GASTRIC CANCER

Menstrual and reproductive factors and gastric cancer risk in a large prospective study of women

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Background: Gastric cancer incidence rates are consistently lower in women than men in both high and low-risk regions worldwide. Sex hormones, such as progesterone and estrogen, may protect women against gastric cancer.

Objective: To investigate the association of menstrual and reproductive factors and gastric cancer risk.

Methods: These associations were prospectively investigated in 73 442 Shanghai women. After 419 260 person-years of follow-up, 154 women were diagnosed with gastric cancer. Hazard ratios (HR) and 95% confidence intervals (CI) were calculated using Cox proportional hazards models adjusted for age, body mass index, education, income, and cigarette use.

Results: No associations were observed between gastric cancer risk and age of menarche, number of children, breast feeding, or oral contraceptive use. In contrast, associations were observed with age of menopause (HR 0.80 per five-year increase in menopausal age, 95% CI 0.66–0.97), years of fertility (participants with less than 30 years of fertility were at increased risk compared with those with 30–36 years of fertility, HR 1.90, 95% CI 1.25–2.90), years since menopause (HR 1.26 per five years, 95% CI 1.03–1.53), and intrauterine device use (HR for users 1.61, 95% CI 1.08–2.39).

Conclusions: These results support the hypothesis that female hormones play a protective role in gastric cancer risk.

Gastric cancer remains the second leading cause of cancer-related mortality worldwide, despite its decline in incidence in the 20th century.¹ Although gastric cancer incidence varies considerably by geographical region, men are two times more likely than women to develop this disease in both high and low-risk areas.² Established gastric cancer risk factors, such as *Helicobacter pylori* infection, smoking, and low fruit and vegetable intake have not been shown to explain fully the gender difference in gastric cancer incidence rates.^{3–10} Data from the cancer registries of over 20 countries suggest that the male/female incidence ratio is greatest in younger patients and decreases after the age of 60 years.² As the most extreme gender differences in gastric cancer incidence occur during the reproductive ages and the rates become more similar after the menopause, one intriguing hypothesis suggests that sex hormones modulate gastric cancer risk.²

Several lines of evidence support this hypothesis. First, the estrogen receptor, progesterone receptor, and androgen receptor, transcriptional regulators that bind to steroid hormones and exert their actions, are expressed in normal and cancerous gastric tissue.^{11–13} Second, male rats are more likely to develop gastric cancer after carcinogen exposure than are female rats.^{14 15} Third, in a retrospective cohort study, prostate cancer patients treated with estrogen were at a reduced risk of developing gastric cancer.¹⁶ Fourth, two randomised controlled trials have shown a non-significantly increased risk of gastric cancer in women treated with tamoxifen, an estrogen antagonist.^{17 18} Finally, nine epidemiological studies, primarily of case-control design, have investigated the association between particular menstrual or reproductive factors and gastric cancer risk in women.^{8 19–27} Results from the studies generally suggest an association with menstrual but not reproductive factors, although few studies observed statistically significant associations.^{8 20 27} To our knowledge, no studies have investigated this association in China, a country with high rates

of gastric cancer.¹ To investigate this hypothesis further, we examined the association between reproductive and menstrual factors and gastric cancer risk in a large prospective study of women from Shanghai, China, and compared our results with studies of this association in other populations.

METHODS

The Shanghai Women's Health Study is a population-based prospective study of women aged 40–70 years at recruitment who lived in seven urban districts of Shanghai, China, and has been described previously.²⁸ A total of 81 170 women were interviewed at baseline between March 1997 and May 2000, yielding a response rate of 93%. Reasons for non-participation included refusal (n = 2407), absence during the recruitment period (n = 2073), and other miscellaneous reasons (n = 1748). In addition, participants who had a prevalent cancer at baseline (n = 1490) or who did not accrue any follow-up time (n = 10) were excluded, resulting in a cohort of 73 442 women for the current study.

