conducted	Exposure(s) studied	Type of study	Cases/ controls (overall follow-up time)	Comparison group	Age range (menopausal status)	Histologic type of cases	Anatomic site of cases	Confounders controlled
Dorigochoo and colleagues 2009 (40)	China	OC use, IDU use, tubal sterilization.	Cohort	168/∼ 66,493	Participants in the Shanghai Women's Health Study	40–70 (pre- and postmenopausal)	No data	No data	Age, education, age at menarche, number of live births, cumulative breast feeding months, BMI, exercised regularly in past 5 years, smoking, menopausal status, first-degree family history of cancer and other contraceptive methods
Freedman and colleagues 2010 (41)	United States	Age at menopause, age at menarche, parity, age at first birth, history of hysterectomy or oophorectomy, duration of OC use, use and duration of HRT.	Cohort	97/∼ 201, 409	Participants in the NIH-AARP Diet and Health Study	50–71 (pre and postmenopausal)	No data	Noncardia: 97	Age, BMI, fruit and vegetable consumption, smoking use, alcohol intake, physical activity, and total energy intake.
Duell and colleagues 2010 (11)	European countries	Age at menarche and menopause, duration of OC use, HRT use, parity, age at first full-term pregnancy, breastfeeding, miscarriage, induced abortion, ovariectomy, hysterectomy, and cumulative duration of menstrual cycling.	Cohort	181/∼ 335,035 (2,927,994 p-y)	Participants in the EPIC	35–70 (pre and postmenopausal)	Intestinal: 48; diffuse: 82; mixed/ unclassified/ unknown: 53	Noncardia: 101; cardia: 31; overlapping/ unknown: 49	Age, center, smoking status, education, BMI, and calorie-adjusted vegetable, fruit, red meat, and processed meat intakes.

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Table 1. Characteristics of observational studies addressing the association of gastric cancer with menstrual and reproductive factors, and with use of estrogen-related therapies (Cont'd)

Authors, year (reference)	Country in which conducted	Exposure(s) studied	Type of study	Cases/controls (overall follow-up time)	Comparison group	Age range (menopausal status)	Histologic type of cases	Anatomic site of cases	Confounders controlled
Chung and colleagues 2011 (42)	Korea	Age at menarche, age at first pregnancy, parity, history of lactation, and OC use.	Case–control	1,495/1,350	Hospital-based controls	18–45 (Pre- and postmenopausal)	No data	No data	Age.
Chang and colleagues 2011 (43)	Taiwan	Parity	Cohort	1,090/~1,291,372 (33,686,828 p-y)	Participants in a cohort of women with a record of a first and singleton childbirth in the Birth Registry between 1978 to 1987	(Pre and postmenopausal)	No data	No data	Age, marital status, years of schooling and birthplace.
Green and colleagues 2011 (44)	United Kingdom	HRT use.	Nested case–control	750/3,722	Participants in the GPRD	50–84 (all postmenopausal)	No data	No data	Age, calendar time and length of observation in GPRD, tobacco smoking, alcohol consumption, and BMI.

Abbreviations: JAAC, Japan Collaborative Cohort Study; JPHC, Japan Public Health Center-based Prospective Study; EPIC, European Prospective Investigation into Cancer and Nutrition; BMI, body mass index; GPRD, UK General Research Database.

[a]Statistically significant result.

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(11, 27, 32, 36, 41, 44), 6 controlled for smoking (11, 30, 32, 36, 41, 44), 4 controlled for family history of gastric cancer (26, 27, 30, 38), 6 controlled for diet-related variables (11, 26, 27, 30, 35, 41), and 5 controlled for multiple menstrual or reproductive-related variables simultaneously (26, 29, 35, 39, 40). However, Frise and colleagues (35) used premenopausal as the referent category for age at menopause, and Freedman and colleagues (41) used nulliparous as the referent category for age at first birth. Hence, these 2 adjusted RRs could not be pooled with others comparing the highest versus the lowest categories, so we calculated and used crude RRs instead.

