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Association between breast cancer and reproductive factors: meta-analysis

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Abstract

Association between breast cancer and reproductive factors: meta-analysis

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Introduction: It is well known that breast cancer (BC) is a main risk for women and its association between reproductive and exogenous hormone factors have already undergone many progressions. Also, there have been many meta-analysis studies of breast cancer and each risk factor. However, contemporary research for each factors is needed, especially for the South Korean (hereafter, Korean) population. The purposes of this study are to systematically review the literature of corresponding studies to define a new estimation of a Korean meta-analysis, and to confirm continuous variables into a categorical status.

Methods: Firsts, systematic and comprehensive research of a systematic review was conducted. Second, statistical analysis of the meta-analysis was sequentially conducted. Third, PICO (**P**opulation, **I**ntervention, **C**omparison, and **O**utcome) statements were used for search strategies and update searching was performed in the journal PubMed until the publication of April 30, 2020. The literature representing the relative risk ratio (RR), odds ratio (OR) or hazard ratio (HR) of the association between breast cancer and reproductive factors and 95% confidential intervals (CIs) were selected. Pooling the effect size was estimated by using the

random effect model. A subgroup analysis was performed according to the study design, country and publication date.

Results: For the results of the Korean population, we set the reference in the direction of larger than 1 to calculate the population attributable risk (PAF) later. As a result, most of the reproductive variables were significant except for parity, duration of breastfeeding and oral contraceptive use. However, the trend of breast cancer and reproductive factors was the same as the global trend. For the Global population, the risk of medication of an oral contraceptive was approximately 10% higher than the general healthy women. On the other hand, the use of the combination of hormone replacement therapy (HRT) had approximately 30% higher risk than the general healthy women. Furthermore, in the subgroup analysis by country of the Global population, if the reproductive factors were at the risk point, the risk was sporadic by the various reproductive factors. Also if the reproductive factors were at the protective point, then Asian countries were more protective to breast cancer then Western countries (age at menarche, parity, number of childbirths, and duration of breastfeeding). In subgroup analysis by publication date, the relation of publication date has revealed in some reproductive factors, but it was difficult to calculate the rationale due to the lack of 1990s publication study.

Conclusions: This study summarized the modifiable factors and unmodifiable factors of breast cancer and confirmed the trend of the risk of breast cancer. Also, in order to calculate the Korean PAF model, we conducted a Korean meta-analysis to produce the latest indicators. Furthermore, we categorized and identified appropriate categories of continuous reproductive variables.

Keywords: Breast cancer, systematic review, meta-analysis, reproductive factors, exogenous hormone, random model effect

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I. Introduction

1. Epidemiology of breast cancer

According to World Health Organization (WHO) cancer statistics, the incidence of 18,078,957 new cancer cases was reported in 2018 and 9,555,027 cases were reported as a mortality of cancer. Especially for breast cancer, even with improvements and the early detection, breast cancer is still the most common and malignant cancer among women worldwide. In 2018, 2,088,849 women developed breast cancer (1).

Breast cancer incidence is known to vary by race. The incidence rates for breast cancer are higher among non-Hispanic white and non-Hispanic black women than other racial and ethnic groups. Asian/Pacific Islander women have the lowest incidence rates, which was 90.7 per 100,000 (2). According to *Breast Cancer Facts & Figures 2017-2018* (3), the incidences of non-Hispanic White and non-Hispanic Black women were 128.7 and 125.5 per 100,000, respectively.

2. The relationship between reproductive factors and exogenous hormone factors

Breast cancer is the combination of many known factors. Factors that cannot be changed by humans are called unmodifiable factors and factors that can be changed by humans are called modifiable factors. Unmodifiable factors include the increasing of age as a natural flow, having genetic mutations of BRCA1 and BRCA2 (Breast Cancer genes 1 and 2), and reproductive histories of early menstrual periods or late menopause, having dense breast and a family history of breast cancer, and so on. For modifiable factors, risk factors are being physically inactive, being overweight or obese after menopause, taking hormones such as oral contraceptives or hormone replacement therapy (HRT) (both estrogen and progesterone), reproductive histories

with late age of first full-term pregnancy, no breastfeeding, or never pregnant and alcohol consumption. These factors were confirm in *Al-Ajmi K et al. (2018)* (4) and many other studies. Therefore, these studies include unmodifiable factors such as age at menarche, age at menopause, family history of breast cancer and modifiable factors such as age at first-full term pregnancy, number of children, duration of breastfeeding, and the use of oral contraceptives HRT.

3. Breast cancer in the Korean population and population attributable risk (PAF)

As already mentioned in breast cancer epidemiology, in particular, the incidence of breast cancer in South Korea (hereafter, Korea) increased continuously for five years since 2010. According to Statistics Korea, the incidence rate rose 24.5 to 37.7 per 100,000 people from 2010 to 2015 (5).

Despite the increasing incidence of breast cancer in Korea, there are still few papers on breast cancer and its related risk factors due to the lack of Korean-specific data. *Boyoung Park et al. (2016*) (6), a study of breast cancer and its associated risk factors, was the most recent meta-analysis for Korea. As mentioned in a previous study, very few studies were added. Furthermore, there were only four risk factors (pregnancy/ age at first birth, total period of breastfeeding, oral contraceptive use, and HRT use) of breast cancer. From the estimated prevalence of exposures in the Korean population and the total summary relative risks (RRs) for each particular risk factor, population attributable risk (PAR) factors can be calculated. PAR, or PAF as mentioned in this research, is the proportion of the incidence of a disease in the population that is due to exposure or the incidence of a disease in the population that

would be eliminated if exposure were eliminated.

4. Objectives

There are several objectives for this research. There are 2 research of systematic review and meta-analysis based on Korean-specific data, which are BMI (7) and diet (8) between the risk of breast cancer, but the association of reproductive factors and breast cancer research is still lack in Korean-specific data. There is one research, which is association of hormone replacement therapy (HRT) (9) and risk of breast cancer in Korean-specific data, but it is based on the hospital case-control studies and the population of research is composed with breast cancer patients. Therefore, we decided to redeem the research. The first objective of this study is to collect the reliable results of summary RR of the Korean population by using the literature review and the analysis of raw data, which will be introduced later. Due to the shortage of Korean studies, the available data were analyzed and supplemented to a systematic review. With the addition of the additional cohort studies, which are Korean National Cancer Center (KNCC), Korean Cancer Prevention Study (KCSP II), Healthcare System Gangnam Center, Kangbuk Samsung Hospital, and Namwon cohort, we expected the heterogeneity of the studies to be lower. Furthermore, we can calculate the PAF of each risk factor to estimate the representative value of Koreans.

