Original Article

Ethnic Heterogeneity in Reproductive Risk Factors for Breast Cancer, With a Focus on Asian Populations: A Meta-analysis

Youjin Hong[1,2,3], Soseul Sung[1,2,4], Woojin Lim[1,2,4], Sungji Moon[5], Kwang-Pil Ko[1,6], Jung Eun Lee[7], Inah Kim[8], Sun Ha Jee[9], Sun-Seog Kweon[10], Min-Ho Shin[10], Sangmin Park[11], Seung-Ho Ryu[12], Sun Young Yang[13], Jeongseon Kim[14], Sang-Wook Yi[15], Sue K. Park[1,2,3,16]

[1]Department of Preventive Medicine, Seoul National University College of Medicine, [2]Cancer Research Institute, Seoul National University, [3]Integrated Major in Innovative Medical Science, Seoul National University Graduate School, [4]Department of Biomedical Sciences, Seoul National University Graduate School, Seoul, [5]Department of Social and Preventive Medicine, Sungkyunkwan University School of Medicine, Suwon, [6]Clinical Preventive Medicine Center, Seoul National University Bundang Hospital, Seongnam, [7]Department of Food and Nutrition, College of Human Ecology, Seoul National University, [8]Department of Occupational and Environmental Medicine, College of Medicine, Hanyang University, [9]Department of Epidemiology and Health Promotion, Institute for Health Promotion, Graduate School of Public Health, Yonsei University, Seoul, [10]Chonnam National University Medical School, Gwangju, [11]Seoul National University College of Medicine, [12]Sungkyunkwan University School of Medicine, Kangbuk Samsung Hospital, [13]Department of Internal Medicine, Healthcare Research Institute, Seoul National University Hospital Healthcare System Gangnam Center, Seoul, [14]Graduate School of Science and Policy, National Cancer Center, Goyang, [15]Kwandong University College of Medicine, Gangneung, [16]Genomic Medicine Institute, Seoul National University Medical Research Center, Seoul, Korea

This study aimed to examine differences in the association between reproductive factors and breast cancer (BC) risk across ethnic groups, particularly Asians and non-Asians, and to explore temporal trends through meta-analysis. The study focused on epidemiologic research published up to August 31, 2022, examining reproductive factors related to BC risk and family history. All effect sizes were calculated using a random-effect model. The protective effect of the higher number of childbirths against BC was stronger in Asians than in Europeans or Americans (childbirths ≥ 2 vs. 1; Asians, relative risk [RR]: 0.66, 95% CI: 0.59-0.74; Europeans, RR: 0.89, 95% CI: 0.86-0.92; Americans, RR: 0.91, 95% CI: 0.87-0.96). Similarly, the effect of high parity was more pronounced in Asians than in Americans and Europeans (Asians, RR: 0.72, 95% CI: 0.58-0.89; Europeans, RR: 0.81, 95% CI: 0.74-0.88; Americans, RR: 0.84, 95% CI: 0.76-0.92). In contrast, no significant differences among populations were found in BC risks associated with combined hormone replacement therapy use. While the association between family history and BC risk appeared to differ by ethnicity, no temporal change was observed (< 2010, RR: 1.58, 95% CI: 1.40-1.78; ≥ 2010, RR: 1.57, 95% CI: 1.46-1.67). These results suggest that some reproductive factors associated with BC differ across ethnicities and time trends, perhaps due to the prevalence of reproductive factors and the baseline hazard of BC.

Key Words Reproductive factors, Breast cancer, Systematic review, Meta-analysis, Asian

INTRODUCTION

According to World Health Organization cancer statistics, breast cancer (BC) is the most common malignant cancer among women worldwide. In 2018, 2,088,849 women developed BC [1]. The incidence rates for BC are higher among non-Hispanic white and non-Hispanic black women than among racial and ethnic groups. The incidences of BC in non-Hispanic white and non-Hispanic black women were 128.7 and 125.5 per 100,000 in 2017-2018, respectively [2]. In contrast, Asian/Pacific Islander women have the lowest incidence of 90.7 per 100,000, according to the Surveillance, Epidemiology, and End Results program [3].

Among the risk factors for BC, reproductive factors, such

as menstruation, pregnancy, childbirth, and breastfeeding, are surrogates for female sex hormones, which are considered causal factors of BC. Oral contraceptives (OCs) and postmenopausal hormone replacement therapy (HRT) are exogenous hormonal factors that act as direct carcinogens in BC. The effect of reproductive factors on BC risk was mainly reported in a collaborative reanalysis of all epidemiological studies published from 1996 to 2012, where the results of investigations into the effects of menarche, menopause, breastfeeding, OCs, and HRT on BC were summarized [4-7]. The subjects included in this collaborative analysis included mostly Caucasians, from European and North American populations.