Literature search for tamoxifen exposure

The two independent literature searches identified 115 citations that were potentially relevant to this reanalysis (Fig. 1B). On the basis of the information provided in the title and abstract, we retrieved for further evaluation 13 articles in which drug therapy in the treatment arm differed from that in the control arm solely by the use of tamoxifen. References of these articles and of 2 previous meta-analyses led to identification of 12 additional studies. Besides irrelevant and duplicate citations, we excluded articles that had either no cases of gastric cancer or did not distinguish them within larger categories (e.g., digestive tract). There were overlapping results from the Danish Breast Cancer Cooperative Group (45, 46), the Christ Hospital Adjuvant Tamoxifen Trial (47, 48), the B-14 trial (49, 50), and the Stockholm Breast Cancer Study Group (51, 52), so data from the more recent articles were extracted (46, 48, 50, 52). In addition, 2 reports based on U.S. cancer registrations overlapped (53, 54), so data from the longer study period were extracted (53). Thus, a total of 14 independent studies, including 9 randomized trials (48, 50, 52, 55–60) and 5 cohorts (46, 53, 61–63), were included in the meta-analysis (Table 2).

Years of fertility

For the analysis of years of fertility, a total of 8 studies were identified (11, 26, 27, 30, 31, 35, 36, 38; Fig. 2A). Study-specific RRs for the longest versus the shortest duration of fertility ranged from 0.55 to 0.99. The pooled RR suggested a significant inverse association with a 26% decreased risk of gastric cancer (Table 3) and low between-study heterogeneity. The pooled RR was robust to the exclusion of any individual study.

Age at menarche

Associations of gastric cancer with age at menarche were reported in 11 studies (11, 26, 27, 29, 30, 35–38, 41, 42). Study-specific RRs for the oldest age at menarche as compared with the youngest age ranged from 0.70 to 1.93, and the pooled RR was 1.0 (Table 3). Between-study heterogeneity was high, but meta-regression analysis of potential explanatory factors failed to explain the variability. A Galbraith plot (not shown) indicated the studies by Frise and colleagues (35) and Persson and colleagues (38) as outliers contributing to this heterogeneity. The pooled RR derived with exclusion of those studies was 0.89 (95% CI: 0.80–1.0). Notably, analysis restricted to the same set of studies ($n = 8$) included in the meta-analysis of years of fertility [including data from Kaneko and colleagues (31) instead of Sakauchi and colleagues (37)], had a pooled RR of 1.08 (95% CI: 0.86–1.35) for oldest age at menarche as compared with the youngest age, similar to the effect based on all 11 studies.

Age at menopause

Ten studies examined the association of gastric cancer and age at menopause (11, 26, 27, 29, 30, 35–38, 41). Study-specific RRs for the oldest age at menopause as compared with the youngest ranged from 0.52 to 1.44. The pooled RR was 0.84 (95% CI: 0.67–1.05), with low heterogeneity across studies. This estimate was robust to the exclusion of any individual study. The pooled RR was 0.81 (95% CI: 0.62–1.06) for the 8 studies [including data from Kaneko and colleagues (31) instead of Sakauchi and colleagues (37)] that also reported on years of fertility.

Parity

Twelve studies provided information on parity (11, 26, 27, 29, 35–39, 41–43), with study-specific RRs for highest number of full-term pregnancies in comparison with the lowest ranging from 0.52 to 1.90. The summary RR was 0.94 (95% CI: 0.74–1.19). For the 5 studies (11, 26, 35, 38, 41) that used nulliparous women as the reference group, the pooled RR was 0.95 (95% CI: 0.66–1.38; $I^2 = 56.3\%$), whereas for the other 7 that used a parous comparison group (either 1 child or 1–2 children), the pooled RR was 0.93 (95% CI: 0.68–1.27; $I^2 = 89.3\%$). High heterogeneity was detected among all 12 studies, but there were no significant explanatory variables in meta-regression analysis. A Galbraith plot (not shown) identified the studies by La Vecchia and colleagues (26), Chung and colleagues (42), and Chang and colleagues (43) as outliers contributing to between-study heterogeneity. In an analysis excluding those 3 studies, the pooled RR was essentially unchanged at 0.96 (95% CI: 0.85–1.07).

Age at first birth

Risk estimates for oldest versus youngest age at first birth were reported in 10 studies (11, 26, 27, 29, 30, 36–39, 41) and ranged from 0.43 to 1.45. The pooled RR was 0.99 (95% CI: 0.85–1.15), with low heterogeneity among the studies (Table 3). This estimate was robust to the exclusion of any individual study.