Cohort follow-up and case identification

Follow-up occurred via in-person interview biennially and linkage with the Shanghai Cancer Registry, the Shanghai Vital Statistics Registry, and the Shanghai Resident Registry²⁸ until the time of first incident cancer diagnosis, death, or 30 June 2004, whichever came first. Possible incident cancer cases were checked manually and verified by home visits. Medical charts from hospitals were reviewed and the pathological characteristics of the tumor recorded. Incident gastric adenocarcinomas (International Classification of Disease version 9 codes of 151.0–151.9) occurred in 154 participants. We collected 12 cases

Abbreviations: CagA, cytotoxin-associated gene A; HR, hazard ratio; HRT, hormone replacement therapy; IQR, interquartile range; IUD, intrauterine device

(7.8%) with International Classification of Disease version 9 code 151.0, which are defined as gastric cardiac cancers. We performed a sensitivity analysis on our results and found no difference in the results whether we included or excluded those 12 cases. The study was approved by all relevant institutional review boards in the People's Republic of China and in the United States.

Exposure assessment

The baseline questionnaire contained two parts and has been described previously.²⁸ Participants were instructed to record age, educational attainment, family income, disease and surgery history, physical activity, and smoking and alcohol drinking practices using a standardised questionnaire; the completeness of the questionnaires was checked at the time of baseline interview. Weight and height were measured and body mass index was calculated (kg/m^2). Fruit and vegetable intake was assessed by trained interviewers using a comprehensive food frequency questionnaire representing 90% of foods consumed in Shanghai in 1996.²⁹ Smokers were defined as subjects who smoked at least one cigarette per day for more than six months. Alcohol drinkers were those who drank alcohol more than three times a week for six months.

In addition, participants were interviewed for information on the number of pregnancies, live births, age of menarche, menstrual status, use of oral contraceptives, contraceptive shots, intrauterine devices (IUD), female hormones, and if applicable, age of menopause, duration of IUD use, and duration of breast feeding for each pregnancy. Years of fertility was calculated by subtracting the age of menarche from the age of menopause. The number of years since menopause was calculated by subtracting age at baseline from age of menopause. If subjects were taking female hormones after menopause (hormone replacement therapy; HRT), they were considered post-menopausal hormone users. If they were pre-menopausal and taking hormones after the age of 40 years, they were considered peri-menopausal hormone users. All others were considered hormone non-users. Months of breast feeding per child was calculated by dividing the total number of months breast feeding by the number of children.

We constructed categories based on the distribution of the variable in the overall cohort for age at menarche, age at menopause, years since menopause, years of fertility, age at first birth, total months breast feeding, and months of breast feeding per child. We selected subjects with the typical values for these parameters, between the 25th and 75th percentile, as the referent group. We included the central 50th percentile of the distribution in the referent group to increase the stability of the estimates and because this facilitated interpretation of the estimates for subjects with high or low values compared with the typical range. Because 47% of the cohort reported no IUD use or IUD use for less than one year, we constructed four categories for analysing the duration of IUD use: non-users, and three categories of users, each containing approximately 18% of the cohort distribution. For analysis of years of fertility and years since menopause in mutually adjusted models, we created dichotomous variables to increase power. Years of fertility was split at the 25th percentile (30 years). Years since menopause was split at the median (11 years).

Statistical analysis

Analysis was performed using SAS version 8.2 (SAS Institute Inc., Cary, North Carolina, USA). An alpha level of less than 0.05 was considered significant and all tests were two sided. Cox proportional hazards regression³⁰ was used to calculate hazard ratios (HR) and 95% confidence intervals (CI). Models were analysed for potential confounders of age, alcohol

drinking, body mass index, cigarette smoking, education, family history of gastric cancer, gastritis, income, intake of fruits, vegetables, soy, and preserved foods, physical activity, and the use of aspirin-based medicines. Only age changed the beta coefficients for menstrual and reproductive variables by more than 10%. We investigated confounding by *Helicobacter pylori* cytotoxin-associated gene A (CagA) seropositivity in a nested case-control set of 114 cases and 228 controls from the cohort (data not shown). *H. pylori* CagA status did not confound estimates, thus we present the data from the entire cohort. To increase our control over age in the models, we used age as the underlying time metric.³¹ For comparison, we present age and multivariate-adjusted models in the tables. For adjustment, we used the categories for covariates in table 1 and five categories for body mass index (<18.5, 18.5–<25, 25–<30, 30–<35, and ≥ 35). Linear trends were examined by treating each level of the categorical variable as an ordinal number, for example 1, 2, 3 or 1, 2, 3, 4. For analysis of age of menarche, menopausal status, years of fertility, age of menopause, and HRT, those missing age of menarche (22 participants, one gastric cancer) or date of menopause (seven participants) were excluded. We also looked for confounding of each of the risk estimates by mutually adjusting for other reproductive and menstrual factors. For the analysis of breast feeding, IUD use, oral contraceptive use, and parity, we also stratified by menopausal status; however, the test for interaction was not significant and the stratified estimates appeared similar. We tested the proportional hazards assumption for each main effect by modeling interaction terms of time and the appropriate variable, and no deviations were found.