The second, objective of this study is to research the previous research studies that represent the association between breast cancer and reproductive factors and to conduct comprehensive systematic reviews for confirming the trend of breast cancer risks. We aim to compare the difference of Koreans and Global population breast cancer risk trends. The hypotheses of breast cancer and its risk factors according to the systematic literature review are as follows:

breast cancer risk increases an early menarche age, a late menopause age, having a family history of breast cancer, a late age of full-term pregnancy, fewer children, no breastfeeding, and a long exposure or ever exposure of an exogenous hormone, especially oral contraceptives and HRT.

The third objective of this study is to integrate the subgroup analysis. The various categories of each risk factors were integrated through a meta-analysis to detect the risks ratio by increasing age.

We will establish the above mentioned goals to obtain Korean breast cancer meta results and to further identify the best categories of Global population, which can be useful to interpret the risk of breast cancer and reproductive factors.

II. Materials and methods

1. Search and selection of literature for systematic review and meta-analysis

This study is quantitative research of a systematic review analysis. Therefore, sensitive search strategies were needed. Using the PICO statements, Global population as P (population), breast cancer risk factor exposures as I (intervention), non- breast cancer population as C (comparison) and breast cancer as O (outcome) were designated (Table 1, Supplementary table 1). Studies included in the systematic review were from the journals PubMed and KoreaMed published between 1990 and April 2020. The inclusion criteria and exclusion criteria are listed in Table 2.

The procedure of selection of the literature will be shown in the flow charts.

The study was funded by the Korean Foundation for Cancer Research. (Grant Number: CB-2017-A-2)

Table 1. Study designing based on the PICO definition for systematic literature reviews

Objective	
P (Population)	• The population of research is based on the general population.*
I (Intervention)	• The intervention of this research is the exposure risk factors of breast cancer. Reproductive factors which were age at menarche, age at menopause, parity, age at first full-term pregnancies, number of children, breastfeeding, duration of breastfeeding and exogenous hormone which were use of oral contraceptives/duration, and use of hormone replacement therapy/ duration included.
C (Comparison)	• The research compares the breast cancer patients and the general population of breast cancer free population.
O (Outcome)	• The outcome of this research is breast cancer which were diagnosed in the breast cancer screening center, hospital or National Health insurance service.
T (Time)	• The research time is the paper publication by 2020/04/30.
SD (Study design)	• This research includes the observational studies which are cohort studies and case-control studies. For case-control studies, population-based or community-based case-control studies were included. For cohort studies, nested case-control studies were also included.

* The population stands for Korea, East Asia (China, Japan), South/West Asia, North America (United States), Central/South America, Europe, Australia/New Zealand, and Africa.

Table 2. Inclusion criteria and exclusion criteria of selection literature

Categories	Contents
Inclusion criteria	• Research that represents the association of reproductive factors (age at menarche, age at menopause, parity, age at first full-term pregnancy, number of children, breastfeeding/ duration of breastfeeding) and usage of exogenous hormone (oral contraceptives and hormone replacement therapy) and breast cancer • Observational studies that are based on the epidemiology study which are cohort studies and case-control studies • Literatures that included the odds ratios (ORs), hazard ratios (HRs), and relative risks (RRs) • Population that included the Korean, Asian, and Global populations
Exclusion criteria	• Literatures that are based on the human research • Non-original research (appraisal, letter, comments), researches on cell and animal experiments, research on effects and techniques of radiation therapy • Literature that are written in Korean and English • Literature that doesn't represent HR, OR, RR and that doesn't involve the effect size

2. Study group for raw data analysis

The Korean Multi-Center Cancer study (KMCC) participants were recruited from the urban and rural areas of Haman, Chungju, Uljin and Pohang from 1993 to 2004. The cohort is based on the cancer-free cohort of the general community population. For cancer case ascertainment, an active surveillance system, which is cancer diagnosed by a physician at hospitals and a passive surveillance system, use the unique ID of the Korea system. The median follow-up year is 12.9 years and the person-year is 155,711. Total 12,401 women were analyzed.

The Korean Breast Cancer Society (KBCS) is population-based case-control study conducted from 2004 to 2013. The cases were newly diagnosed breast cancer cases who enrolled in the KBCS Registry Program from 1974 to 2016. The controls were breast cancer-free female health examinees from 2004 to 2015 in the Korean Genome and Epidemiology Study-Health Examinees (KoGES-HEXA). The controls

and cases were restricted to the age of 40 and above from 2004 to 2013. For analysis, 124,065 cases and 110,729 controls were included.

Also, five additional cohorts, which is mentioned previously, are included in as Korean-specific data. The additional cohorts are Korean National Cancer Center (KNCC), Korean Cancer Prevention Study (KCSP II), Healthcare System Gangnam Center, Kangbuk Samsung Hospital, and Namwon cohort.

3. Data Extraction

We chose observational studies, particularly cohort studies and case-controls studies (population-based case-control study and nested case-control study). Especially for the PCCS definition, we newly define PCCS for this research. There are three different definitions of PCCS. First, breast cancer cases and controls were randomly selected by the cancer registry. Second, the selection of breast cancer patients in the multicenter study and the selection of controls were population based or community based or large multicenter based. Third, the selection of breast cancer patients at one center with the number more than 500 patients. Fourth, for the Korean population, the hospital-based case-control (community) studies were included because of the shortage of Korean studies that analyze according to the corresponding subject. The literature listing the association between breast cancer and reproductive factors of relative risk (RRs, HRs, and ORs) were chosen as the final study collection for systematic review.

4. Statistical analysis

A. Systematic review and meta-analysis

In this study, the estimation of summary relative risk (RRs) and 95% confidential intervals (95% CIs) and forest plots were used by using random-effects models for

the association between breast cancer and reproductive factors. The total estimation RRs were calculated at first, and then the subgroup analysis were conducted. Subgroup analysis results were presented in the study design as cohort and case-control studies and by the countries (or continents) such as N/S America, Europe, and Asia. For country subgroup analysis, the variables of a family history of breast cancer and the use of estrogen only HRT do not have literature review results of the Korean population. As a way to reduce the heterogeneity of each result, subgroup analysis of publication date was further conducted.