Oral contraceptive use

Risk estimates for ever versus never OC use were reported in 4 studies (26, 35, 40, 42) and ranged from 0.79 to 2.50. In addition, the studies by Duell and colleagues (11) and Freedman and colleagues (41) reported 2 to 3 RRs depending on duration of use, which we pooled to obtain overall RRs for ever use of 1.18 (95% CI: 0.89–1.56) for Duell and colleagues (11) and 0.85 (95% CI: 0.54–1.34) for Freedman and colleagues (41). The proportion of OC

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Table 2. Characteristics of randomized trials and observational studies addressing the association of gastric cancer with tamoxifen therapy

						Tamoxifen-treated group			Tamoxifen-untreated group		
Authors, year (reference)	**Country in which conducted**	**Study name or target population**	**Study Type**	**Median follow-up time in years**	**Age range or menopausal status**	**Treatment regimen (daily dose and duration)**	**Gastric cancer cases**	**n/women-years at risk**	**Treatment regimen**	**Gastric cancer cases**	**n/women-years at risk**
Ribeiro and colleagues 1992 (48)	United Kingdom	The Christie Hospital Adjuvant Tamoxifen trial	RCT	10	Postmenopausal	TAM (20 mg/1 y)	2	282/*2,820*	No treatment	0	306/*3,060*
Ryden and colleagues 1992 (55)	Sweden	The Southern Sweden Breast Cancer Trial	RCT	9	Postmenopausal	RT + TAM (30 mg/1 y)	2	239/1,847[a]	RT	0	236/1,812[a]
Cummings and colleagues 1993 (56)	United States	Eastern Cooperative Oncology Group	RCT	TAM: 7.4 placebo: 4.4	65–84	TAM (20 mg/1 y)	1	85/*629*	Placebo	1	83/*365*
Rivkin and colleagues 1994 (57)	United States	The Southern Oncology Group Study	RCT	6.5	Postmenopausal	CHEMO + TAM (20 mg/1 y)	1	303/*1,970*	CHEMO	0	300/*1,950*
Rutqvist and colleagues 1995 (52)	Sweden	The Stockholm Breast Cancer Study Group	RCT	9	Postmenopausal	TAM (40 mg/2 or 5 y)	5	1372/9,610	No treatment	2	1357/9,378
Fisher and colleagues 1996 (50)	United States and Canada	(NSABP) B-14	RCT	10.4 (mean)	Mean age: 55 y	TAM (20 mg/5 or 10 y)	4	1404/*14,602*	Placebo	2	1414/*14,706*
Cuzick and colleagues 2002 (58)	United Kingdom	The International Breast Cancer Intervention Study (IBIS-I)	RCT	4.2	35–70	TAM (20 mg/5 y)	1	3578/*15,028*	Placebo	3	3574/*15,011*
Fisher and colleagues 2005 (59)	United States	The National Surgical Adjuvant Breast and Bowel Project Breast Cancer Prevention trial (P-1)	RCT	6.2 (mean)	≥35	TAM (20 mg/5 y)	2	6,681/40,844	Placebo (including crossovers after unblinding)	2	6,707/40,648

(Continued on the following page)

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Table 2. Characteristics of randomized trials and observational studies addressing the association of gastric cancer with tamoxifen therapy (Cont'd)

