Original Article

Effects of Reproductive Factors on Lauren Intestinal-Type Gastric Cancers in Females: A Multicenter Retrospective Study in South Korea

Yoon Ju Jung[1], Hee Jin Kim[2], Cho Hyun Park[3], Seun Ja Park[4], and Nayoung Kim[5,6]

[1]Division of Gastrointestinal Surgery, Department of Surgery, Incheon St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Incheon, [2]Department of Internal Medicine, Gyeongsang National University Changwon Hospital, Gyeongsang National University College of Medicine, Changwon, [3]Division of Gastrointestinal Surgery, Department of Surgery, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, [4]Department of Internal Medicine, Kosin University College of Medicine, Busan, [5]Department of Internal Medicine, Seoul National University Bundang Hospital, Seongnam, and [6]Department of Internal Medicine and Liver Research Institute, Seoul National University College of Medicine, Seoul, Korea

Corresponding Author

Nayoung Kim
ORCID https://orcid.org/0000-0002-9397-0406
E-mail nakim49@snu.ac.kr

Seun Ja Park
ORCID https://orcid.org/0000-0003-3217-5115
E-mail parksj6406@daum.net

Yoon Ju Jung and Hee Jin Kim contributed equally to this work as first authors.

Background/Aims: Gastric cancers (GCs), particularly the Lauren intestinal type, show a male predominance. The aim of this study was to investigate the effects of reproductive factors on GCs in females, according to Lauren classification.

Methods: Medical records of 1,849 males and 424 females who underwent radical gastrectomy or endoscopic resection for GCs between 2010 and 2018 were reviewed. The incidences of intestinal-type GCs were compared between males and groups of females stratified according to postmenopausal period. Associations between reproductive factors in females and intestinal-type GCs were analyzed using multivariate models.

Results: The proportions of intestinal-type GCs were significantly lower in premenopausal (19%), less than 10 years postmenopausal (30.4%), and 10 to 19 years postmenopausal females (44.1%) than in males (61.0%) (p<0.05 for all). Females ≥20 years postmenopause had a proportion of intestinal-type GCs similar to that in males (60.6% vs 61.0%; p=0.948). Multivariate analysis revealed that age (odds ratio [OR], 1.075; 95% confidence interval [CI], 1.039 to 1.113; p<0.001) and parity ≥3 (OR, 1.775; 95% CI, 1.012 to 3.114; p=0.045) were positively associated with an increased risk of intestinal-type GCs in postmenopausal females, while long fertility duration (OR, 1.147; 95% CI, 1.043 to 1.261; p=0.005) was positively associated with an increased risk of intestinal-type GCs in premenopausal females.

Conclusions: There were no significant differences in the proportions of intestinal-type GCs between males and females ≥20 years postmenopause, suggesting that female reproductive factors play a role in the prevention of intestinal-type GC. **(Gut Liver 2022;16:706-715)**

Key Words: Gastric; Cancer; Female; Reproductive

INTRODUCTION

The incidence of gastric cancer (GC) is 2-fold to 3-fold greater in males than in females in most populations.[1] A lower GC incidence in females may partly be caused by lower exposure to risk factors, such as cigarette smoking,[2] alcohol use, *Helicobacter pylori* infections,[3] and obesity; however, these factors do not fully explain the disparity. This has led to the hypothesis that sex hormones are in-

volved in GC development. This notion is also supported by the observation that the male-to-female ratio in GC incidence rates peaks at 2.5 at the age of 60 years; it then declines to 1.5, suggesting diminished postmenopausal protection.[4]

Estrogens are involved in various physiologic processes, primarily via binding to estrogen receptors, which are potent transcriptional regulators. Estrogen has oncogenic and angiogenic effects;[5] it has crucial roles in the cardio-

vascular, nervous, and immune systems.[6] Epidemiological studies have demonstrated some level of protection against GC with longer fertility duration and hormone replacement therapy.[7] Recently, a large cohort study of 333,919 European females demonstrated a negative association of the age at first pregnancy, and a positive association of bilateral ovariectomies, with the incidences of gastric non-cardiac cancers.[8] However, most recent evidence comes from Western studies, and no studies have demonstrated associations of estrogen exposure factors with GC on the basis of histologic subtypes.