It has been suggested that reproductive and hormonal factors have different prevalence rates among different ethnic populations [8,9]. Within each ethnic group, particularly the Asian group, the prevalence rates of reproductive factors in women changed markedly by calendar time trend and birth cohort [10-12].

The meta-analysis research papers based on Asian populations have been already reported. Among various reproductive risk factors for BC, previous evidence remains limited. One meta-analysis focused solely on oral contraceptive use with a dose-response approach, while another pooled analysis included only Japanese women from nine cohort studies [13,14]. Although a meta-analysis evaluating modifiable and non-modifiable BC risk factors women in Southeast Asia has been published, it incorporated only a single cohort study and included very few countries, which could be the limitation [15]. Consequently, it remains unclear whether ethnic differences and temporal changes in reproductive factors influence both the baseline risk of BC.

Due to the observation of the differences in the prevalence of BC risk factors between Asian and Western populations and, in particular, the prevalence of reproductive factors is changing more rapidly in Asians, it is necessary to investigate whether BC risk factors are same in Asians and Western populations, whether the strength of the association is similar between two populations and lastly, whether the strength of the association is similar despite the change of prevalence of BC risk factors by the publication year.

MATERIALS AND METHODS

Literature search and study selection

We designed a protocol for systematic review and meta-analysis of the evidence regarding association between BC and reproductive/hormonal factors by following the guidelines Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) (Fig. 1). PubMed, EMBASE, and MEDLINE databases were searched since inception and up to August 31, 2020. The combination of search keywords is
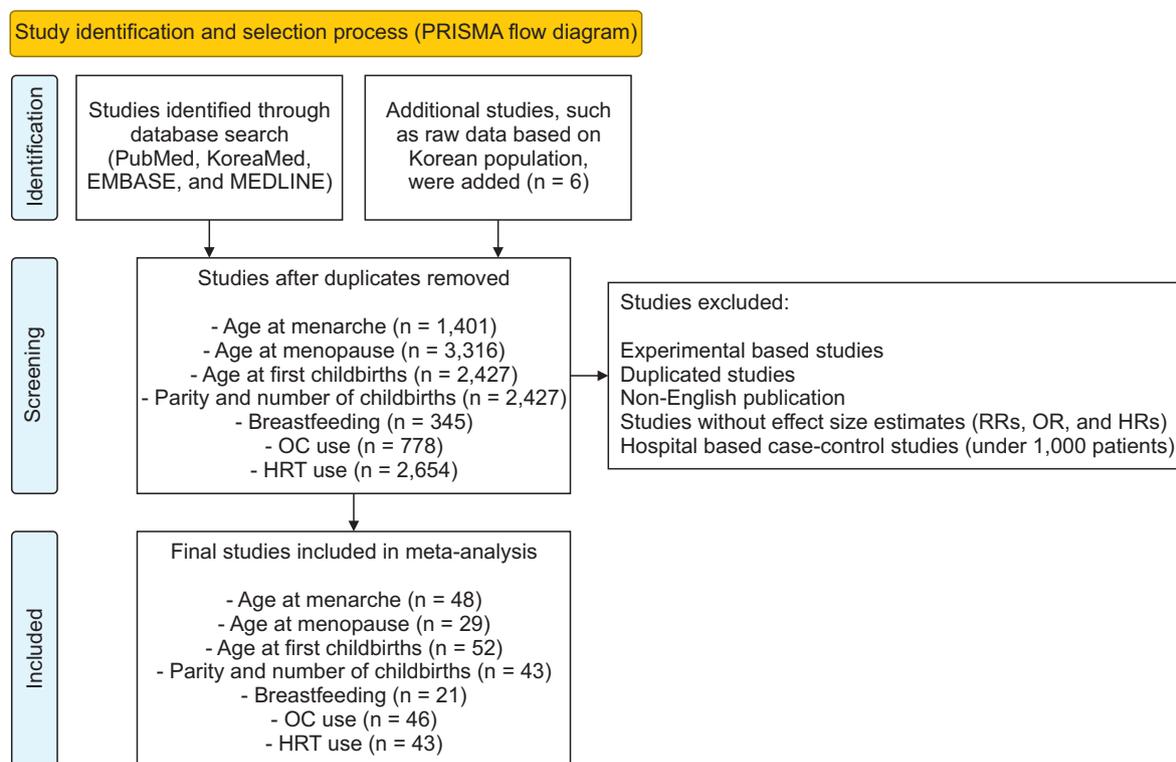