Authors, year (reference)	Country in which conducted	Study name or target population	Study Type	Median follow-up time in years	Age range or menopausal status	Tamoxifen-treated group			Tamoxifen-untreated group		
						Treatment regimen (daily dose and duration)	Gastric cancer cases	n/women-years at risk	Treatment regimen	Gastric cancer cases	n/women-years at risk
Veronesi and colleagues 2007 (60)	Italy	Italian Randomized Tamoxifen Prevention Trial	RCT	9.1 (mean)	35–70	TAM (20 mg/5 y)	1	2700/30,303	Placebo	4	2,708/30,310
Curtis and colleagues 1996 (53)	United States	Cancer registration data from 1980 to 1992	Cohort	12 (maximum)	≥50 y	Hormone therapy for their first course of therapy	15	14,358/39,736	No hormonal therapy/unknown	118	72,965/348,393
Matsuyama and colleagues 2000 (61)	Japan	9 medical institutions	Cohort	TAM: 7.64 Non-TAM: 8.1	Adult women	TAM (20 mg/≤2 y mainly)	32	3,497/*26717*	CHEMO or no further treatment	19	2,529/*20,485*
Ursic-Vrscaj and colleagues 2001 (62)	Slovenia	Population-based registry from 1987 to 1994	Cohort	8.5 (mean); 5–12 (range)	≥55 y	TAM (20 mg/3.33 y, median)	2	*440/3,740*	No TAM	0	190/*1,615*
Fowble and colleagues 2001 (63)	United States	University of Pennsylvania or Fox Chase Cancer Center	Cohort	TAM: 7.4 Non-TAM: 9.6	Pre- and postmenopausal[b]	TAM (-/1 y)	0	*234/1,732*	No TAM	1	681/*6,538*
Andersson and colleagues 2008 (46)	Denmark	Patients registered by the population based Danish Breast Cancer Cooperative Group (DBCG)	Cohort	7.8	19–89	TAM (-/1 y)	19	7,204/47,465	Other treatment	38	24,614/209,098

Abbreviations: RCT, randomized clinical trial; RT, radiotherapy; TAM, tamoxifen; CHEMO, chemotherapy.

[a]Person-time estimates taken from Rutqvist and colleagues 1995 (52).

[b]All women received radiotherapy.

Italicized numbers were approximated based on reported data.

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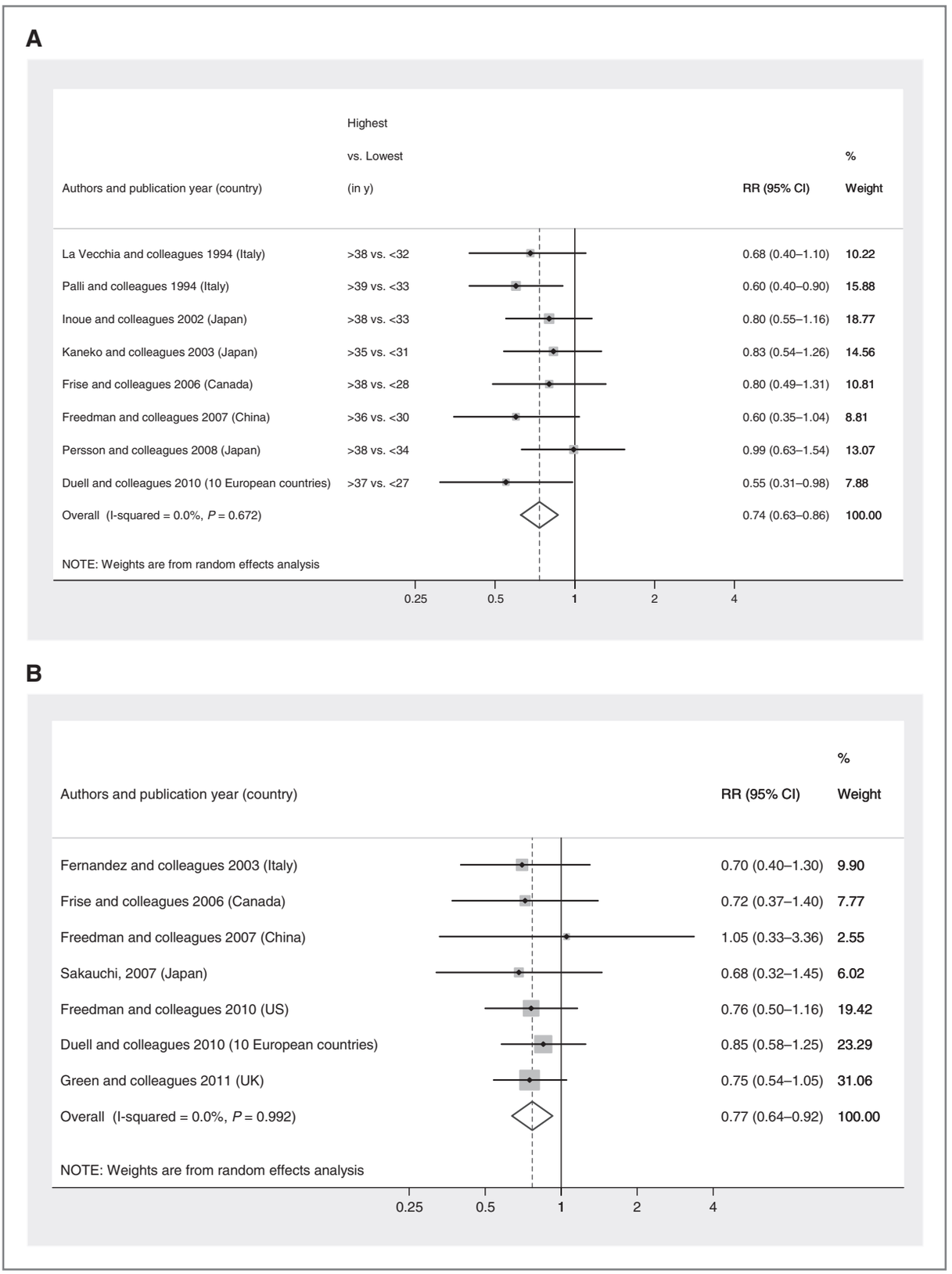