GC can be classified into two histologic subtypes according to the Lauren classification (i.e., intestinal and diffuse); these subtypes are distinct in terms of microscopic and gross morphologies, epidemiology, pathogenesis, genetics, and prognosis.[9,10] Diffuse-type GCs occur more frequently in females and at younger ages; they have a greater tendency to invade the gastric walls and metastasize, leading to a worse prognosis compared with intestinal-type GCs.[11] In contrast, intestinal-type GCs occur more frequently in males and at older ages; environmental factors, rather than genetic factors, contribute to their development.[11] Typically, intestinal-type GCs arise through a multi-step process that involves atrophic gastritis, intestinal metaplasia, and dysplasia; these steps are associated with chronic inflammatory processes caused by *H. pylori*.[12]

Sex is a biological status based on reproductive systems and functions, assigned on the basis of chromosomal type.

In contrast, gender includes manners, feelings, and behaviors that are associated with sex stereotypes in a particular culture.[13,14] Sex is a crucial factor in the pathogenesis, risk, progression, and prognosis of various diseases; it occasionally determines drug responses.[15,16] However, GC was not much evaluated in terms of sex-specific medicine. We hypothesized that the effects of estrogen on GC development differed on the basis of the Lauren histologic type and reproductive factors. This study aimed to investigate associations between reproductive factors and GC development according to the Lauren classification in a nationwide multicenter study of Korean females.

MATERIALS AND METHODS

1. Study populations

This study included patients who were diagnosed with GCs and underwent endoscopic or curative surgical resections at the St. Mary's Hospital (Seoul), Kosin University Hospital (Busan), and Seoul National University Bundang Hospital (Seongnam), between February 1, 2010, and December 31, 2018. Medical records were retrospectively reviewed. All included patients had been diagnosed with gastric adenocarcinomas or poorly cohesive carcinomas on the final pathology reports of surgical or endoscopic resection specimens. Patients were excluded if they had other non-gastric malignancies within 5 years from the time of
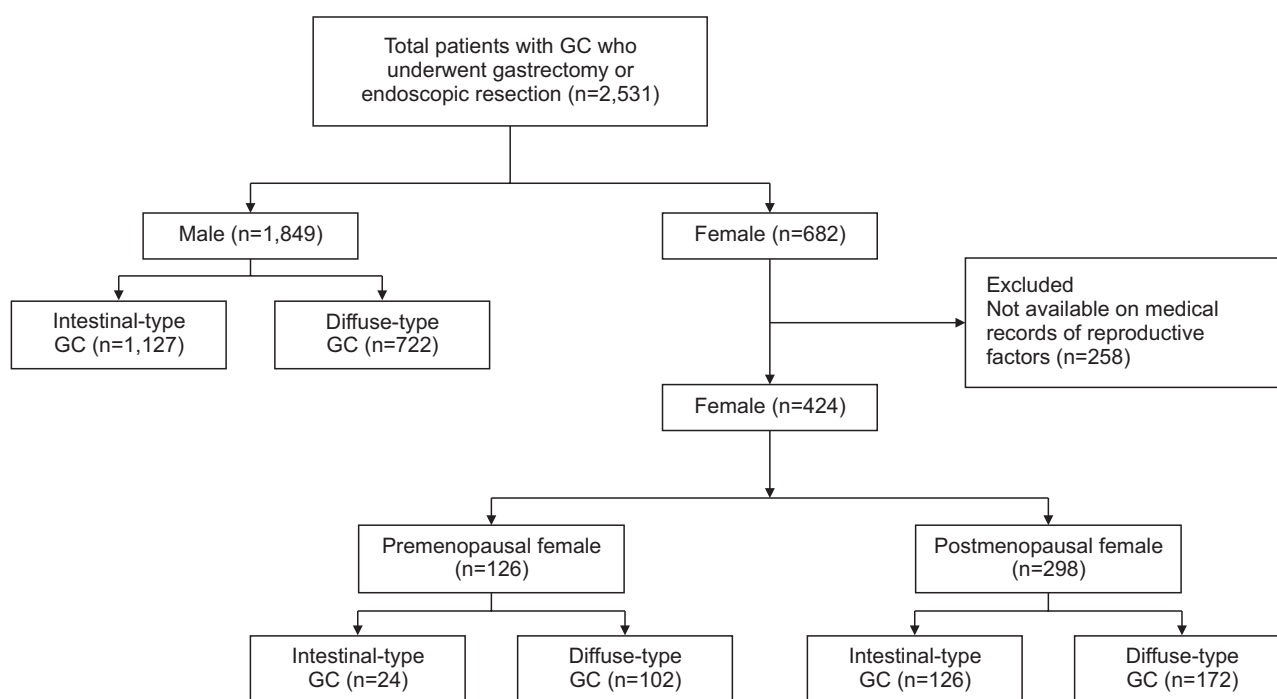