RESULTS

Of the 73 442 participants in the cohort, 154 were diagnosed with gastric cancer over 419 260 person-years of follow-up. In table 1, we present the characteristics of women in the overall cohort and women diagnosed with gastric cancer. Gastric cancer patients were older, had received less education, and were more likely to smoke, but had similar levels of household income and body mass index as women in the cohort overall.

We examined the association between menstrual factors and gastric cancer in models adjusted for age alone and multivariate models adjusted for categorical variables of body mass index, education, income, and smoking status (ever/never) and continuous variables for age and smoking dose (packs per day; table 2). We present multivariate-adjusted estimates in the text.

No significant associations were observed with the age of menarche. Women who had natural or surgically induced menopause were at increased risk of gastric cancer (natural menopause, HR 1.22, 95% CI 0.60–2.45; surgically induced menopause, HR 2.37, 95% CI 1.11–5.05). Similarly, risk was also increased in women who underwent hysterectomy (HR 2.03, 95% CI 1.22–3.37) or ovariectomy (HR 2.28, 95% CI: 1.29–4.03). As a continuous variable, age at menopause was inversely associated with cancer risk (HR 0.80 per five years, 95% CI 0.66–0.97). Compared with women whose menopause occurred between 46 and 51 years, those with an age of menopause less than 46 years were at a significantly increased risk (HR 1.88, 95% CI 1.25–2.82). Duration of fertility (age of menopause minus age of menarche) was inversely associated with risk. Participants with less than 30 years of fertility were at an increased risk compared with those with 30–36 years of fertility (HR 1.90, 95% CI 1.25–2.90).

Years of fertility and age of menopause had a Pearson correlation of 0.92. The median years of fertility among those with surgically induced menopause (28, interquartile range (IQR) 25–32) was lower than those with natural menopause (34, IQR 31–36). We examined models mutually adjusted for

Table 1 Selected characteristics of 73 442 women in Shanghai, China, at study baseline (1997–2000)

Characteristics*	Cohort	Cases
	Person-years (%)†	No. (%)†
Age‡	50 (44–60)	62 (51–65)
Body mass index (kg/m ²)‡	23.7 (21.6–26.1)	24.3 (21.6–26.4)
Income (yuan)		
<10 000	66 100 (15.8)	26 (16.9)
10 000–20 000	158 572 (37.8)	63 (40.9)
20 000–30 000	119 233 (28.4)	45 (29.2)
>30 000	75 257 (18.0)	20 (13.0)
Education		
College or higher	58 481 (14.0)	17 (11.0)
High school	117 077 (27.9)	30 (19.5)
Middle school	154 967 (37.0)	36 (23.4)
Elementary/less	88 662 (21.2)	71 (46.1)
Alcohol use		
Ever	9463 (2.3)	2 (1.3)
Never	409 797 (97.7)	152 (98.7)
Smoking		
Ever	11 442 (2.7)	8 (5.2)
Never	407 818 (97.3)	146 (94.8)

*Categories may not add up to 419 260 person-years or 154 cases as a result of missing data.

†Unless otherwise specified.

‡Median, interquartile range.