Figure 1. PRISMA flow diagram of study selection for the association between reproductive factors and breast cancer risk. PRISMA, Preferred Reporting Items for Systematic reviews and Meta-Analyses; OC, oral contraceptive; HRT, hormone replacement therapy; RR, relative risk; HR, Hazard ratio.

shown in Table S1, and the summary of each reproductive factors and breast cancer risks is listed in Table S2-S5. Two authors participated in the initial screening of titles and abstracts. All studies were written in English. Also, we included cohort studies, population-based case-control studies, and large-scale hospital-based case–control studies (defined as hospital-based case-control studies over 1,000 BC cases or multicenter studies), which provided information on the ORs, hazard ratios (HRs), relative risks (RRs), and their 95% CIs. For exclusion criteria, unrelated articles and studies with duplicated populations were excluded. For duplicated studies, the latest published studies and/or the study with larger sample size were selected. Because the number of Korean cohort studies and population-group patient-control studies obtained from systematic reviews is small, we calculated RRs (95% CIs) and ORs (95% CIs) using raw data from Korean cohort studies and population-based case-control studies. Raw data analysis included five cohort studies and one population-based case-control study.

For the continental subgroup meta-analysis, we divided the data into three continental population groups: Europe, the United States, and Asia. Subjects consisting only of individuals from Oceania were omitted because of the small number of studies. In addition, some data were divided according to the year of publications. Most studies were divided into ≥ 2010 and < 2010; however, due to the study's publication date issue, some factors were divided into ≥ 2005 and < 2005.

Statistical analysis

The meta-analysis used random-effects models based on maximum likelihood estimation to estimate the summary RR. Ethnic differences were evaluated using subgroup analyses with tests for between-group heterogeneity [16]. The heterogeneity among studies was estimated using Higgins and Thompson's I^2 statistic and P-values in Cochran's Q statistics [17]. The bias of I^2 can be small or large, positive or negative; however, the bias of I^2 is largest when the number of studies is small, especially with 7 studies [18]. Therefore, the I^2 statistic results of meta-analysis listed in Tables are indicated only more than 75% with more than 8 studies above. Publication bias was evaluated using P-values from Egger and Begg tests. All statistical analyses were conducted using the SAS statistical package (version 9.4; SAS Institute) and R (version 3.5.2; https://www.r-project.org/) statistical software.

Ethics statement

The Institutional Review Board of Seoul National University Hospital approved the study (IRB approval No.1911-188-18-084). The requirement for informed consent was waived due to the nature of this meta-analysis.

RESULTS

Table 1 and 2 summarize the meta-analysis estimates of BC risks associated with reproductive factors and family history by continent and by combination of continent and study design. The summary BC RRs for the number of childbirths and parity were found to be significantly different across ethnic groups. The link between more than having 3 children and BC risk in Asians was stronger than that in Europeans and Americans (Asians, RR: 0.57, 95% CI: 0.49-0.66; Europeans, RR: 0.80, 95% CI: 0.74-0.86; North and South Americans, RR: 0.80, 95% CI: 0.72-0.89). This inverse association was more pronounced than in having more than 2 childbirths (Fig. S1). The effect of high parity in reducing the risk of BC was observed more strongly in Asians than in Americans and Europeans, also (Asians, RR: 0.72, 95% CI: 0.58-0.89; Europeans, RR: 0.81, 95% CI: 0.74-0.88; North and South Americans, RR: 0.84, 95% CI: 0.76-0.92) (Fig. S2). In contrast, the associations between age at menarche or age at menopause and BC risk showed similar directions across populations, with no substantial differences in effect estimates. Also, combined HRT use was consistently associated with an increased BC risk in all three populations (Asians, RR: 1.49, 95% CI: 1.23-1.81; Europeans, RR: 1.38, 95% CI: 1.18-1.60; North and South Americans, RR: 1.18, 95% CI: 1.03-1.34). As for association between family history and BC risk, Asians showed the highest risk of BC (RR: 2.42, 95% CI: 1.64-3.57) (Table 1).

Although, there was no difference in the case-control studies, the reproductive factors that differ among three continents in the cohort studies were consistent as those described in Table 1 (Fig. S1 and S2). The differences in BC risk by number of childbirths across ethnic groups were observed in a meta-analysis of cohort studies (Asians, RR: 0.51, 95% CI: 0.38-0.68; Europeans, RR: 0.78, 95% CI: 0.74-0.82; North and South Americans, RR: 1.03, 95% CI: 0.92-1.15). The association between combined HRT and BC risks was stronger in Asians (RR: 1.72, 95% CI: 1.36-2.19) than Europeans (RR: 1.48, 95% CI: 1.19-1.84) and Americans (RR: 1.20, 95% CI: 0.98-1.46). In a summary of 2 cohort studies reporting family history of BC among Asian populations, family history was associated with approximately 3 times more BC risk (RR: 3.02, 95% CI: 1.93-4.73) than other populations (Table 2).