Heterogeneity among articles was estimated using the I^2 statistic and *P* values associated with *Q* statistics. The I^2 statistic indicates the percentage of total variability explained by heterogeneity. In this research, the value of $0\% \leq I^2 \leq 25\%$ was assigned as low heterogeneity, $25\% \leq I^2 \leq 50\%$ as moderate heterogeneity, $50\% \leq I^2 \leq 75\%$ as relative high heterogeneity and $75\% \leq I^2 \leq 100\%$ as high heterogeneity. The study plotted funnel plots and calculated the publication bias by using the Begg and Egger test. All statistical analyses were conducted with R (version 3.5.2) statistical software.

B. Raw data analysis

The available data analysis for the additional Korean data were derived from the KMCC study, which is a cohort study of an observational study, and KBCS which are population-based case-control study of an observational study. The factors associated with the breast cancer risk of the cohort study were analyzed using the Cox proportional hazards regression model by adjusting confounding factors of age, enrollment year, smoking status, alcohol consumption, weekly exercising, and body mass index (BMI). For the case-control studies, data were analyzed using the logistic regression model by adjusting confounding factors of age, education, age at menarche, age at menopause, age at first child birth among parous women, number of children, duration of breastfeeding, and exercising, smoking, and drinking status.

The available data are analyzed into three groups: total women, premenopausal women, and postmenopausal women because of some reproductive factors that are linked to the women's menstrual cycles. For data that does not have the variable of menstrual information, we randomly assigned the menopausal status at the age of 50 years old.

The additional cohorts were analyzed by each cohort researcher using the same statistical technique presented above. However, if there is less than 5 or no breast cancer patients corresponding to each reproductive factor variables, we decided to use the Poisson regression, especially the calculation of binary outcome. Also some of the cohort have the mortality data of breast cancer patients, which are KMCC, Korean Genome and Epidemiology Study (KoGES), and Korean National Health and Nutrition Examination Survey (KNHANES), were analyzed by using the Poisson regression.

All statistical analyses were two-sided and were performed using the SAS statistical package (version 9.4; SAS institute, Cary, NC).

III. Results

1. Results of the Korean meta-analysis for estimating the summary RR of each reproductive factors

A. Incidence of breast cancer

The following tables show the raw data analysis and the systematic review of the Korean population. Each of the reproductive factors of breast cancer are listed in the appearance in a direction greater than 1, which indicates the risk. The reason is that when calculating the PAF value, this mechanism prevents of getting the negative values.

For the overall analysis of '≤ 14' ***vs.*** '≥ 17' [reference] of age at menarche and breast cancer, the estimation of summary RR of BC was 1.39 (95% CI=1.08-1.77) with high heterogeneity (I^2=92%). No significant publication bias was founded (Begg's test *p*=0.24, Egger's test *p*=0.22). For the overall analysis of '15-16' ***vs.*** '≥ 17' [reference] of age at menarche and breast cancer, the estimation of summary RR of BC was 1.18 (95% CI=1.04-1.33) with high heterogeneity (I^2=78%). No significant publication bias was founded (Begg's test *p*=0.33, Egger's test *p*=0.66). (Table 3)

For the overall analysis of '48-52' ***vs.*** '< 48' [reference] of age at menopause and breast cancer, the estimation of summary RR of BC was 1.25 (95% CI=1.15-1.37) with moderate heterogeneity (I^2=36%). No significant publication bias was founded (Begg's test *p*=0.83, Egger's test *p*=0.72). For the overall analysis of '≥ 53' ***vs.*** '< 48' [reference] of age at menopause and breast cancer, the estimation of summary RR of BC was 1.36 (95% CI=1.29-1.45) with no heterogeneity (I^2=0%). No significant publication bias was founded (Begg's test *p*=0.68, Egger's test *p*=0.30). (Table 3)

For the overall analysis of 'Nulliparous' ***vs.*** 'Parous' [reference] of parity and breast cancer, the estimation of summary RR of BC was 1.28 (95% CI=0.90-1.81) with

high heterogeneity (I^2=96%). No significant publication bias was founded (Begg's test p=0.45, Egger's test p=0.62). (Table 3)

For the overall analysis of '1' ***vs.*** '≥ 3' [reference] of number of childbirths and breast cancer among parous women, the estimation of summary RR of BC was 2.11 (95% CI=1.61-2.77) with moderate heterogeneity (I^2=48%). No significant publication bias was founded (Begg's test p=0.09, Egger's test p=0.17). For the overall analysis of '2' ***vs.*** '≥ 3' [reference] of number of childbirths and breast cancer among parous women, the estimation of summary RR of BC was 1.74 (95% CI=1.27-2.38) with high heterogeneity (I^2=79%). No significant publication bias was founded (Begg's test p=0.57, Egger's test p=0.03). (Table 3)

For the overall analysis of '20-30' ***vs.*** '< 20' [reference] of age at first-full term pregnancy and breast cancer among parous women, the estimation of summary RR of BC was 1.08 (95% CI=0.99-1.18) with low heterogeneity (I^2=15%). No significant publication bias was founded (Begg's test p=0.02, Egger's test p=0.04). For the overall analysis of '≥ 30' ***vs.*** '< 20' [reference] of age at first-full term pregnancy and breast cancer among parous women, the estimation of summary RR of BC was 1.42 (95% CI=1.35-1.51) with no heterogeneity (I^2=0%). No significant publication bias was founded (Begg's test p=0.00, Egger's test p=0.27). (Table 3)

For the overall analysis of 'Never' ***vs.*** 'Ever' [reference] of breastfeeding and breast cancer, the estimation of summary RR of BC was 1.42 (95% CI=1.27-1.60) with low heterogeneity (I^2=14%). No significant publication bias was founded (Begg's test p=0.19, Egger's test p=0.19). (Table 3)

For the overall analysis of 'Never' ***vs.*** '≥ 6 months' [reference] of duration of breastfeeding and breast cancer, the estimation of summary RR of BC was 1.85 (95% CI=0.54-6.35) with high heterogeneity (I^2=99%). No significant publication bias was founded (Begg's test p=0.60, Egger's test p=0.36). For the overall analysis of 'Never' ***vs.*** '< 6 months' [reference] of duration of breastfeeding and breast cancer, the

estimation of summary RR of BC was 1.32 (95% CI=1.17-1.50) with moderate heterogeneity (I^2=39%). No significant publication bias was founded (Begg's test p=0.12, Egger's test p=0.44). (Table 3)