Table 2 Adjusted hazard ratios and 95% confidence intervals for menstrual factors and gastric cancer risk in 73 442 women from 1997 to 2004 in Shanghai, China

Characteristics†	Cohort	Cases	Age-adjusted	Multivariate-adjusted*
	Person-years (%)	No. (%)	HR (95% CI)	HR (95% CI)
Age of menarche				
Continuous			0.98 (0.90 to 1.08)	0.96 (0.87 to 1.05)
<14	93 007 (22.2)	30 (19.6)	1.01 (0.67 to 1.53)	1.09 (0.71 to 1.65)
14 to 16	252 018 (60.1)	93 (60.8)	1.00 (Ref)	1.00 (Ref)
>16	74 074 (17.7)	30 (19.6)	0.84 (0.55 to 1.27)	0.78 (0.51 to 1.19)
p Value for trend			0.466	0.213
Menstrual status				
Currently menstruating	213 976 (51.2)	33 (21.6)	1.00 (Ref)	1.00 (Ref)
Natural menopause	183 612 (43.9)	104 (68.0)	1.22 (0.61 to 2.46)	1.22 (0.60 to 2.45)
Surgically induced menopause	20 404 (4.9)	16 (10.5)	2.33 (1.09 to 4.95)	2.37 (1.11 to 5.05)
Hysterectomy				
No	397 924 (94.9)	137 (89.0)	1.00 (Ref)	1.00 (Ref)
Yes	21 336 (5.1)	17 (11.0)	1.96 (1.18 to 3.25)	2.03 (1.22 to 3.37)
Ovariectomy				
No	402 768 (96.1)	141 (91.6)	1.00 (Ref)	1.00 (Ref)
Yes	16 492 (3.9)	13 (8.4)	2.19 (1.24 to 3.87)	2.28 (1.29 to 4.03)
Age at menopause‡				
Continuous variable/5 years			0.79 (0.65 to 0.95)	0.80 (0.66 to 0.97)
<46	44 713 (21.8)	37 (30.8)	1.88 (1.25 to 2.83)	1.88 (1.25 to 2.82)
46 to 51	122 102 (59.5)	64 (53.3)	1.00 (Ref)	1.00 (Ref)
>51	38 309 (18.7)	19 (15.8)	0.94 (0.56 to 1.58)	0.97 (0.58 to 1.64)
p Value for trend			0.007	0.01
Years of fertility‡				
Continuous variable/5 years			0.83 (0.69 to 0.99)	0.85 (0.70 to 1.02)
<30	38 684 (18.9)	34 (28.3)	1.96 (1.29 to 2.98)	1.90 (1.25 to 2.90)
30 to 36	123 356 (60.1)	63 (52.5)	1.00 (Ref)	1.00 (Ref)
>36	43 084 (21.0)	23 (19.2)	1.08 (0.67 to 1.75)	1.14 (0.70 to 1.86)
p Value for trend			0.022	0.044
Years since menopause‡				
Continuous variable/5 years			1.27 (1.05 to 1.54)	1.26 (1.03 to 1.53)
<5	43 982 (21.4)	11 (9.2)	0.46 (0.21 to 1.00)	0.47 (0.22 to 1.01)
5 to 17	117 788 (57.4)	67 (55.8)	1.00 (Ref)	1.00 (Ref)
>17	43 354 (21.1)	42 (35.0)	1.36 (0.84 to 2.19)	1.34 (0.83 to 2.16)
p Value for trend			0.033	0.039
HRT				
None	404 432 (96.5)	150 (98.0)	1.00 (Ref)	1.00 (Ref)
Post-menopausal HRT	8618 (2.1)	3 (2.0)	0.94 (0.30 to 2.96)	1.05 (0.33 to 3.36)
Peri-menopausal HRT [§]	6050 (1.4)	0 (0.0)		

HR, hazard ratio; HRT, hormone replacement therapy; Ref, reference.

*Adjusted for age, body mass index, education, income, cigarette smoking status (ever, never), and smoking dose (packs/day).

†Categories may not add up to 419 260 person-years or 154 cases as a result of missing data.

‡Restricted to post-menopausal women.

§Zero cases in this category.

both years of fertility and surgically induced menopause. In multivariate-adjusted models restricted to post-menopausal women, those with surgically induced menopause were at 2.01 (95% CI 1.17–3.46) times the risk of those with natural menopause. In a model additionally adjusted for years of fertility, the association between surgically induced menopause and gastric cancer was partly attenuated (HR 1.66, 95% CI 0.94–2.92), whereas the association between years of fertility and gastric cancer was similar to that observed in the non-mutually adjusted models (<30 years of fertility compared with 30–36 years of fertility, HR 1.75, 95% CI 1.13–2.71). Similar results were observed when age of menopause was included in the model instead of years of fertility (data not shown).