In the meta-analysis according to publication year, the summary RRs of BC risk for parity, the number of childbirths, and the combined HRT use were observed to be significantly different between the two categories of the publication year. In particular, the effect of parity and ≥ 2 childbirths on BC risk reduction showed a stronger association in earlier publication years (< 2010; parous vs. nulliparous: RR: 0.74, 95% CI: 0.67-0.81; Childbirths ≥ 2 vs. Childbirths 1, RR: 0.85, 95% CI: 0.82-0.89) than in recent publication years (≥ 2010; parous vs. nulliparous, RR: 0.86, 95% CI: 0.79-0.93; Childbirths ≥ 2 vs. Childbirths 1, RR: 0.92, 95% CI: 0.89-0.96). On the other hand, combined HRT was observed to have a stronger association with BC in recent publication years (RR: 1.34, 95% CI: 1.18-1.51) than in earlier publication years (RR: 1.25, 95%

Table 1. Meta-analysis of BC risk associated with reproductive factors and a family history by continent

Risk factors	Europe		North and South America		Asia	
	N	RR (95% CI)	N	RR (95% CI)	N	RR (95% CI)
Age at menarche						
≤ 14	12	1.00	18	1.00	18	1.00
15-16		0.95 (0.90-1.00)		0.96 (0.93-0.99)		0.89 (0.78-1.00)[a,d]
≥ 17		0.89 (0.82-0.96)		0.87 (0.81-0.93)		0.82 (0.72-0.95)[a,d]
≥ 17	12	1.00	18	1.00	18	1.00
< 17		1.12 (1.04-1.22)		1.15 (1.08-1.23)		1.22 (1.05-1.39)
Age at menopause[b]						
< 48	7	1.00	9	1.00	13	1.00
48-52		1.12 (1.07-1.18)		1.23 (1.18-1.29)		1.27 (1.18-1.36)
≥ 53		1.17 (1.09-1.25)[d]		1.35 (1.23-1.48)		1.38 (1.30-1.47)
Age at first childbirths[c]						
< 20	15	1.00	22	1.00	15	1.00
20-30		1.08 (1.01-1.16)[a]		1.09 (1.03-1.17)		1.12 (1.03-1.22)[d]
≥ 30		1.26 (1.15-1.39)[a]		1.34 (1.23-1.46)		1.36 (1.23-1.51)
Parity						
Nulliparous	12	1.00	17	1.00	13	1.00
Parous		0.81 (0.74-0.88)[a]		0.84 (0.76-0.92)[a]		0.72 (0.58-0.89)[a]
Number of childbirths[c]						
1	16	1.00	16	1.00	11	1.00
2		0.91 (0.88-0.95)		0.95 (0.90-1.01)		0.80 (0.67-0.95)
≥ 3		0.80 (0.74-0.86)		0.80 (0.72-0.89)		0.57 (0.49-0.66)
1	16	1.00	16	1.00	11	1.00
≥ 2		0.89 (0.86-0.92)		0.91 (0.87-0.96)		0.66 (0.59-0.74)
Duration of breastfeeding[c]						
Never	4	1.00	12	1.00	5	1.00
< 6 mo		1.00 (0.85-1.17)[a]		0.92 (0.88-0.95)		0.72 (0.39-1.34)
≥ 6		0.96 (0.81-1.15)[a]		0.89 (0.82-0.96)		0.61 (0.27-1.37)
OC use						
Never	19	1.00	16	1.00	11	1.00
Ever		1.06 (0.96-1.18)[a]		1.07 (1.00-1.14)		1.06 (0.84-1.32)[a,d]
Combination HRT[b]						
Never	17	1.00	19	1.00	7	1.00
Ever		1.38 (1.18-1.60)[a]		1.18 (1.03-1.34)		1.49 (1.23-1.81)
Estrogen only HRT[b]						
Never	13	1.00	16	1.00	1	1.00
Ever		1.17 (1.03-1.32)		1.07 (1.01-1.14)		1.40 (0.53-3.69)
Family history of BC						
Never	8	1.00	19	1.00	4	1.00
Ever		1.69 (1.49-1.92)[a]		1.51 (1.42-1.60)[a]		2.42 (1.64-3.57)

RR, relative risk; OC, oral contraceptives; HRT, hormone replacement therapy; BC, breast cancer. [a]Heterogeneity: $I^2 \geq 75\%$, [b]In postmenopausal women, [c]In parous women, [d]Evidence of publication bias was observed for age at menarche, age at menopause, age at first childbirth, and oral contraceptive use ($P \leq 0.01$ in Begg's and/or Egger's tests).