Fig. 1. Algorithm for the inclusion and classification of study participants.
GC, gastric cancer.

the enrollment and/or if they had incomplete medical records regarding estrogen exposure factors.

The following baseline characteristics were assessed: age, sex, smoking and drinking status, first-degree family history of GC, and body mass index. Clinicopathological data, including final pathology reports and computed tomography results, were collected using the electronic medical chart system. GCs were staged using the 7th edition of the TNM staging system of the American Joint Committee on Cancer (2010), based on the final pathology reports. The location, size, and number of the tumors were evaluated, as were the histologic type and Lauren classification. A patient was considered positive for *H. pylori* infection if at least one of the following yielded positive results: *Campylobacter*-like organism test and histological examination (hematoxylin and eosin or modified Giemsa staining).

A questionnaire was used to obtain histories regarding reproductive factors, such as the age at first menstrual period, menopausal status, age at last menstrual period, number of live births, use and duration of oral contraceptive pills and/or intrauterine devices, hormone replacement therapy (age at initiation and the total number of years used), history of hysterectomy or oophorectomy, and duration of breast feeding for each pregnancy. Fertility duration was calculated as the interval between the age at menarche and age at menopause in postmenopausal females; it was calculated as the interval between the age at menarche and GC diagnosis in premenopausal females. The study protocol was approved by the Ethical Committees at St. Mary's Hospital (IRB number: KC19RIDE0906), Kosin University Hospital (IRB number: 2020-06-032), and Seoul National University Bundang Hospital (IRB number: B-2002-595-104). This study is a retrospective study using medical record review and so informed consent was waived.

2. Statistical analysis

SPSS Statistics software (version 22.0; IBM Corp., Armonk, NY, USA) was used to perform the statistical analysis. The chi-square test and the Fisher exact test were used to evaluate associations among categorical variables. The Student t-test was used to evaluate associations among continuous variables. Multivariate logistic regression anal-

Table 1. Clinicopathologic Characteristics of Total Patients According to Sex

Characteristics	Male (n=1,849)	Female (n=424)	p-value
Age, yr	61.61±11.24	57.18±11.94	<0.001*
<40	48 (2.6)	35 (8.3)	<0.001*
40–49	217 (11.7)	76 (17.9)	
50–59	500 (27.0)	121 (28.5)	
60–69	583 (31.5)	121 (28.5)	
≥70	501 (27.1)	71 (16.7)	
Smoking			
Never	760 (41.1)	367 (86.6)	<0.001*
Ex/current smoker	1,089 (58.9)	57 (13.4)	
Drinking			
No	178 (9.6)	272 (64.2)	<0.001*
Yes	1,671 (90.4)	152 (35.8)	
Body mass index, kg/m^{2†}	23.78±3.09	22.40±3.23	<0.001*
<25	1,224 (66.2)	305 (79.2)	<0.001*
≥25	625 (33.8)	80 (20.8)	
Helicobacter pylori infection[†]			
Negative	105 (48.2)	87 (31.0)	<0.001*
Positive	113 (51.8)	194 (69.0)	
Tumor location[†]			
Lower	972 (53.6)	185 (44.0)	<0.001*
Middle	552 (30.5)	180 (42.9)	
Upper	288 (15.9)	55 (13.1)	
Tumor number[†]			
Single	1,079 (92.5)	408 (97.1)	<0.001*
Multiple	138 (7.5)	12 (2.9)	
Tumor size, cm[†]	4.54±5.20	4.30±5.63	0.398
Lauren classification			
Intestinal	1,127 (61.0)	150 (35.4)	<0.001*
Diffuse	722 (39.0)	274 (64.6)	

Data are presented as the mean±SD or number (%).