Furthermore, the risk of gastric cancer increased with increasing years since menopause (*p* for trend 0.039). Each

five-year period after menopause was associated with 1.26 times (95% CI 1.03–1.53) the risk. We examined the independent effect of years of fertility and years since menopause on gastric cancer risk using dichotomous variables in mutually adjusted models. The estimates for years since menopause and years of fertility were attenuated (<30 years of fertility, HR 1.64, 95% CI 1.07–2.51; >11 years since menopause, HR 1.66, 95% CI 0.88–3.12), but remained similar to the non-mutually adjusted estimates (HR 1.85 for <30 years of fertility and 2.10 for >11 years past menopause, respectively).

The gastric cancer risk was not significantly related to the number of pregnancies, number of live births, total months of breast feeding, or average months of breast feeding per child (table 3). As a continuous variable, an older age at first birth was associated with a borderline reduced gastric cancer risk

Table 3 Adjusted hazard ratios and 95% confidence intervals for reproductive factors and gastric cancer risk in 73 442 women from 1997 to 2004 in Shanghai, China

Characteristics [†]	Cohort Person-years (%)	Cases No. (%)	Age-adjusted HR (95% CI)	Multivariate-adjusted* HR (95% CI)
Pregnancies				
Continuous variable			1.02 (0.91 to 1.13)	0.99 (0.89 to 1.11)
0	11 062 (2.6)	4 (2.6)	0.95 (0.31 to 2.87)	0.95 (0.31 to 2.88)
1	67 003 (16.0)	16 (10.4)	1.00 (Ref)	1.00 (Ref)
2	122 848 (29.3)	23 (14.9)	0.69 (0.36 to 1.30)	0.69 (0.37 to 1.31)
3	101 418 (24.2)	43 (27.9)	1.13 (0.62 to 2.04)	1.11 (0.61 to 2.01)
≥4	116 929 (27.9)	68 (44.2)	0.95 (0.52 to 1.73)	0.88 (0.48 to 1.62)
<i>p</i> Value for trend			0.675	0.950
Live births				
Continuous variable			1.01 (0.88 to 1.17)	0.96 (0.83 to 1.12)
0	13 648 (3.3)	4 (2.6)	0.73 (0.25 to 2.08)	0.69 (0.24 to 2.00)
1	229 076 (54.6)	49 (31.8)	1.00 (Ref)	1.00 (Ref)
2	89 810 (21.4)	37 (24.0)	0.78 (0.47 to 1.32)	0.77 (0.45 to 1.30)
3	43 676 (10.4)	27 (17.5)	0.82 (0.44 to 1.52)	0.70 (0.37 to 1.34)
≥4	43 050 (10.3)	37 (24.0)	0.91 (0.49 to 1.70)	0.73 (0.38 to 1.41)
<i>p</i> Value for trend			0.909	0.574
Age at first birth [‡]				
Continuous variable			0.96 (0.92 to 1.00)	0.96 (0.92 to 1.01)
<24	100 383 (24.6)	63 (42.0)	1.03 (0.71 to 1.50)	0.93 (0.63 to 1.39)
24 to 29	234 204 (57.4)	72 (48.0)	1.00 (Ref)	1.00 (Ref)
>29	73 610 (18.0)	15 (10.0)	0.75 (0.43 to 1.31)	0.77 (0.44 to 1.35)
<i>p</i> Value for trend			0.379	0.708
Total months breast feeding [‡]				
Continuous Variable/10 months			0.99 (0.97 to 1.02)	0.99 (0.97 to 1.02)
<10	101 035 (24.8)	19 (12.7)	0.78 (0.46 to 1.33)	0.81 (0.47 to 1.39)
10 to 60	206 394 (50.6)	98 (65.3)	1.00 (Ref)	1.00 (Ref)
>60	100 768 (24.7)	33 (22.0)	0.75 (0.50 to 1.12)	0.75 (0.50 to 1.12)
<i>p</i> Value for trend			0.562	0.484
Months breast feeding per child [‡]				
Continuous variable (months)			1.00 (0.99 to 1.00)	1.00 (0.99 to 1.01)
<4	95 309 (23.3)	21 (14.0)	0.85 (0.52 to 1.39)	0.89 (0.54 to 1.47)
4 to 14	212 661 (52.1)	97 (64.7)	1.00 (Ref)	1.00 (Ref)
>14	100 227 (24.6)	32 (21.3)	0.78 (0.52 to 1.17)	0.79 (0.53 to 1.18)
<i>p</i> Value for trend			0.578	0.499
IUD use				
No	188 853 (45.0)	90 (58.4)	1.00 (Ref)	1.00 (Ref)
Yes	230 407 (55.0)	64 (41.6)	1.56 (1.06 to 2.31)	1.61 (1.08 to 2.39)
IUD duration (months)				
Continuous Variable/5 months			1.14 (1.02 to 1.27)	1.14 (1.02 to 1.28)
Non-users or used for <1 year	195 958 (46.7)	92 (59.7)	0.60 (0.37 to 0.97)	0.58 (0.36 to 0.95)
0 to 14	77 146 (18.4)	25 (16.2)	1.00 (Ref)	1.00 (Ref)
14 to 20	90 429 (21.6)	16 (10.4)	0.83 (0.43 to 1.58)	0.83 (0.44 to 1.59)
>20	55 720 (13.3)	21 (13.6)	1.03 (0.57 to 1.87)	1.04 (0.57 to 1.90)
<i>p</i> Value for trend			0.044	0.032
Oral contraceptive use				
No	333 571 (79.6)	121 (78.6)	1.00 (Ref)	1.00 (Ref)
Yes	85 688 (20.4)	33 (21.4)	1.04 (0.70 to 1.54)	1.05 (0.70 to 1.56)
Received contraceptive shot				
No	408 448 (97.4)	149 (96.8)	1.00 (Ref)	1.00 (Ref)
Yes	10 805 (2.6)	5 (3.3)	1.36 (0.56 to 3.33)	1.38 (0.56 to 3.38)