CI: 1.09-1.44) (Table S6).

DISCUSSION

We investigated continent-based ethnic and temporal differences in the summary effects of reproductive factors on breast cancer risk. Our updated meta-analysis found that Asians had a stronger risk of BC than Europeans and Americans, showing ethnic differences in high birth rates (≥ 2), parity, and family history of BC. Our results showed that the risk of BC due to most reproductive factors, particularly parity

and the number of childbirths, was stronger in earlier publication years than in recent publication years, while the risk of BC due to combined HRT was stronger in recent publication years.

The number of childbirths affected the risk of BC. Childbirth decreased the BC risk by approximately 10% in Caucasians and 34% in Asians in this study. In a Danish cohort, consisting of 2,311,332 women, women who had given birth before 30 years of age experienced a 5.0% reduced risk (95% CI: 2.1-7.8%) for the first childbirth, 6.4% reduced risk (95% CI: 3.9-8.8%) for the second childbirth, and 9.4% reduced risk

Table 2. Meta-analysis of BC risk associated with reproductive factors and a family history by combination of continent and study design

Risk factor	Europe Cohort study N	Summary RR (95% CI)	Europe Case-control study N	Summary RR (95% CI)	N&SA Cohort study N	Summary RR (95% CI)	N&SA Case-control study N	Summary RR (95% CI)	Asia Cohort study N	Summary RR (95% CI)	Asia Case-control study N	Summary RR (95% CI)
Age at menarche												
≤14		1.00		1.00		1.00		1.00		1.00		1.00
15-16	4	0.98 (0.89-1.08)	8	0.93 (0.87-1.00)	6	0.96 (0.90-1.02)	12	0.96 (0.91-1.01)	12	0.84 (0.75-0.95)	6	0.96 (0.81-1.13)[a,d]
≥17		0.90 (0.77-1.06)[a]		0.88 (0.78-0.98)		0.90 (0.84-0.97)		0.84 (0.75-0.95)		0.80 (0.59-1.07)[a]		0.84 (0.69-1.04)[a,d]
≤14 vs. ≥17		1.11 (0.94-1.30)		1.14 (1.02-1.28)		1.11 (1.03-1.19)		1.33 (1.05-1.33)		1.25 (0.93-1.69)		1.19 (0.96-1.45)[a]
Age at menopause[b]												
<48		1.00		1.00		1.00		1.00		1.00		1.00
48-52	5	1.11 (1.03-1.19)	2	1.14 (1.07-1.21)	2	1.19 (1.05-1.35)	7	1.25 (1.16-1.34)	9	1.33 (1.15-1.54)	4	1.24 (1.10-1.40)
≥53		1.17 (1.05-1.30)[d]		1.19 (1.06-1.34)		1.32 (1.10-1.58)		1.36 (1.20-1.55)		1.75 (1.44-2.11)		1.35 (1.27-1.43)
Age at first childbirths[c]												
<20		1.00		1.00		1.00		1.00		1.00		1.00
20-30	6	1.16 (1.11-1.22)[d]	9	1.05 (0.93-1.18)[a]	6	1.02 (0.86-1.21)[a]	16	1.12 (1.06-1.20)	10	1.28 (1.10-1.48)	5	1.05 (0.98-1.13)
≥30		1.34 (1.17-1.53)		1.23 (1.04-1.45)[a]		1.23 (1.02-1.49)		1.38 (1.25-1.52)		1.60 (1.34-1.91)		1.25 (1.07-1.46)
Parity												
Nulliparous		1.00		1.00		1.00		1.00		1.00		1.00
Parous	7	0.81 (0.76-0.87)	5	0.85 (0.67-1.08)[a]	5	0.92 (0.77-1.09)[a]	12	0.76 (0.68-0.84)[a]	9	0.77 (0.63-0.93)	4	0.64 (0.44-0.93)[a]
Number of childbirths[c]												
1		1.00		1.00		1.00		1.00		1.00		1.00
2	7	0.88 (0.83-0.94)	9	0.93 (0.90-0.97)	4	1.04 (0.96-1.14)	12	0.91 (0.86-0.97)	9	0.78 (0.62-0.98)	2	0.83 (0.67-1.02)
≥3		0.78 (0.74-0.82)		0.79 (0.69-0.90)		1.03 (0.92-1.15)		0.74 (0.68-0.81)		0.51 (0.38-0.68)		0.59 (0.56-0.62)
1		1.00		1.00		1.00		1.00		1.00		1.00
≥2	7	0.82 (0.79-0.85)	9	0.92 (0.89-0.95)[a]	4	1.04 (0.95-1.13)	12	0.85 (0.81-0.89)	9	0.66 (0.55-0.79)	2	0.60 (0.57-0.63)
Duration of breastfeeding[c]												
Never		1.00		1.00		1.00		1.00		1.00		1.00
< 6 mo	2	1.04 (0.94-1.15)	2	0.90 (0.51-1.58)	4	0.93 (0.89-0.97)	8	0.88 (0.82-0.94)	2	1.12 (0.54-2.32)[a]	3	0.54 (0.24-1.18)
≥ 6 mo		1.00 (0.92-1.08)		0.90 (0.52-1.55)		0.96 (0.86-1.06)		0.85 (0.77-0.94)		0.73 (0.55-0.96)		0.52 (0.18-1.52)
OC use												
Never		1.00		1.00		1.00		1.00		1.00		1.00
Ever	12	1.09 (1.02-1.16)[d]	7	1.00 (0.79-1.28)[a]	2	1.10 (0.94-1.29)	14	1.06 (0.99-1.14)	8	0.94 (0.86-1.04)	3	1.35 (1.03-1.78)[a]
Combination HRT[b]												
Never		1.00		1.00		1.00		1.00		1.00		1.00
Ever	11	1.48 (1.19-1.84)[a]	6	1.16 (0.98-1.37)	10	1.20 (0.98-1.46)[a]	9	1.21 (1.03-1.43)	4	1.72 (1.36-2.19)	3	1.37 (1.01-1.86)[a]
Estrogen only HRT[b]												
Never		1.00		1.00		1.00		1.00		1.00		1.00
Ever	8	1.19 (1.05-1.34)	5	1.13 (0.89-1.45)[a]	7	1.13 (1.06-1.21)	9	1.01 (0.92-1.11)	1	1.40 (0.53-3.69)	0	NA
Family history of BC												
Never		1.00		1.00		1.00		1.00		1.00		1.00
Ever	4	1.76 (1.52-2.04)	4	1.57 (1.18-2.11)	10	1.48 (1.42-1.53)	9	1.51 (1.29-1.76)[a]	2	3.02 (1.93-4.73)	2	2.04 (1.06-3.96)