*Statistically significant, p<0.05; [†]Some data were missing.

ysis was performed to evaluate risk factors for GC development. All results with p<0.05 were considered statistically significant.

RESULTS

1. Baseline clinicopathological characteristics

The algorithm for participant inclusion and exclusion is shown in Fig. 1. We enrolled 2,531 patients (1,849 males and 682 females) in this study. Among them, 258 females who had incomplete medical records regarding reproductive factors were excluded, and the remaining 424 females were analyzed.

The clinicopathological characteristics of the participants are summarized in Table 1. The mean ages of males and females were 61.61±11.24 years and 57.18±11.94 years, respectively (p<0.001). Significantly greater proportions of males were ex-smoker or current smoker (males 58.9% vs females 13.4%; p<0.001), used alcohol (90.4% vs 35.8%; p<0.001), were obese (body mass index ≥25 kg/m^2: 33.8% vs 20.8%; p<0.001), had GCs in the lower third of the stomach (53.6% vs 44.0%; p<0.001), had multiple GCs (7.5% vs 2.9%; p<0.001), and had intestinal-type GCs (61.0% vs 35.4%; p<0.001), compared with females. Compared with males, a significantly greater proportion of females had a positive *H. pylori* infection status (males 51.8% vs females 69.0%; p<0.001), although the *H. pylori* infection status of many patients was unknown. No significant differences were observed in tumor sizes.

To analyze differences between sexes, we compared the proportions of Lauren subtypes in subgroups classified on the basis of smoking status (never, ex-smoker, or current smoker), drinking status (none, social drinking, or heavy drinking), obesity (body mass index <25 kg/m^2 or ≥25 kg/m^2), and *H. pylori* infection (negative or positive). Intestinal-type GCs were prevalent in males, while diffuse-type GCs were prevalent in females in all subgroups (Supplementary Table 1).

2. Proportions of intestinal-type GCs in males and females

Intestinal-type GCs were significantly less frequent in premenopausal females (19.0%, p<0.001) and postmenopausal females with <10 years (30.4%, p<0.001) or 10 to 19 years (44.1%, p=0.001) since menopause, compared with males (61.0%) (Fig. 2). There was no significant difference in the proportion of intestinal-type GCs between males and ≥20 years postmenopausal females (60.6% vs 61.0%; p=0.518) (Fig. 2).
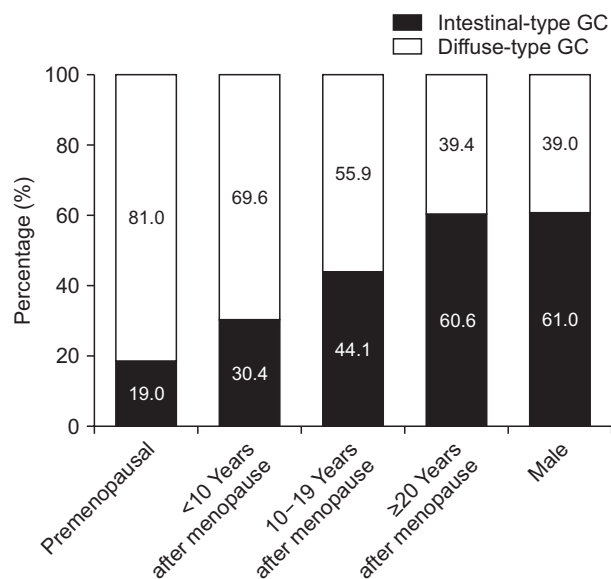

Fig. 2. Proportions of intestinal-type gastric cancers (GCs) in premenopausal and postmenopausal females, compared with in males. Intestinal-type GCs were significantly less frequent in premenopausal (19.0%), <10 years postmenopausal (30.4%), and 10 to 19 years postmenopausal females (44.1%) than in males (61%) (p<0.05 for all). No significant differences in the proportion of intestinal-type GCs were found between males and ≥20 years postmenopausal females (60.6% vs 61%; p=0.518).