Figure 2. A and B, random-effects estimates and 95% CIs of gastric cancer relative risk (RR) associated with (A) years of fertility (highest vs. lowest category) and (B) HRT (ever vs. never). Study-specific RRs are shown as squares, with the size of the symbol inversely proportional to the study-specific variance. Pooled RRs are shown as diamonds, with the middle corresponding to the point estimate and the width representing the 95% CI.

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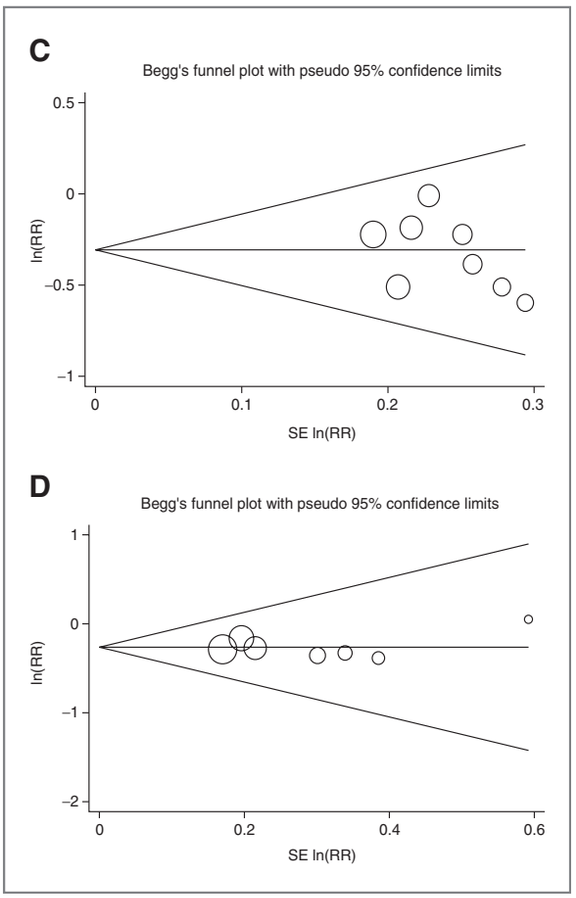

Figure 2. (*Continued*) C and D, Begg's funnel plots with pseudo 95% CIs for gastric cancer RRs associated with (C) years of fertility and (D) HRT.

users ranged from 3% in a study from Italy using data collected before 1993 (26) to 55% in the European Prospective Investigation into Cancer and Nutrition Study, which included women enrolled from 1992 to 1998 (11). The overall pooled RR of gastric cancer for ever users versus never users of OC was 1.15 (95% CI: 0.71–1.88). We found high heterogeneity among the studies, but none of the available variables significantly explained this variation. A Galbraith plot (not shown) indicated the studies by Dorjgochoo and colleagues (40), Freedman and colleagues (41), and Chung and colleagues (42) as outliers contributing to this heterogeneity. The pooled RR derived with exclusion of those studies was 1.11 (95% CI: 0.87–1.42).