BC, breast cancer; OC, oral contraceptive; HRT, hormone replacement therapy; RR, relative risk; NA, not available. [a]Heterogeneity: $I^2 \geq 75\%$; [b]In postmenopausal women; [c]In parous women; [d]Evidence of publication bias was observed for age at menarche (15-16 and ≥ 17), age at menopause, parity, oral contraceptive use, and estrogen-only HRT (Egger's test, $P < 0.05$).

(95% CI: 6.4-12.2%) for the third childbirth. In addition, women who had childbirths after 30 years of age had a decreased risk of BC after their second (3.4%, 95% CI: 0.7-6.0%) and third childbirths (5.3%, 95% CI: 2.7-7.8%), even though delivering the first child after 30 years had reverse relative risk [19]. These results suggested that the decrease in risk of BC by the number of childbirths in Asian women was similar to that in the European population. On the other hand, among Japanese population, a representative of Asian country, women who had ≥ 2 childbirths had 61% (adjusted HR: 0.39, 95% CI: 0.19-0.81) and 72% (adjusted HR: 0.28, 95% CI: 0.15-0.53) decreased risk of BC [14]. Even though that study was conducted only with a Japanese population, these two studies revealed that the risk of BC according to the number of childbirths had a more protective effect in Asians than in Caucasians, which was similar to the results of this updated meta-analysis.

This research suggests that family history of BC for BC risks differs from ethnic groups, while the temporal trend for changes in the strength of association seemed similar (Yes vs. No: ≥ 2010; RR: 1.57, 95% CI: 1.46-1.67, < 2010; RR: 1.58, 95% CI: 1.40-1.78). The consistency of the past and present referred not only the family history of BC is the only element that does not have an exogenous action, but also the family cohesion due to the similarity of family life patterns. However, this research seemed that Asians were highly linked with a family history of BC rather than Caucasians. These phenomena were the estimation result of the Japanese cohort study (RR: 3.22, 95% CI: 1.52-6.84) [20] and the Chinese case study (RR: 3.25, 95% CI: 1.34-7.89) [21], and the family history increased the BC risks approximately about 142% in Asians. In case of family history of BC, it is necessary to re-analyze it by additional studies, due to the high possibilities of the degree of the BC history or genes involved in BC.