For the overall analysis of 'Ever' ***vs.*** 'Never' [reference] of use of oral contraceptives and breast cancer, the estimation of summary RR of BC was 1.10 (95% CI=0.83-1.46) with high heterogeneity (I^2=87%). No significant publication bias was founded (Begg's test p=0.88, Egger's test p=0.01). (Table 3)

For the overall analysis of 'Ever' ***vs.*** 'Never' [reference] of use of hormone replacement therapy and breast cancer, the estimation of summary RR of BC was 1.50 (95% CI=1.18-1.90) with high heterogeneity (I^2=71%). No significant publication bias was founded (Begg's test p=0.35, Egger's test p=0.56). (Table 3)

Table 3. Summary relative risks of breast cancer related to each reproductive factors in Korean women (Incidence)

Reproductive factors	Studies	Summary	Heterogeneity	Publication bias	
	N	RR (95% CI)[1]	I^2 (%)	P_{Begg}	P_{Egger}
Age at menarche					
≤ 14	10	**1.39 (1.08-1.77)**	92%, $p < 0.01$	0.24	0.02
15-16		**1.18 (1.04-1.33)**	78%, $p < 0.01$	0.33	0.06
≥ 17		1.00			
Age at menopause*					
< 48	9	1.00			
48-52		**1.25 (1.15-1.37)**	36%, p=0.13	0.83	0.72
≥ 53		**1.36 (1.29-1.45)**	0%, p=0.73	0.68	0.30
Parity					
Nulliparous	7	1.28 (0.90-1.81)	96%, $p < 0.01$	0.45	0.62
Parous		1.00			
Number of childbirths					
1	6	**2.11 (1.61-2.77)**	48%, p=0.09	0.09	0.17
2		**1.74 (1.27-2.38)**	79%, $p < 0.01$	0.57	0.03
≥ 3		1.00			
Age at first-full term pregnancy					
< 20	7	1.00			
20-30		*1.08 (0.99-1.18)*	15%, p=0.31	0.02	0.04
≥ 30		**1.42 (1.35-1.51)**	0%, p=0.49	0.00	0.27
Breastfeeding					
Never	6	**1.42 (1.27-1.60)**	14%, p=0.32	0.19	0.19
Ever		1.00			
Duration of breastfeeding					
Never	3	1.85 (0.54-6.35)	99%, $p < 0.01$	0.60	0.36
< 6 months		**1.32 (1.17-1.50)**	39%, p=0.19	0.12	0.44
≥ 6 months		1.00			
Oral contraceptives					
Never**	7	1.00			
Ever		1.10 (0.83-1.46)	87%, $p < 0.01$	0.88	0.01
Hormone replacement therapy*					
Never	6	1.00			
Ever		**1.50 (1.18-1.90)**	71%, $p < 0.01$	0.35	0.56

1. Estimation of summary relative risks (RRs) are calculated by random effect model.
*Corresponding variables are evaluated only in postmenopausal women.
**The cohort study, which is conducted in the hospital of Gangnam Center, was excluded by the sensitivity analysis.

B. Mortality of breast cancer

The following tables show the raw data analysis and the systematic review of the Korean population. Each of the reproductive factors of breast cancer are listed in the appearance in a direction greater than 1, which indicates the risk of breast cancer. There is few research of breast cancer mortality results.

For the overall analysis of '≤ 14' ***vs.*** '≥ 17' [reference] of age at menarche and breast cancer, the estimation of summary RR of BC was 1.72 (95% CI=0.97-3.05) with no heterogeneity (I^2=0%). For the overall analysis of '15-16' ***vs.*** '≥ 17' [reference] of age at menarche and breast cancer, the estimation of summary RR of BC was 1.16 (95% CI=0.70-1.91) with high heterogeneity (I^2=0%). No significant publication bias was founded (Begg's test *p*=0.85, Egger's test *p*=0.33). (Table 4)

For the overall analysis of '48-52' ***vs.*** '< 48' [reference] of age at menopause and breast cancer, the estimation of summary RR of BC was 0.48 (95% CI=0.12-1.88) with no heterogeneity (I^2=0%). For the overall analysis of '≥ 53' ***vs.*** '< 48' [reference] of age at menopause and breast cancer, the estimation of summary RR of BC was 0.92 (95% CI=0.18-4.80) with no heterogeneity (I^2=0%). No significant publication bias was founded (Begg's test *p*=0.17, Egger's test *p*=0.59). (Table 4)

For the overall analysis of 'Nulliparous' ***vs.*** 'Parous' [reference] of parity and breast cancer, the estimation of summary RR of BC was 2.22 (95% CI=0.96-5.12). There was 1 study analyzed, which was KoGES. Therefore, publication bias was not available to calculate. (Table 4)

For the overall analysis of '1' ***vs.*** '≥ 3' [reference] of number of childbirths and breast cancer among parous women, the estimation of summary RR of BC was 1.44 (95% CI=0.51-4.03) with no heterogeneity (I^2=0%). For the overall analysis of '2' ***vs.*** '≥ 3' [reference] of number of childbirths and breast cancer among parous women, the estimation of summary RR of BC was 2.34 (95% CI=0.58-9.38) with moderate heterogeneity (I^2=62%). No significant publication bias was founded (Begg's test

p=1.00, Egger's test *p*=0.81). (Table 4)

For the overall analysis of '20-30' ***vs.*** '< 20' [reference] of age at first-full term pregnancy and breast cancer among parous women, the estimation of summary RR of BC was 1.61 (95% CI=0.79-3.26) with low heterogeneity (I^2=13%). For the overall analysis of '≥ 30' ***vs.*** '< 20' [reference] of age at first-full term pregnancy and breast cancer among parous women, the estimation of summary RR of BC was 2.50 (95% CI=1.04-6.03) with low heterogeneity (I^2=16%). No significant publication bias was founded (Begg's test *p*=0.35, Egger's test *p*=0.14). (Table 4)

For the overall analysis of 'Never' ***vs.*** 'Ever' [reference] of breastfeeding and breast cancer, the estimation of summary RR of BC was 1.59 (95% CI=1.27-1.60) with no heterogeneity (I^2=0%). (Table 4)

For the overall analysis of 'Never' ***vs.*** '≥ 12 months' [reference] of duration of breastfeeding and breast cancer, the estimation of summary RR of BC was 0.91 (95% CI=0.18-4.68). For the overall analysis of 'Never' ***vs.*** '< 12 months' [reference] of duration of breastfeeding and breast cancer, the estimation of summary RR of BC was 0.28 (95% CI=0.03-2.42). There was 1 study analyzed, which was KNHANES. Therefore, publication bias was not available to calculate. (Table 4)