Hormone replacement therapy

Figure 2B represents a forest plot of the effect size distribution for the 7 studies that reported on postmenopausal HRT (11, 32, 35–37, 41, 44). The proportion of HRT users ranged from 2% in China (36) to 55% in the United States (41). The pooled RR of gastric cancer for ever users of HRT as compared with never users was 0.77 (95% CI: 0.64–0.92), and there was low heterogeneity among all studies. The average pooled RR was robust to the exclusion of any one study from the overall meta-analysis. In a sensitivity analysis restricted to the 4 studies that adjusted for a proxy variable of SES (11, 32, 35, 36), the point pooled RR was minimally changed, but statistical significance was lost (RR = 0.80; 95% CI: 0.60–1.06).

Tamoxifen therapy

Table 2 summarizes studies with data for comparison of primary gastric cancer incidence among women treated or untreated with tamoxifen. Nine randomized controlled trials including 33,329 patients reported a total of 19 gastric cancer cases in the tamoxifen arms and 14 in the control arms. Five separate observational cohort studies reported combined incidence rates of 0.57 and 0.30 gastric cancers per 1,000 patient-years in the tamoxifen-treated and tamoxifen-untreated groups, respectively. Thus, tamoxifen treatment was associated with a nonsignificantly increased risk in the randomized trials (RR = 1.35; 95% CI: 0.64–2.92) and a significantly increased risk in the observational studies (RR = 1.90; 95% CI: 1.41–2.52). A meta-analysis of these 2 marginal RRs (with inverse variance weights of 13% and 87%, respectively) found a significantly increased gastric cancer risk among women treated with tamoxifen (RR = 1.82; 95% CI: 1.39–2.38).

Publication bias

The *P* values for Egger's test of publication bias were greater than 0.1 for all exposure variables with the exception of OC use ($P = 0.10$; Table 3). Figure 2 presents Begg's funnel plots for years of fertility (2C) and HRT (2D), the 2 variables found to be significantly associated with gastric cancer risk.

Discussion

Although much has been learned about the epidemiology of gastric cancer, it is still unclear why males have higher risk than females. Our meta-analysis identified decreased gastric cancer risks among women with longer duration of fertility or exposure to HRT and increased risk with exposure to the antiestrogenic agent tamoxifen. However, we found no significant associations with age at menarche, age at menopause, parity, age at first birth, or OC use. On balance, these findings support the notion that estrogen exposure influences the risk of gastric cancer in women.

Given the narrow range of age at menarche, variation of years of fertility is mainly determined by age at menopause. Accordingly, we expected similar associations of gastric cancer with these latter 2 variables, at least with restriction to the common set of 8 studies in which both variables were reported. A potential explanation for the discrepancy in our results, not addressable with aggregated data, may be inconsistency between these variables in categorizing individuals as having high (or low) exposure within a given study.

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Table 3. Summary of meta-analytic results

Exposure	Exposure categories		Study design			Pooled RR for gastric cancer (95% CI)	P_Q	I^2 (%)	Outlier studies[b]	$P_{Egger's}$
	Highest (min to max)	Lowest[a] (min to max)	Cohorts	Case–control studies	RCT					
Years of fertility	>35 to >39	<27 to <34	4	4	0	0.74 (0.63–0.86)	0.67	0	None	0.29
Age at menarche (y)	>14 to >16	<13 to <16	6	5	0	1.0 (0.85–1.19)	0.03	50.4	Frise and colleagues (35) and Persson and colleagues (38).	0.25
Age at menopause (y)	>50 to >55	<45 to 50–54	6	4	0	0.84 (0.67–1.05)	0.18	28.9	None	0.41
Parity (number of children)	>2 to >4	0 to 1–2	7	5[c]	0	0.94 (0.74–1.19)	<0.001	83.4	La Vecchia and colleagues (26), Chung and colleagues (42), and Chang and colleagues (43).	0.19
Age at first birth (y)	>25 to >34	<20 to 20–30	6	4	0	0.99 (0.85–1.15)	0.23	23.1	None	0.92
OC use	Ever	Never	3	3	0	1.15 (0.71–1.88)	<0.001	89.7	Dorjgochoo and colleagues (40), Freedman and colleagues (41), and Chung and colleagues (42).	0.10
HRT	Ever	Never	4	3	0	0.77 (0.64–0.92)	0.99	0	None	0.95
Tamoxifen treatment	Treated	Untreated	5	0	9	1.82[d] (1.39–2.38)	0.41	0	N/A	N/A

Abbreviations: P_Q, p from Q statistics; $P_{Egger's}$, p from Egger's test; RCT, randomized clinical trials; N/A, nonapplicable.