3. Risk factors for intestinal-type GCs in females

Reproductive factors were compared between intestinal-type and diffuse-type GCs in females (Table 2). Patients with intestinal-type GCs were significantly older than patients with diffuse-type GCs (mean age: 63.02±10.33 years vs 53.98±11.55 years; p<0.001). Patients with intestinal-type GCs had delayed menarche (intestinal-type GCs of 15.81±1.89 years vs diffuse-type GCs of 15.25±1.80 years; p=0.003), greater fertility duration (31.89±5.70 years vs 30.25±6.80 years; p=0.008), more children (parity ≥3: 43.3% vs 18.6%; p<0.001), and longer breast feeding periods (≥6 months: 73.2 months vs 55.4 months; p<0.001), as well as more frequent postmenopausal status (84.0% vs 62.8%; p<0.001), compared with patients who had diffuse-type GCs. Among the reproductive factors that were significantly associated with intestinal-type GCs in univariate analysis, age at diagnosis of GC (odds ratio [OR], 1.066; 95% confidence interval [CI], 1.042 to 1.091; p<0.001) and parity ≥3 (OR, 1.700; 95% CI, 1.055 to 2.878; p=0.048) remained significantly associated with intestinal-type GC development in multivariate analysis (Table 3).

Separate analyses of postmenopausal and premenopausal females were performed (Tables 2 and 3). Females with intestinal-type GCs were more frequently postmenopausal for ≥20 years, compared with females who had diffuse-type GCs (34.1% vs 16.3%; p<0.001). Among postmeno-

Table 2. Differences between Intestinal-Type and Diffuse-Type Gastric Cancer According to Reproductive Factors in Total, Postmenopausal and Premenopausal Females

Variable	Total females			Postmenopausal females			Premenopausal females		
	Diffuse (n=274)	Intestinal (n=150)	p-value	Diffuse (n=172)	Intestinal (n=126)	p-value	Diffuse (n=102)	Intestinal (n=24)	p-value
Age, yr	53.98±11.55	63.02±10.33	<0.001*	60.69±8.03	65.99±8.05	<0.001*	42.68±6.80	47.41±6.06	0.002*
<40	31 (11.3)	4 (2.7)	<0.001*	0	0	<0.001*	31 (30.4)	4 (16.7)	0.161
40–49	62 (22.6)	14 (9.3)		9 (5.1)	2 (1.5)		53 (52.0)	12 (50.0)	
50–59	90 (32.8)	31 (20.7)		72 (41.9)	23 (18.3)		18 (17.6)	8 (33.3)	
60–69	67 (24.5)	54 (36.0)		67 (39.0)	54 (42.9)		0	0	
≥70	24 (8.8)	47 (31.3)		24 (14.0)	47 (37.3)		0	0	
Smoking									
Never	235 (85.8)	132 (88.0)	0.519	154 (89.5)	112 (88.9)	0.859	81 (79.4)	20 (83.3)	0.665
Ex/current smoker	39 (14.2)	18 (12.0)		18 (10.5)	14 (11.1)		21 (20.6)	4 (16.7)	
Drinking									
No	168 (61.3)	104 (69.3)	0.100	119 (69.2)	94 (74.6)	0.306	49 (48.0)	10 (41.7)	0.573
Yes	106 (38.7)	46 (30.7)		53 (30.8)	32 (25.4)		53 (52.0)	14 (58.3)	
Body mass index, kg/m^2[†]									
<25	203 (80.2)	102 (77.3)	0.496	123 (75.5)	86 (76.8)	0.800	80 (88.9)	16 (80.0)	0.281
≥25	50 (19.8)	30 (22.7)		40 (24.5)	26 (23.2)		10 (11.1)	4 (20.0)	
Helicobacter pylori infection[†]									
Negative	116 (67.1)	78 (72.2)	0.362	45 (38.1)	25 (26.6)	0.076	12 (21.8)	5 (35.7)	0.309
Positive	57 (32.9)	30 (27.8)		73 (61.9)	69 (73.4)		43 (78.2)	9 (64.3)	
Age at menarche, yr	15.25±1.80	15.81±1.89	0.003*	15.63±1.75	16.07±1.82	0.034*	14.62±1.71	14.46±1.61	0.679
<14	44 (16.1)	13 (8.7)	0.033*	19 (11.0)	6 (4.8)	0.053	25 (24.5)	7 (29.2)	0.637
≥14	230 (83.9)	137 (91.3)		153 (89.0)	120 (95.2)		77 (75.5)	17 (70.8)	
Fertility duration, yr	30.25±6.80	31.89±5.70	0.008*	50.26±6.01	50.83±5.39	0.399	26.56±5.79	31.04±5.40	0.001*
<30	103 (37.6)	48 (32.0)	0.250	35 (20.3)	38 (30.2)	0.052	68 (66.7)	10 (41.7)	0.023*
≥30	171 (62.4)	102 (68.0)		137 (79.7)	88 (69.8)		34 (33.3)	14 (58.3)	
No. of live births									
0	31 (11.3)	5 (3.3)	<0.001*	11 (6.4)	4 (3.2)	<0.001*	20 (19.6)	1 (4.2)	0.139
1	35 (12.8)	20 (13.3)		13 (7.6)	17 (13.5)		22 (21.6)	3 (12.5)	
2	157 (57.3)	60 (40.0)		102 (59.3)	42 (33.3)		55 (53.9)	18 (75.0)	
≥3	51 (18.6)	65 (43.3)		46 (26.7)	63 (50.0)		5 (4.9)	2 (8.3)	
Breast feeding[†]									
Never & <6 mo	119 (44.6)	38 (26.8)	<0.001*	59 (35.5)	25 (21.2)	0.009*	60 (59.4)	13 (54.2)	0.640
≥6 mo	148 (55.4)	104 (73.2)		107 (64.5)	93 (78.8)		41 (40.6)	11 (45.8)	
Use of contraceptives[†]									
No	143 (71.5)	80 (70.8)	0.895	89 (73.6)	64 (68.8)	0.447	54 (68.4)	16 (80.0)	0.307
Yes	57 (28.5)	33 (29.2)		32 (26.4)	29 (31.2)		25 (31.6)	4 (20.0)	
<1 yr	46 (80.7)	24 (72.7)	0.417	24 (75.0)	20 (69.0)	0.640	22 (88.0)	4 (100.0)	1.000
≥1 yr	11 (19.3)	9 (27.3)		8 (25.0)	9 (31.0)		3 (12.0)	0	