For the overall analysis of 'Ever' ***vs.*** 'Never' [reference] of use of oral contraceptives and breast cancer, the estimation of summary RR of BC was 1.06 (95% CI=0.29-3.82) with moderate heterogeneity (I^2=68%). No significant publication bias was founded (Begg's test *p*=0.60, Egger's test *p*=0.89). (Table 4)

For the overall analysis of 'Ever' ***vs.*** 'Never' [reference] of use of hormone replacement therapy and breast cancer, the estimation of summary RR of BC was 0.87 (95% CI=0.44-1.71) with no heterogeneity (I^2=0%). No significant publication bias was founded (Begg's test *p*=0.60, Egger's test *p*=0.23). (Table 4)

Table 4. Summary relative risks of breast cancer related to each reproductive factors in Korean women (Mortality)

Reproductive factors	Studies	Summary	Heterogeneity	Publication bias	
	N	RR (95% CI)[1]	I^2 (%)	P_{Begg}	P_{Egger}
Age at menarche					
≤ 14	3	1.72 (0.97-3.05)	0%, *p*=0.98	0.85	0.33
15-16		1.16 (0.70-1.91)	0%, *p*=0.92		
≥ 17		1.00			
Age at menopause*					
< 48	2	1.00			
48-52		0.48 (0.12-1.88)	0%, *p*=0.99	0.17	0.59
≥ 53		0.92 (0.18-4.80)	0%, *p*=0.57		
Parity					
Nulliparous	1	2.22 (0.96-5.12)	-	-	-
Parous		1.00			
Number of childbirths					
1	2	1.44 (0.51-4.03)	0%, *p*=0.51	1.00	0.81
2		2.34 (0.58-9.38)	62%, *p*=0.11		
≥ 3		1.00			
Age at first-full term pregnancy					
< 20	3	1.00			
20-30		1.61 (0.79-3.26)	13%, *p*=0.32	0.35	0.14
≥ 30		**2.50 (1.04-6.03)**	16%, *p*=0.30		
Breastfeeding					
Never	2	1.59 (0.52-4.82)	0%, *p*=0.73	1.00	0.81
Ever		1.00			
Duration of breastfeeding					
Never	1	0.91 (0.18-4.68)	-	-	-
< 12 months		0.28 (0.03-2.42)			
≥ 12 months		1.00			
Oral contraceptives					
Never	3	1.00			
Ever		1.06 (0.29-3.82)	68%, *p*=0.05	0.60	0.89
Hormone replacement therapy*					
Never	3	1.00			
Ever		0.87 (0.44-1.71)	0%, *p*=0.76	0.60	0.23

1. Estimation of summary relative risks (RRs) are calculated by random effect model.
*Corresponding variables are evaluated only in postmenopausal women.

Furthermore, the subgroup analysis was conducted as the division of the study design. In subgroup analysis of study design, six reproductive factors, which are age at menarche, age at menopause, parity, age at first full term pregnancy, breastfeeding, and use of HRT, were significant in the cohort study design. To give you one example, for the analysis of '≤ 14yrs' ***vs.*** '≥ 17yrs' [reference] age at menarche and breast cancer, the estimation of summary RR of BC was 1.44 (95% CI=1.32-1.58) and the analysis of '15-16yrs' ***vs.*** '≥ 17yrs' [reference] age at menarche and breast cancer, the estimation of summary RR of BC was 1.21 (95% CI=1.12-1.31).

In subgroup analysis of study design, five reproductive factors, which are age at menopause, number of childbirths, age at first-full term pregnancy, breastfeeding, and use of OC, were significant in the case-control study design. (Table 5)

Table 5. Subgroup analysis of summary relative risks of breast cancer related to each reproductive factors in Korean women as in study design (Incidence)

	Cohort study			Case-control study		
Reproductive factors	**Study N**	**Summary RR (95% CI)[1]**	**I^2(%)**	**Study N**	**Summary RR (95% CI)[1]**	**I^2(%)**
Age at menarche						
≤ 14	7	**1.44 (1.32-1.58)**	0%	3	1.39 (0.81-2.39)	93%
15-16		**1.21 (1.12-1.31)**	0%		1.19 (0.93-1.52)	91%
≥ 17		1.00			1.00	
Age at menopause						
< 48	6	1.00		3	1.00	
48-52		**1.36 (1.14-1.63)**	0%		**1.21 (1.06-1.39)**	81%
≥ 53		**1.66 (1.33-2.08)**	0%		**1.34 (1.26-1.43)**	0%
Parity						
Nulliparous	4	**1.12 (1.08-1.16)**	0%	3	1.38 (0.76-2.51)	94%
Parous		1.00			1.00	
Number of childbirths						
1	4	**3.03 (2.10-4.39)**	0%	2	**1.79 (1.72-1.86)**	0%
2		**2.27 (1.72-2.99)**	0%		**1.28 (1.08-1.53)**	47%
≥ 3		1.00			1.00	
Age at first-full term pregnancy						
< 20	5	1.00		2	1.00	
20-30		***1.26 (1.00-1.58)***	16%		***1.05 (1.00-1.10)***	0%
≥ 30		**1.66 (1.33-2.06)**	0%		**1.34 (1.10-1.62)**	50%
Breastfeeding						
Never	4	**1.35 (1.14-1.60)**	6%	2	**1.51 (1.25-1.81)**	36%
Ever		1.00			1.00	
Duration of BF						
Never	1	1.24 (0.79-1.94)	-	2	2.25 (0.49-10.32)	100%
< 6 months		**1.96 (1.25-3.07)**	-		**1.29 (1.22-1.37)**	0%
≥ 6 months		1.00			1.00	
Use of OC						
Never**	4	1.00	0%	3	1.00	78%
Ever		0.91 (0.76-1.09)			**1.37 (1.06-1.78)**	
Use of HRT						
Never	3	1.00	5%	3	1.00	86%
Ever		**1.81 (1.33-2.44)**			1.36 (0.97-1.92)	

Abbreviation: BF; breastfeeding, OC; oral contraceptives, HRT; hormone replacement therapy

1. Estimation of summary relative risks (RRs) are calculated by random effect model.

*Corresponding variables are evaluated only in postmenopausal women.