[a]Reference category.

[b]Studies identified based on visual inspection of Galbraith plots.

[c]Excludes the study by Inoue and colleagues (30) which reported a linear trend without stratum-specific estimates.

[d]Based on the marginal RR estimates for cohort studies and RCT.

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The other null associations of our analysis may also be understood in context. OC use is not a strong risk factor for breast cancer, an estrogen-driven malignancy (64, 65). Hence, it may not be surprising that OC use does not seem to be associated with gastric cancer risk, for which estrogen exposure presumably has a smaller role. Furthermore, parity and age at first birth do not have clear interpretations with regard to quantitative exposure to estrogen, so the failure to find significant associations with these variables is less relevant to the estrogen hypothesis.

The studies we included vary with respect to the factors controlled in the original analyses. Although we used the reported multivariable adjusted RRs where available, there may have been residual confounding. In the case of HRT, it is possible that postmenopausal women who used hormone therapy may have differed from never users in ways that influence their risk of gastric cancer. Nevertheless, the 4 studies that adjusted for these differences with a proxy variable for SES had a similar pooled RR as all 7 studies of HRT. Thus, confounding by SES would not explain the association between HRT use and gastric cancer, to the extent that these proxies adequately controlled for SES differences without residual confounding.

As a selective estrogen receptor modulator, tamoxifen has both antiestrogenic (e.g., breast tissue) and estrogenic (e.g., bone) effects (66). In a mouse model of gastric cancer, tamoxifen upregulated estrogen-responsive pathways and prevented gastric cancer development (67). We found an opposite effect on risk of gastric cancer in humans, which may speculatively reflect species differences in gastric epithelial susceptibility to the dual tamoxifen effects. Additional potential explanations for the inconsistency between animal and epidemiologic studies include differences in relative age, dose, and duration of treatment as well as drug metabolism.

Chronic infection with *H. pylori* is the primary cause of gastric cancer, and this bacterium is designated a Class I carcinogen by the World Health Organization (68). Sex differences in age at acquisition and infection prevalence have been proposed as potential explanations for differences in gastric cancer incidence between males and females (3, 69, 70). Indeed, a meta-analysis of international population-based surveys (71) found that males had slightly higher infection prevalence among adults (adjusted OR = 1.16) but not among children. Studies measuring spontaneous clearance of *H. pylori* infection by sex have varied, with some studies indicating slightly higher seroreversion rates for women than men (72–74), although others found similar rates (75–77). With regard to therapeutic eradication, no significant variation by sex has been reported. In sum, the small magnitude of these sex differences in *H. pylori* acquisition and clearance cannot fully explain the 2:1 incidence gap.

Steroid-based molecules are incorporated by *H. pylori* into its membrane lipids and differ in their potential effects on bacterial survival (78, 79). Free cholesterol, for example, is glucosylated after incorporation into *H. pylori* and acts to inhibit specific T-cell responses (80). *In vitro*, estradiol is bacteriostatic whereas progesterone and androstenedione are bactericidal (81). In *H. pylori*–infected insulin–gastrin transgenic (INS-GAS) male mice, estradiol supplementation results in decreased expression of *IFNG*, *TNFA*, and *IL1B*, and increased expression of *IL-10* in the epithelial mucosa. Interestingly, these effects are associated with attenuation of gastric lesions and in some models protect against the development of cancer (67, 82, 83). In addition, infected mice treated with estradiol have reduced gastric mRNA expression and serum levels of the neutrophil chemoattractant CXCL1 (67), suggesting that estradiol may limit mucosal injury caused by activated neutrophils. Another study based on a chemically induced model of gastric cancer found that estrogen-treated male rats, as well as female rats, have a lower risk than nontreated male controls (84).