Table 2. Continued

Variable	Total females			Postmenopausal females			Premenopausal females		
	Diffuse (n=274)	Intestinal (n=150)	p-value	Diffuse (n=172)	Intestinal (n=126)	p-value	Diffuse (n=102)	Intestinal (n=24)	p-value
Hysterectomy/oophorectomy status									
No hysterectomy/oophorectomy	236 (86.1)	128 (85.3)	0.130	144 (83.7)	105 (83.3)	0.535	92 (90.2)	23 (95.8)	0.330
Hysterectomy with no ovary removed	10 (3.6)	12 (8.0)		9 (5.2)	11 (8.7)		1 (1.0)	1 (4.2)	
Oophorectomy without hysterectomy	16 (5.8)	4 (2.7)		9 (5.2)	4 (3.2)		7 (6.9)	0	
Hysterectomy + ovaries removed (number unknown)	12 (4.4)	6 (4.0)		10 (5.8)	6 (4.8)		2 (1.9)	0	
Hormone replacement therapy[†]									
Never & past <1 yr				149 (89.8)	104 (87.4)	0.533			
Past ≥1 yr & current				17 (10.2)	15 (12.6)				
Years since menopause									
<10 yr				87 (50.6)	38 (30.2)	<0.001*			
10–20 yr				57 (33.1)	45 (35.7)				
≥20 yr				28 (16.3)	43 (34.1)				
Menopausal status									
Premenopausal	102 (37.2)	24 (16.0)	<0.001*						
<10 yr after menopause	87 (31.8)	38 (25.3)							
10–20 yr after menopause	57 (20.8)	45 (30.0)							
≥20 yr after menopause	28 (10.2)	43 (28.7)							
Tumor location[†]									
Lower	101 (37.0)	84 (57.1)	<0.001*						
Middle	142 (52.0)	38 (25.9)							
Upper	30 (11.0)	25 (17.0)							
Tumor number[†]									
Single	269 (96.4)	146 (97.3)	0.358						
Multiple	8 (2.9)	4 (2.7)							
Tumor size, cm	4.14±5.62	4.59±5.68	0.435						

Data are presented as the mean±SD or number (%). *H. pylori* infection status was evaluated in a small portion of gastric cancer patients.
*Statistically significant, p<0.05; [†]Some data were missing.