**The cohort study, which is conducted in the hospital of Gangnam Center, was excluded by the sensitivity analysis.

2. Meta-analysis of the Global population

The results listed below are the estimation of summary RR of each reproductive factors and breast cancer in Global population. In this analysis, the first categories of each reproductive variable is the reference.

For the overall analysis of the menarche age and breast cancer, we included 44 studies. For the analysis of the association between age at menarche and breast cancer, the '15-16 years' ***vs.*** '≤ 14 years' [reference] risks ratio was 0.95 (95% CI=0.90-0.99) with high heterogeneity (I^2=80%, p<0.01). The category of '≥ 17years' ***vs.*** '≤ 14 years' [reference] risks ratio was 0.85 (95% CI=0.79-0.91) with high heterogeneity (I^2=87%, p<0.01).

For the overall analysis of the menopause age and breast cancer, we included 28 studies. For the analysis of the association between age at menopause and breast cancer, '48-52 years' ***vs***. '< 48years' [reference] risk ratio was 1.21 (95% CI=1.13-1.25) with moderate heterogeneity (I^2=27%, p=0.09). The category of '≥ 53 years' ***vs.*** '< 48years' [reference] risk ratio was 1.32 (95% CI=1.25-1.40) with moderate heterogeneity (I^2=38%, p=0.02).

For the overall analysis of family history and breast cancer, we included 31 studies. For the overall analysis of 'Ever' ***vs.*** 'Never' [reference] of family history and breast cancer, the estimation of summary RR of BC was 1.58 (95% CI=1.48-1.69) with high heterogeneity (I^2=84%, p<0.01).

For the overall analysis of the parity and breast cancer, we included 42 studies. For the overall analysis of 'Parous' ***vs.*** 'Nulliparous' [reference] of parity and breast cancer, the estimation of summary RR of BC was 0.79 (95% CI=0.74-0.85) with high heterogeneity (I^2=89%, p<0.01).

For the overall analysis of number of childbirths and breast cancer among parous women, we included 40 studies. For the analysis of the association between number

of childbirths and breast cancer, '2' ***vs***. '1' [reference] risk ratio was 0.91 (95% CI=0.86-0.96) with high heterogeneity (I^2=84%, p<0.01). The category of '≥ 3' ***vs.*** '1' [reference] risk ratio was 0.77 (95% CI=0.71-0.83) with high heterogeneity (I^2=86%, p<0.01).

For the overall analysis of age at first full-term pregnancy and breast cancer among parous women, we included 53 studies. The category of '20-30 years' ***vs***. '< 20 years' [reference] risk ratio was 1.10 (95% CI=1.06-1.14) with relatively high heterogeneity (I^2=72%, p<0.01). The category of '≥ 30 years' ***vs.*** '< 20 years' [reference] risk ratio was 1.31 (95% CI=1.24-1.38) with moderate heterogeneity (I^2=68%, p<0.01).

For the overall analysis of duration of breastfeeding and breast cancer, we included 20 studies. The category of '< 6 months' ***vs***. 'Never' [reference] risk ratio was 0.82 (95% CI=0.64-1.06) with high heterogeneity (I^2=99%, p<0.01). The category of '≥ 6 months' ***vs.*** 'Never' [reference] risk ratio was 0.80 (95% CI=0.58-1.11) with high heterogeneity (I^2=99%, p=0.00).

For the overall analysis of use of oral contraceptives and breast cancer, we included 45 studies. For the overall analysis of 'Ever' ***vs.*** 'Never' [reference] of oral contraceptives and breast cancer, the estimation of summary RR of BC was 1.07 (95% CI=0.99-1.15) with high heterogeneity (I^2=90%, p<0.01).

For the overall analysis of duration of oral contraceptives and breast cancer, we included 29 studies. The category of '< 5 years' ***vs***. 'Never' [reference] risk ratio was 1.07 (95% CI=1.02-1.13) with relatively high heterogeneity (I^2=52%, p<0.01). The category of '≥ 5 years' ***vs.*** 'Never' [reference] risk ratio was 1.10 (95% CI=1.04-1.17) with relatively high heterogeneity (I^2=58%, p<0.01).

For the overall analysis of use of combination HRT and breast cancer, we included 42 studies. For the overall analysis of 'Ever' ***vs.*** 'Never' [reference] of combination

of HRT and breast cancer, the estimation of summary RR of BC was 1.29 (95% CI=1.18-1.41) with high heterogeneity (I^2=86%, p<0.01). For the overall analysis of use of estrogen only HRT and breast cancer, we included 30 studies. For the overall analysis of 'Ever' ***vs.*** 'Never' [reference] of estrogen only HRT and breast cancer, the estimation of summary RR of BC was 1.11 (95% CI=1.04-1.18) with moderate heterogeneity (I^2=52%, p<0.01). (Table 6)

Table 6. Summary relative risks of breast cancer related to each reproductive factors in Global population

Reproductive factors	Studies	Summary	Heterogeneity	Publication bias	
	N	RR (95% CI)[1]	I^2 (%)	P_{Begg}	P_{Egger}
Age at menarche					
≤ 14	44	1.00			
15-16		**0.95 (0.90-0.99)**	80%, $p < 0.01$	0.13	0.06
≥ 17		**0.85 (0.79-0.91)**	87%, $p < 0.01$	0.72	0.00
Age at menopause*					
< 48	28	1.00			
48-52		**1.21 (1.16-1.25)**	27%, p =0.09	0.53	0.90
≥ 53		**1.32 (1.25-1.40)**	38%, p =0.02	0.04	0.26
Family history of BC					
Never	31	1.00			
Ever		**1.58 (1.48-1.69)**	84%, $p < 0.01$	0.85	0.88
Parity					
Nulliparous	42	1.00			
Parous		**0.79 (0.74-0.85)**	89%, $p < 0.01$	0.91	0.34
Number of childbirths					
1	40	1.00			
2		**0.91 (0.86-0.96)**	84%, $p < 0.01$	0.23	0.94
≥ 3		**0.77 (0.71-0.83)**	86%, $p < 0.01$	0.07	0.65
Age at first-full term pregnancy					
< 20	53	1.00			
20-30		**1.10 (1.06-1.14)**	72%, $p < 0.01$	0.02	0.92
≥ 30		**1.31 (1.24-1.38)**	68%, $p < 0.01$	0.06	0.38
Duration of breastfeeding					
Never	20	1.00			
< 6 months		0.82 (0.64-1.06)	99%, $p < 0.01$	0.03	0.22
≥ 6 months		0.80 (0.58-1.11)	99%, p =0.00	0.00	0.33
Oral contraceptives					
Never	45	1.00			
Ever		*1.07 (0.99-1.15)*	90%, $p < 0.01$	0.14	0.22
Duration of OC use					
Never	29	1.00			
< 5 years		**1.07 (1.02-1.13)**	52%, $p < 0.01$	0.71	0.26
≥ 5 years		**1.10 (1.04-1.17)**	58%, $p < 0.01$	0.27	0.71
Hormone replacement therapy*					
Combination HRT					
Never	42	1.00			
Ever		**1.29 (1.18-1.41)**	86%, $p < 0.01$	0.45	0.17
Estrogen only HRT					
Never	30	1.00			
Ever		**1.11 (1.04-1.18)**	52%, $p < 0.01$	0.68	0.14