There are several lines of evidence that estrogens may protect against gastric cancer: (i) estrogens interact with receptors in normal, precancerous, and cancerous gastric cells (85, 86), which could regulate the growth and clonal expansion of these cells; (ii) CpG islands in the estrogen receptor gene promoters become hypermethylated with aging, leading to reduced expression with effects on tumor suppressor activity (87); (iii) estrogens increase expression of *trefoil factor* family genes, which encode products that protect gastric mucosa from endogenous and exogenous insults (88); (iv) estrogens increase apoptosis in human gastric cancer cells *in vitro* (89); (v) estrogens increase the strength of the immune response to bacterial pathogens by directly blocking expression of caspase-12 (90); (vi) estrogens retard cell migration after simulated "epithelial wounding" in primary cultured cells and particularly in cancer cell lines (91); (vii) high concentrations of plasma isoflavones from phytoestrogens are associated with decreased risk of gastric cancer (92); (viii) polymorphisms in genes involved in estrogen inactivation and hormone bioavailability have been associated with gastric cancer risk (93); and (ix) men with prostate cancer potentially exposed to therapeutic exogenous estrogens had a reduced incidence of gastric cancer as compared with an age-matched reference population (94).

Smoking may facilitate persistence of *H. pylori* infection (95), increases risk of eradication failure (96), and is considered to have a causal role in the development of gastric cancer (97). Thus, sex differences in smoking patterns may contribute to the male predominance of gastric cancer incidence. However, Freedman and colleagues (5) found roughly similar male/female ratios for cancer incidence among smokers and nonsmokers, suggesting that the difference in smoking does not entirely explain the marked sex difference in gastric cancer risk.

About 9% of gastric cancers harbor Epstein–Barr virus (EBV) infection (98, 99). Furthermore, tumors in males are more than twice as likely to be EBV-positive than tumors in females. Given this sex difference in incidence rates overall, the 2-fold sex difference in EBV positivity

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implies that the incidence of EBV-positive gastric cancer is 4 times higher in males than females.

Differences in diet between men and women might also be related to sex differences in gastric cancer incidence. In particular, low consumption of fresh fruits and vegetables may increase the risk of noncardia tumors (100), and some studies have suggested that women eat fruits and vegetables both more frequently and in greater quantities than men (101, 102). Other factors that may potentially explain the higher risk of gastric cancer among males, as compared with females, are differences in medication and occupational exposures.

Our analysis was limited by the inconsistent categorization of the exposure variables, particularly those with more than 2 strata. As with any meta-analysis, we cannot exclude the possibility that other studies may have been missed during our literature search, or that studies that observed null effects were absent from the literature altogether. Nevertheless, we found little evidence of publication bias. A greater potential concern with regard to data completeness is that some of the published studies on HRT or tamoxifen did not specifically report incidence of gastric cancer, and many registered tamoxifen trials are still unpublished (7).

Our inability to detect significant between-study heterogeneity may be due to the insensitivity of the Q statistic and/or limited sample sizes. Furthermore, insufficient data precluded analyses for histologic and anatomic subtypes, which might have varying associations with the reviewed exposures. We were also unable to evaluate HRT formulation (unopposed estrogen vs. estrogen plus progesterone compounds) and duration of therapy.

Our finding about tamoxifen primarily reflects observational studies with unmeasured confounding of treatment assignment. Nevertheless, limited data from randomized controlled trials was consistent. The analyses of both the randomized trial and the observational cohort data were hampered by inclusion of groups with zero events, which we addressed by marginal analyses. Although this analytic approach has recognized limitations (103), alternative approaches such as continuity corrections also have drawbacks (104). Furthermore, we could not account for the differences in dose and duration of tamoxifen treatment among studies. Thus, these results should be interpreted with caution.

We restricted our meta-analysis to associations with overt gastric cancer. However, given the recognized multistep process of gastric carcinogenesis (105), it is necessary to consider how estrogens might influence earlier stages such as intestinal metaplasia and dysplasia. Direct assessment of estrogens would be additionally informative, as studies to date are almost exclusively based on surrogate measures. Furthermore, the effect of other selective estrogen receptor modulating drugs on gastric carcinogenesis could be usefully examined.

In conclusion, our results are consistent with the hypothesis that effects of estrogen may lower the risk of gastric cancer in women. Further studies are needed to extend these observations and identify the biological bases of this epidemiologic association. Better understanding of how sex differences influence carcinogenesis would provide important insights into gastric cancer etiology.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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