HR, hazard ratio; IUD, intrauterine device; Ref, reference.

*Adjusted for age, body mass index, education, income, cigarette smoking status (ever, never), and smoking dose (packs/day).

[†]Categories may not add up to 419 260 person-years or 154 cases as a result of missing data.

[‡]Restricted to parous women.

Table 4 Comparison of epidemiological studies for the association between years of fertility, age at menarche, and age of menopause and gastric cancer

First author [reference]	Design	Study location	Cases/controls	Referent group (years)	Exposed group (years)	Risk ratio* (95% CI)
Years of fertility						
Palli ²⁷	Retrospective	Italy	339/515	<33	≥40	0.6 (0.4 to 0.9)
La Vecchia ²⁶	Retrospective	Italy	227/606	<32	≥39	0.66 (0.4 to 1.1)
Inoue ^{†,23}	Retrospective	Japan	365/1825	≤32	≥39	0.80 (0.55 to 1.16)
Kaneko ^{†24}	Prospective	Japan	156/40 535	<31	>35	0.83 (0.54 to 1.26)
Frise ^{†20}	Retrospective	Canada	269/261	<27	>38	0.80 (0.49 to 1.31)
This study [†]	Prospective	China	120/35 944	<30	>36	0.60 (0.35 to 1.04)
Age at menarche						
Palli ²⁷	Retrospective	Italy	339/515	<13	≥15	1.0 (0.6 to 1.4)
La Vecchia ²⁶	Retrospective	Italy	228/608	<13	≥15	0.77 (0.5 to 1.2)
Heuch ²¹	Prospective	Norway	554/63 090	≤12	≥17	0.7 (0.5 to 1.1)
Inoue ²³	Retrospective	Japan	365/1825	≤12	≥15	1.15 (0.73 to 1.81)
Kaneko ²⁴	Prospective	Japan	156/40 535	<14	>15	0.86 (0.52 to 1.41)
Frise ²⁰	Retrospective	Canada	326/326	<13	≥15	1.94 (1.21 to 3.10)
This study	Prospective	China	153/73 413	<14	>16	0.72 (0.42 to 1.22)
Age of menopause						
Palli ²⁷	Retrospective	Italy	339/515	<45	≥55	0.6 (0.3 to 1.0)
La Vecchia ²⁶	Retrospective	Italy	228/608	<45	≥53	0.57 (0.3 to 1.1)
Heuch ²¹	Prospective	Norway	315/22 151	≤45	≥54	0.9 (0.5 to 1.6)
Inoue ²³	Retrospective	Japan	365/1825	≤44	≥55	0.92 (0.44 to 1.90)
Kaneko ²⁴	Prospective	Japan	156/40 535	<47	>51	0.93 (0.60 to 1.44)
Frise ^{†20}	Retrospective	Canada	326/326	<45	Pre-menopausal	0.57 (0.29 to 1.12)
This study	Prospective	China	120/35 944	<46	>51	0.52 (0.30 to 0.91)