Our findings on the temporal trend for changes in the strength of association of reproductive factors with BC between earlier and recent periods seem to reflect changes over time in the distribution of reproductive factors. Age at menarche and at menopause has slightly changed over time, beginning at a slightly younger age or stopping at a slightly older age than in the past [22]. The fertility rates and the number of childbirths have decreased rapidly over time, particularly among Asians, and the use of postmenopausal HRT has increased over time [23,24]. Performance bias related to HRT use may have contributed to the absence of population-level differences in breast cancer risk associated with combined or estrogen-only HRT. For current users of HRT, the BC risk was 37% higher among current estrogen-only HRT users than never-users, and 11% higher in those who used a combination of estrogen and progestogen [23]. The BC risk increased by approximately 20% when combination HRT was used for less than 1 year and approximately 151% when used for more than 15 years. On the other hand, the BC risk does not

increase with use of estrogen-only HRT for less than 1 year, but is 17% higher with 1-4 years of use, and 58% higher with more than 15 years of use. Additionally, there were not many cohort studies that indicated the duration of using combination HRT in Asian populations. Moreover, postmenopausal women who have been prescribed HRT more than 4 years in succession were very rare. Therefore, the duration of HRT use was combined as an Ever-used HRT for the estimation.

The present study has several strengths. One of the key strengths of this study is its improved representation of the Asian population, particularly Koreans. Previous meta-analysis of BC risks and reproductive/hormone factors have rarely included Korean population-based cohorts and mostly relied heavily on a limited number of Chinese studies. Moreover, our study systematically integrated data from multiple Korean cohorts, providing more representative and reliable estimation of the BC risk and reproductive factors relevant to the Korean population.

However, there are several limitations to consider. First, we only searched for studies based on BC in general, without distinguishing between molecular or histological subtypes. Since BC can be classified into various subtypes, and many recent studies have focused on analysis by hormone receptor status, this may have limited the precision of our findings [25]. Second, despite the inclusion of Korean population-based data, several reproductive factors, such as menarche, breastfeeding, and oral contraceptives were difficult to compare between Asians and Caucasians populations due to heterogeneity. Third, when categorizing age at menarche and menopause, the age ranges differed by country, which may have introduced challenges in accurately observing ethnic differences related to menstrual status. Finally, out literature search included studies published up to 2020. Although this analysis did not include studies published after 2020, it still provides a comprehensive synthesis of the available evidence up to that point and offers valuable insights into the association between BC risks and reproductive factors.

In conclusion, some reproductive factors, such as a high number of childbirths, parity and family history of BC, which are associated with BC, differed across continent-specified ethnicities. In terms of temporal trends, a stronger association was observed for combined HRT use in recent publications, while a stronger association was found for most reproductive factors, particularly parity per se and a high parity. These ethnic differences and temporal changes may have occurred due to ethnic differences in baseline hazards, such as BC incidence and mortality rates, and temporal changes in the background prevalence of reproductive factors. Although this study observed an association between total BC risks and reproductive factors, further prospective research is required to consider the histological and hormonal subtypes of BC.

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CONFLICTS OF INTEREST

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SUPPLEMENTARY MATERIALS

Supplementary materials can be found via https://doi.org/10.15430/JCP.25.042.

ORCID

Youjin Hong, https://orcid.org/0000-0002-3978-0214
Soseul Sung, https://orcid.org/0000-0002-5801-3379
Woojin Lim, https://orcid.org/0000-0001-8305-0246
Sungji Moon, https://orcid.org/0000-0002-6668-3065
Kwang-Pil Ko, https://orcid.org/0000-0002-7788-2887
Jung Eun Lee, https://orcid.org/0000-0003-1141-878X
Inah Kim, https://orcid.org/0000-0003-3568-4484
Sun Ha Jee, https://orcid.org/0000-0001-9519-3068
Sun-Seog Kweon, https://orcid.org/0000-0003-2378-8550
Min-Ho Shin, https://orcid.org/0000-0002-2217-5624
Sangmin Park, https://orcid.org/0000-0002-7498-4829
Seung-Ho Ryu, https://orcid.org/0000-0002-3927-8646
Sun Young Yang, https://orcid.org/0000-0003-4766-3752
Jeongseon Kim, https://orcid.org/0000-0002-0889-2686
Sang-Wook Yi, https://orcid.org/0000-0002-6656-6205
Sue K. Park, https://orcid.org/0000-0001-5002-9707