Abbreviation: OC; oral contraceptive, HRT; hormone replacement therapy

1. Estimation of summary relative risks (RRs) are calculated by random effect model.

*Corresponding variables are evaluated only in postmenopausal women.

3. Subgroup analysis of Global population

Furthermore, to reduce the high heterogeneity of each reproductive factors, subgroup analysis was conducted. Total studies, which are collected for systematic review, were analyzed as subgroup using study design, country (continent), and publication year. For the subgroup analysis of the publication date, raw data were excluded.

A. Study design

As shown in Table 7, subgroup analysis by study design was conducted. For the analysis of the association between age at menarche and breast cancer, only the cohort study design was significant in the study of subgroup design. For the analysis of the association between age at menarche and breast cancer, the '15-16 years' ***vs.*** '≤ 14 years' [reference] risks ratio was 0.94 (95% CI=0.89-0.99) with moderate heterogeneity (I^2=65%, p<0.01). The category of '≥ 17years' ***vs.*** '≤ 14 years' [reference] risks ratio was 0.84 (95% CI=0.76-0.92) with high heterogeneity (I^2=79%, p<0.01).

For the analysis of the association between number of childbirths and breast cancer among parous women, only the case-control study design was significant in the study of subgroup design. For the analysis of the association between number of childbirths and breast cancer, '2' ***vs***. '1' [reference] risk ratio was 0.90 (95% CI=0.84-0.97) with high heterogeneity (I^2=89%, p<0.01). The category of '≥ 3' ***vs.*** '1' [reference] risk ratio was 0.74 (95% CI=0.68-0.81) with high heterogeneity (I^2=84%, p<0.01).

For the overall analysis of use of oral contraceptives and breast cancer, only the cohort study design was significant in the study of subgroup design. For the overall analysis of 'Ever' ***vs.*** 'Never' [reference] of oral contraceptives and breast cancer, the estimation of summary RR of BC was 1.06 (95% CI=1.00-1.12) with moderate heterogeneity (I^2=52%, p<0.01). The risk value was marginally significant.

For the overall analysis of duration of oral contraceptives and breast cancer, only the case-control study design was significant in the study of subgroup design. The

category of '< 5 years' ***vs***. 'Never' [reference] risk ratio was 1.07 (95% CI=1.00-1.15) with relatively high heterogeneity (I^2=59%, p<0.01). The category of '≥ 5 years' ***vs.*** 'Never' [reference] risk ratio was 1.16 (95% CI=1.00-1.14) with relatively high heterogeneity (I^2=51%, p<0.01).

For the overall analysis of use of estrogen only HRT and breast cancer, only the cohort study design was significant in the study of subgroup design. For the overall analysis of 'Ever' ***vs.*** 'Never' [reference] of estrogen only HRT and breast cancer, the estimation of summary RR of BC was 1.16 (95% CI=1.09-1.22) with no heterogeneity (I^2=0%, p<0.01).

For the analysis of the association between age at menopause, family history of BC, parity, age at first full-term pregnancy, combination HRT and breast cancer, both study design, which are cohort and case-control study, was significant in the study of subgroup design.

For the analysis of the association between duration of breastfeeding and breast cancer neither the study design was significant (Table 7).

Table 7. Summary relative risks of breast cancer related to each reproductive factors in Global population of subgroup analysis by study design

	Cohort study			Case-control study		
Reproductive factor	**Studies N**	**Summary RR (95% CI)[1]**	**Heterogeneity I^2 (%)**	**Studies N**	**Summary RR (95% CI)[1]**	**Heterogeneity I^2 (%)**
Age at menarche						
≤ 14	18	1.00		26	1.00	
15-16		**0.94 (0.89-0.99)**	65%, $p < 0.01$		0.96 (0.89-1.02)	81%, $p < 0.01$
≥ 17		**0.84 (0.76-0.92)**	79%, $p < 0.01$		**0.86 (0.78-0.95)**	87%, $p < 0.01$
Age at menopause*						
< 48	15	1.00		13	1.00	
48-52		**1.19 (1.14-1.24)**	0%, $p = 0.62$		**1.22 (1.15-1.29)**	50%, $p = 0.02$
≥ 53		**1.36 (1.23-1.51)**	48%, $p = 0.02$		**1.31 (1.22-1.40)**	25%, $p = 0.20$
Family history of BC						
No	16	1.00		15	1.00	
Yes		**1.59 (1.46-1.72)**	88%, $p < 0.01$		**1.56 (1.38-1.76)**	78%, $p < 0.01$
Parity						
Nulliparous	20	1.00		22	1.00	
Parous		**0.85 (0.80-0.92)**	83%, $p < 0.01$		**0.75 (0.67-0.84)**	90%, $p < 0.01$
Number of childbirths						
1	16	1.00		24	1.00	
2		*0.93 (0.86-1.01)*	63%, $p < 0.01$		**0.90 (0.84-0.97)**	89%, $p < 0.01$
≥ 3		**0.82 (0.72-0.93**)	83%, $p < 0.01$		**0.74 (0.68-0.81)**	84%, $p < 0.01$
Age at first-full term pregnancy						
< 20	22	1.00		31	1.00	
20-30		**1.12 (1.03-1.21)**	67%, $p < 0.01$		**1.09 (1.04-1.15)**	75%, $p < 0.01$
≥ 30		**1.34 (1.23-1.47)**	45%, $p = 0.01$		**1.30 (1.21-1.39)**	74%, $p < 0.01$
Duration of breastfeeding						
Never	6	1.00		14	1.00	
< 6 months		0.95 (0.89-1.02)	56%, $p = 0.05$		0.78 (0.55-1.11)	99%, $p < 0.01$
≥ 6 months		0.95 (0.87-1.03)	66%, $p = 0.01$		0.78 (0.49-1.23)	99%, $p < 0.01$
Oral contraceptives						
Never	20	1.00		25	1.00	
Ever		***1.06 (1.00-1.12)***	52%, $p < 0.01$		1.08 (0.96-1.23)	94%, $p < 0.01$
Duration of OC use						
Never	8	1.00		21	1.00	
< 5 years		*1.08 (0.99-1.17)*	26%, $p = 0.22$		***1.07 (1.00-1.15)***	59%, $p < 0.01$
≥ 5 years		**1.18 (1.10-1.27)**	30%, $p = 0.19$		***1.06 (1.00-1.14)***	51%, $p < 0.01$
Hormone replacement therapy*						
Combination HRT						
Never	24	1.00		18	1.00	
Ever		**1.36 (1.18-1.56)**	87%, $p < 0.01$		**1.21 (1.06-1.38)**	85%, $p < 0.01$
Estrogen only HRT						
Never	15	1.00		15	1.00	
Ever		**1.16 (1.09-1.22)**	0%, $p = 0.52$		1.06 (0.95-1.17)	70%, $p < 0.01$