*Odds ratio for retrospective studies and hazard ratio for prospective studies.

†Restricted to post-menopausal women.

‡Referent group and subsequent odds ratio inverted for consistent presentation.

(HR 0.96, 95% CI 0.92–1.01). Women who gave birth after 29 years of age had a non-significantly reduced risk compared with those who gave birth between 24 and 29 years of age (HR 0.77, 95% CI 0.44–1.35). The *p* for trend across increasing categories of age at first birth was, however, not significant (*p* = 0.708).

We found no association between oral contraceptive or contraceptive shot use and gastric cancer risk (table 3). IUD users had a 61% (95% CI 1.08–2.39) increase in risk compared with non-users. A borderline significant association between the duration of IUD use and gastric cancer was also observed (as a continuous variable per five years, HR 1.14, 95% CI 1.02–1.28) and the *p* for trend was 0.032). As the use of IUD in Shanghai was strongly age dependent, we stratified the analysis by the median age (62 years) of women diagnosed with gastric cancer but found no effect modification by age. The risk was 1.51 (95% CI 0.92–2.49) among those 62 years or younger and 1.82 (95% CI 0.97–3.39) for those older than 62 years. Mutually adjusting for other menopausal and reproductive factors did not alter the risk estimates.

DISCUSSION

We investigated the association between gastric cancer and hormonal and reproductive factors in the Shanghai Women's Health prospective cohort study, with the hypothesis that exposure to hormones, such as estrogen, would be associated with reduced gastric cancer risk. We found significant positive associations with menopausal status, a history of ovariectomy or hysterectomy, years since menopause, and IUD use, and significant inverse associations with age at menopause and years of fertility. A suggestive inverse association between age at first birth and gastric cancer risk was also observed.

Our results were consistent with those of previous studies in other countries that generally observed an inverse association of gastric cancer risk with both increased years of fertility and late menopause, and no association with age of menarche (table 4).

Of the studies^{20 23 24 26 27} that examined the association between years of fertility and gastric cancer risk, all had an odds or hazard ratio below 1.0 for participants in the highest category compared with the lowest category, but only one study reported a significant association.²⁷ For age of menopause, three studies observed borderline significant associations for the odds or risk ratios of those in the highest category compared with the lowest category,^{20 26 27} whereas the point estimates were slightly below one but were not significant for three other studies.^{21 23 24} Except for a recent case-control study that reported a significantly elevated risk of gastric cancer with late age of menarche,²⁰ the majority of studies, including this one, reported no or a non-significant reduction in risk with late age of menarche (table 4). In contrast to several previous studies,^{8 19 20 24 26} our results did not suggest an association between HRT and reduced gastric cancer risk. Just 2% (1518 participants and three cases) of our cohort reported ever using post-menopausal HRT.

We found no significant associations between pregnancies, live births, breast feeding, or oral contraceptive use and gastric cancer risk. Results in other studies for these exposures have been mixed, with most studies showing no association.^{20–27} Consistent with three studies,^{20 23 26} we did observe a borderline inverse association with age at first birth.

We observed a significant association between IUD use and gastric cancer risk. IUD was used by over 50% of the women in this cohort (table 1). As far as we know, ours is the only study to investigate this possible association. The mechanism by which IUD use might increase gastric cancer risk is unclear, as the type of IUD most commonly used in China does not contain hormones. It is possible that the observed association is spurious and it needs to be replicated in other studies.