Table 3. Reproductive Factors Associated with Intestinal-Type Gastric Cancer Risk in Multivariate Analysis

Factor	Odds ratio (95% CI)	p-value
Total females		
Age at diagnosis of gastric cancer	1.066 (1.042–1.091)	<0.001*
Age at menarche	0.974 (0.694–1.366)	0.877
Fertility years	0.962 (0.702–1.313)	0.799
Parity ≥3 (vs nulliparity or parity <3)	1.700 (1.055–2.878)	0.048*
Breast feeding ≥6 mo (no or <6 mo)	1.131 (0.665–1.924)	0.651
Menopause (vs premenopausal status)	0.538 (0.252–1.147)	0.109
Postmenopausal females		
Age at diagnosis of gastric cancer	1.075 (1.039–1.113)	<0.001*
Age at menarche	1.073 (0.914–1.260)	0.833
Parity ≥3 (vs nulliparity or parity <3)	1.775 (1.012–3.114)	0.045*
Breast feeding ≥6 mo (no or <6 mo)	1.144 (0.614–2.134)	0.672
≥20 yr after menopause (vs <20 yr after menopause)	0.908 (0.352–2.340)	0.841
Premenopausal females		
Age at diagnosis	0.893 (0.694–1.148)	0.378
Fertility years	1.147 (1.043–1.261)	0.005*
Parity ≥2	2.577 (0.783–8.486)	0.119

CI, confidence interval.
*Statistically significant, p<0.05.

pausal females, age at diagnosis of GC (OR, 1.075; 95% CI, 1.039 to 1.113; p<0.001), and parity ≥3 (OR, 1.775; 95% CI, 1.012 to 3.114; p=0.045) were factors significantly associated with intestinal-type GCs (Table 3). Among premenopausal females, long fertility duration (OR, 1.147; 95% CI, 1.043 to 1.261; p=0.005) was significantly associated with intestinal-type GCs (Table 3).

DISCUSSION

In the present study, the proportions of intestinal-type GCs were significantly lower in premenopausal females and <20 years postmenopausal females than in males. Females ≥20 years postmenopause had an intestinal-type GC prevalence similar to the prevalence in males. Age and parity were positively associated with an increased risk of intestinal-type GCs in postmenopausal females, while long fertility duration was positively associated with an increased risk of intestinal-type GCs in premenopausal females.

A reported 10- to 15-year delay in the onset of intestinal-type GCs in females suggests that a protective effect is mediated by estrogen.[4] However, only a few studies have examined relationships between reproductive factors and GC risk based on Lauren subtypes.[17-19] A case-control study conducted in Canada found that age at menopause, parity (>4 live births), and oral contraceptive use had greater associations with intestinal-type GCs than with diffuse-type GCs.[17] A large cohort study in Japan found that females with early menarche (≤12 years) had an almost 50% re-

duced risk of GCs, compared with females who had late menarche (≥15 years); in subgroup analyses according to histologic subtype, lower risk of differentiated-type GC was observed in females with early menarche (13 to 14 years), but no risk reduction was observed for undifferentiated-type GC.[18] A recent single center study in Korea found no premenopausal females with intestinal-type GCs; it reported that the incidence of intestinal-type GCs increased over time after menopause, approaching the incidence in males at 10 years postmenopause. That study also revealed an association between parity and an increased risk of intestinal-type GCs in postmenopausal females.[19] Based on previous studies and our findings, the risk reduction associated with estrogen was significant only for intestinal-type GCs. There have been inconsistent results regarding the relationships between reproductive factors and GC risk in previous studies, which may be related to different proportions of intestinal-type GCs that have been present in those studies.

In the present study, we classified parity as 0, 1 to 2, or ≥3 births to allow analysis over longer periods. We found that ≥3 births were more strongly associated with intestinal-type GCs than with 0 or 1 to 2 births in postmenopausal females, while fertility duration was the only significant factor in premenopausal females. While some previous studies have suggested a positive association between parity and GCs, the results have been inconsistent. Most of the previous studies have not shown any associations with parity or increased number of births.[20,21] A meta-analysis of 10 cohort studies found no significant association between parity and the risk of developing GCs.[21] In contrast