REFERENCES

1. Ghoncheh M, Pournamdar Z, Salehiniya H. Incidence and mortality and epidemiology of breast cancer in the world. Asian Pac J Cancer Prev 2016;17:43-6.
2. Breast cancer Facts & Figures 2017-2018. American Cancer Society Press, 2017.
3. Daly B, Olopade OI. Race, ethnicity, and the diagnosis of breast cancer. JAMA 2015;313:141-2.
4. Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and hormonal contraceptives: collaborative reanalysis of individual data on 53,297 women with breast cancer and 100,239 women without breast cancer from 54 epidemiological studies. Lancet 1996;347:1713-27.
5. Breast cancer and hormone replacement therapy: collaborative reanalysis of data from 51 epidemiological studies of 52,705 women with breast cancer and 108,411 women without breast cancer. Collaborative Group on Hormonal Factors in Breast Cancer. Lancet 1997;350:1047-59.
6. Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and breastfeeding: collaborative reanalysis of individual data from 47 epidemiological studies in 30 countries, including 50,302 women with breast cancer and 96,973 women without the disease. Lancet 2002;360:187-95.
7. Collaborative Group on Hormonal Factors in Breast Cancer. Menarche, menopause, and breast cancer risk: individual partici-pant meta-analysis, including 118,964 women with breast cancer from 117 epidemiological studies. Lancet Oncol 2012;13:1141-51.
8. Butts SF, Seifer DB. Racial and ethnic differences in reproductive potential across the life cycle. Fertil Steril 2010;93:681-90.
9. Xie C, Shao N, He L, Li X, Li C, Li J, et al. Exploration of racial differences in reproductive factors for breast cancer among women aged 55-74. J Cancer 2018;9:469-78.
10. InterLACE Study Team. Variations in reproductive events across life: a pooled analysis of data from 505,147 women across 10 countries. Hum reprod 2019;34:881-93.
11. Gottschalk MS, Eskild A, Hofvind S, Gran JM, Bjelland EK. Temporal trends in age at menarche and age at menopause: a population study of 312,656 women in Norway. Hum Reprod 2020;35:464-71.
12. Park SK. Epidemiological characteristics of breast cancer in Koreans. J Korean Med Assoc 2019;62:424-36.
13. Ji LW, Jing CX, Zhuang SL, Pan WC, Hu XP. Effect of age at first use of oral contraceptives on breast cancer risk: An updated meta-analysis. Medicine (Baltimore) 2019;98:e15719.
14. Takeuchi T, Kitamura Y, Sobue T, Utada M, Ozasa K, Sugawara Y, et al; Research Group for the Development, Evaluation of Cancer Prevention Strategies in Japan. Impact of reproductive factors on breast cancer incidence: Pooled analysis of nine cohort studies in Japan. Cancer Med 2021;10:2153-63.
15. Nindrea RD, Aryandono T, Lazuardi L. Breast cancer risk from modifiable and non-modifiable risk factors among women in Southeast Asia: a meta-analysis. Asian Pac J Cancer Prev 2017; 18:3201-6.
16. Payton ME, Greenstone MH, Schenker N. Overlapping confi-dence intervals or standard error intervals: what do they mean in terms of statistical significance? J Insect Sci 2003;3:34.
17. Higgins JPT TJ, Chandler J, Cumpston M, Li T, Page MJ, Welch VA. Cochrane Handbook for Systematic Reviews of Interventions version 6.3 (updated February 2022). www.training.cochrane.org/handbook (Accessed Aug 22, 2024).
18. von Hippel PT. The heterogeneity statistic I(2) can be biased in small meta-analyses. BMC Med Res Methodol 2015;15:35.
19. Husby A, Wohlfahrt J, Øyen N, Melbye M. Pregnancy duration and breast cancer risk. Nat Commun 2018;9:4255.
20. Liu R, Kitamura Y, Kitamura T, Sobue T, Sado J, Sugawara

Y, et al; Three-Prefecture Cohort Study Group. Reproductive and lifestyle factors related to breast cancer among Japanese women: An observational cohort study. Medicine (Baltimore) 2019;98:e18315.

21. Wang L, Liu L, Lou Z, Ding L, Guan H, Wang F, et al. Risk prediction for breast Cancer in Han Chinese women based on a cause-specific Hazard model. BMC Cancer 2019;19:128.

22. Perry CS, Otero JC, Palmer JL, Gross AS. Risk factors for breast cancer in East Asian women relative to women in the West. Asia Pac J Clin Oncol 2009;5:219-31.

23. Collaborative Group on Hormonal Factors in Breast Cancer. Type and timing of menopausal hormone therapy and breast cancer risk: individual participant meta-analysis of the worldwide epidemiological evidence. Lancet 2019;394:1159-68.

24. Yoo TK, Han KD, Kim D, Ahn J, Park WC, Chae BJ. Hormone replacement therapy, Breast cancer risk Factors, and breast cancer risk: a nationwide population-based cohort. Cancer Epidemiol Biomarkers Prev 2020;29:1341-7.

25. Yip CH, Rhodes A. Estrogen and progesterone receptors in breast cancer. Future Oncol 2014;10:2293-301.