The rates of gastric cancer increase slowly in women compared with men until the age of 60 years. After 60 years of age, gastric cancer rates in women increase rapidly and become more similar to those in men.² Data from this study and others suggest that a long duration of fertile years and the associated higher levels of hormones later in life are associated

with decreased gastric cancer risk (table 4). The association observed between surgically induced menopause, ovariectomy, and hysterectomy and increased gastric cancer risk is also consistent with this hypothesis, as the median years of fertility among those with surgically induced menopause (28, IQR 25–32) was lower than those with natural menopause (34, IQR 31–36). We note that cancer risk increased in the years after menopause, further suggesting that low hormone levels are associated with reduced risk. In mutually adjusted models, both increasing years after menopause and shorter years of fertility were associated with an increased risk of gastric cancer. The possible protective association between HRT and gastric cancer incidence, observed in other populations with higher HRT use, is also consistent with this hypothesis.^{8 19 20 24 26}

Sex hormones, such as estrogens, might protect against gastric cancer by interfering with gastric cancer development and progression. In the leading model of gastric carcinogenesis, inflammation plays a central role in the development of gastric cancer.^{32–34} Estrogens regulate numerous physiological processes primarily by binding to estrogen receptors, which are potent transcriptional regulators.³⁵ As estrogen receptors are present in gastric epithelial tissue^{11 13} and have been shown to inhibit inflammation,^{36–38} it is biologically plausible that estrogens could protect against gastric cancer.

It is also possible that length of fertility is a surrogate for other environmental factors, such as better nutrition and other privileged lifestyles that cannot be easily measured. Adjustment for *H. pylori* CagA seropositivity, alcohol intake, body mass index, cigarette smoking, education, income, intake of fruits, vegetables, soy products, and preserved foods, and physical activity did not meaningfully affect risk estimates in this study. This hypothesis needs further evaluation in other populations and also in molecular epidemiological and laboratory studies to determine the biological feasibility of this association.

Our study has several strengths. Detailed reproductive and menstrual factors were collected prospectively and we were able to investigate possible confounding by most gastric cancer risk factors. We were also the first study to investigate this association in the Chinese population. Our study, however, had limited power to examine effect modification by other gastric cancer risk factors, including *H. pylori*.

In conclusion, consistent with the hypothesis that hormones such as estrogen and progesterone protect against the development of gastric cancer in women during the reproductive years, we found associations of gastric cancer risk with late age of menopause, increased years of fertility, and years after menopause in a large prospective study of women.

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EDITOR'S QUIZ: GI SNAPSHOT

Answers

From questions on page 1664

Figure 1 (see question) shows an ulcer at the superior aspect of the pylorus (white arrow) and a double pyloric channel (double arrow head) into a single first part of the duodenum. This rare complication of peptic ulcer disease is called double pylorus or antro-duodenal fistula.

A CLO test was positive and the patient was given a 7-day course of triple drug *H pylori* eradication, followed by 6 weeks of pantoprazole 40 mg daily to heal the ulcer. *H pylori* eradication was confirmed with a negative C-13 urea breath test 10 weeks later. Gastrosocopy in November 2003 confirmed ulcer healing and persistent double pylorus (fig 1, below). The patient remains asymptomatic and was receiving no treatment at a recent review.

Double pylorus is congenital or acquired with a prevalence of 0.06–0.4%.¹ Four to 9% of cases are congenital.² Double pylorus was first recognised in 1861,³ but only two reported cases of double pylorus from the UK^{4 5} can be found. Lack of further reports might be due to under-reporting or to a true non-occurrence in the UK.

Acquired double pylorus is a complication of peptic ulcer disease due to perforation of an antral ulcer into the duodenal bulb or vice versa. The double pylorus in our patient was most probably peptic ulcer induced, as suggested, by a new ulcer nearby. Diagnosis by direct inspection using a gastroscope is probably better than barium studies. Symptoms respond well to proton pump inhibitors. *H pylori* eradication is important with evidence of infection and peptic ulcer disease. Rarely, obstructive symptoms require division of the intervening septum by surgery or endoscopy using a sphincterotome.

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Figure 1 Endoscopic appearance of gastric antrum at repeat gastroscopy.