to the results of previous studies, we found a significant association between parity and intestinal-type GCs.[18,22] This may be explained by the effect of childbirth on lifetime exposure to sex hormones. Pregnant females have markedly elevated serum levels of certain hormones, including estrogen,[23] although a history of more full-term pregnancies is not directly associated with levels of circulating estrogens. Increased parity is associated with an overall increase in exposure to sex hormones. Because the exposure period during the lifespan of a female is insufficient to have an appreciable effect on gastric carcinogenesis, parity might be an inadequate indicator of overall exposure to sex hormones.[23] Estrogen levels increase markedly during pregnancy, then decrease after childbirth and during lactation.[24] Parity influences estrogen levels later in life; females with greater parity exhibit lower circulating estrogen levels, compared with females who have lower parity or nulliparity.[24] Postmenopausal serum-free estradiol decreases with increasing number of childbirths.[25] Therefore, greater parity might be a risk factor for intestinal-type GCs in postmenopausal females. There have been studies showing an increased number of pregnancies is associated with Alzheimer dementia, consistent with the neuroprotective effects of estrogen in females.[26-28] Such a discrepancy between postmenopausal and premenopausal females might have been derived from higher prevalence and grade of atrophic gastritis and intestinal metaplasia[29] with *H. pylori* rates of the aged population compared to young females,[30] because age and parity ≥3 were risk factors for intestinal-type GC in postmenopausal females. To verify this, data on *H. pylori* infection status (past, current, or naive) should be added and analyzed. However, it was difficult for getting enough information regarding histologic atrophy and intestinal metaplasia and *H. pylori* infection status in the present study. In addition, only 13 premenopausal females had more than three full-term pregnancies; among these females, only four had intestinal-type GCs. The small number of patients may have affected the results in premenopausal females.

The effects of estrogen on GC development based on Lauren histologic subtypes have not been investigated. Estrogen acts via estrogen receptors (genomic pathway) and transcriptional cross-talk (non-genomic pathway); several studies have investigated the role of estrogen receptors in GC. Wang *et al.*[31] reported that well-differentiated gastric adenocarcinomas had higher levels of estrogen receptor-β expression, and that poorly differentiated disease was associated with the reduction or loss of estrogen receptor-β. Yi *et al.*[32] demonstrated that estrogen receptor-α expression was associated with diffuse-type GCs and shorter disease-free survival. Several studies have reported that

17-β-estradiol (E2), the most potent isoform of estrogen, downregulated E-cadherin levels via estrogen receptor-α signaling;[33-35] this downregulation may contribute to the onset of diffuse-type GCs. Further research is necessary to analyze the sex-specific aspects of GCs.

This study had several limitations. First, it used self-reports of reproductive factors, which may be subject to recall bias. Second, this study lacked information regarding *H. pylori* status in some patients. An increased susceptibility to *H. pylori* infection during pregnancy might be related to increased GC risk.[36] However, *H. pylori* infection reportedly did not influence the associations of menstrual and reproductive factors with GC risk.[37] In addition, we did not have information regarding specific types of hormone replacement therapies and oral contraceptives; we also lacked information concerning socioeconomic status, education, and dietary factors. Finally, we did not include patients with unresectable GCs.

In conclusion, we found that age and parity were associated with an increased risk of intestinal-type GCs in postmenopausal females, while longer fertility duration was positively associated with an increased risk of intestinal-type GCs in premenopausal females. The role of estrogen may vary according to GC histology.

CONFLICTS OF INTEREST

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AUTHOR CONTRIBUTIONS

Study concept and design: Y.J.J., S.J.P., N.K. Data acquisition: Y.J.J., C.H.P., S.J.P., N.K. Data analysis and interpretation: Y.J.J., H.J.K. Drafting of the manuscript; critical revision of the manuscript for important intellectual content: Y.J.J., H.J.K. Statistical analysis: H.J.K. Obtained funding: Y.J.J. Administrative, technical, or material support; study supervision: S.J.P., N.K. Approval of final manuscript: all authors.

ORCID

Yoon Ju Jung   https://orcid.org/0000-0002-3406-1464
Hee Jin Kim   https://orcid.org/0000-0001-9608-0348
Cho Hyun Park   https://orcid.org/0000-0001-5152-4371
Seun Ja Park   https://orcid.org/0000-0003-3217-5115
Nayoung Kim   https://orcid.org/0000-0002-9397-0406

SUPPLEMENTARY MATERIALS

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