Abbreviation: OC; oral contraceptive, HRT; hormone replacement therapy

1. Estimation of summary relative risks (RRs) are calculated by random effect model.

*Corresponding variables are evaluated only in postmenopausal women.

B. Country (Continent)

As shown in Table 8, subgroup analysis by country was conducted. For the analysis of the association between age at menarche and breast cancer, the result of Europe and N/S America was significant. For the analysis of the association between age at menarche and breast cancer of subgroup analysis by country in Europe, the '15-16 years' ***vs.*** '≤ 14 years' [reference] risks ratio was 0.94 (95% CI=0.90-0.99) and the category of '≥ 17years' ***vs.*** '≤ 14 years' [reference] risks ratio was 0.89 (95% CI=0.82-0.96). For the analysis of the association between age at menarche and breast cancer of subgroup analysis by country in N/S America, the '15-16 years' ***vs.*** '≤ 14 years' [reference] risks ratio was 0.96 (95% CI=0.93-0.99) and the category of '≥ 17years' ***vs.*** '≤ 14 years' [reference] risks ratio was 0.87 (95% CI=0.81-0.93). Further analysis of secondary subgroups by study design from primary subgroup results, the result of Asia was significant in the cohort study design and the result of Europe was significant in the case-control study design.

For the analysis of the association between age at menopause and breast cancer, all results were significant. For the analysis of the association between age at menopause and breast cancer of subgroup analysis by country in Europe, the '48-52 years' ***vs.*** '< 48 years' [reference] risks ratio was 1.13 (95% CI=1.08-1.19) and the category of '≥ 53years' ***vs.*** '< 48 years' [reference] risks ratio was 1.18 (95% CI=1.10-1.27). For the analysis of the association between age at menopause and breast cancer of subgroup analysis by country in N/S America, the '48-52 years' ***vs.*** '< 48 years' [reference] risks ratio was 1.23 (95% CI=1.18-1.29) and the category of '≥ 53years' ***vs.*** '< 48 years' [reference] risks ratio was 1.35 (95% CI=1.23-1.48). For the analysis of the association between age at menarche and breast cancer of subgroup analysis by country in Asia, the '48-52 years' ***vs.*** '< 48 years' [reference] risks ratio was 1.25 (95% CI=1.16) and the category of '≥ 53years' ***vs.*** '< 48 years'

[reference] risks ratio was 1.38 (95% CI=1.30-1.46). Further analysis of secondary subgroups by study design from primary subgroup results, all results were also significant in both study design.

For the analysis of the association between family history and breast cancer, all results were significant. For the analysis of the association between family history and breast cancer of subgroup analysis by country in Europe, the 'Yes' ***vs.*** 'No' [reference] risks ratio was 1.69 (95% CI=1.49-1.92). For the analysis of the association between family history and breast cancer of subgroup analysis by country in N/S America, the 'Yes' ***vs.*** 'No' [reference] risks ratio was 1.51 (95% CI=1.43-1.60). For the analysis of the association between family history and breast cancer of subgroup analysis by country in Asia, the 'Yes' ***vs.*** 'No' [reference] risks ratio was 2.42 (95% CI=1.64-3.57). Further analysis of secondary subgroups by study design from primary subgroup results, all results were also significant in both study design.

For the analysis of the association between parity and breast cancer, all results were significant. For the analysis of the association between parity and breast cancer of subgroup analysis by country in Europe, the 'Parous' ***vs.*** 'Nulliparous' [reference] risks ratio was 0.84 (95% CI=0.77-0.91). For the analysis of the association between parity and breast cancer of subgroup analysis by country in N/S America, the 'Parous' ***vs.*** 'Nulliparous' [reference] risks ratio was 0.81 (95% CI=0.74-0.88). For the analysis of the association between parity and breast cancer of subgroup analysis by country in Asia, the 'Parous' ***vs.*** 'Nulliparous' [reference] risks ratio was 0.72 (95% CI=0.55-0.93). Further analysis of secondary subgroups by study design from primary subgroup results, the result of Europe was significant in the cohort study design and the result of N/S America and Asia were significant in the case-control study design.

For the analysis of the association between number of childbirths and breast cancer among parous women, the result of Europe was significant. For the analysis of the association between number of childbirths and breast cancer of subgroup analysis by country in Europe, the '2 children' ***vs.*** '1 child' [reference] risks ratio was 0.91 (95% CI=0.88-0.95) and the category of '≥ 3 children' ***vs.*** '1 child' [reference] risks ratio was 0.80 (95% CI=0.74-0.86). Further analysis of secondary subgroups by study design from primary subgroup results, the result of Europe was significant in the cohort study design and the result of Europe and N/S America was significant in the case-control study design.

For the analysis of the association between age at first full-term pregnancy and breast cancer, all results were significant. For the analysis of the association between age at first full-term pregnancy and breast cancer of subgroup analysis by country in Europe, the '20-30 years' ***vs.*** '< 20 years' [reference] risks ratio was 1.09 (95% CI=1.02-1.17) and the category of the '≥ 30 years' ***vs.*** '< 20 years' [reference] risks ratio was 1.26 (95% CI=1.15-1.38). For the analysis of the association between age at first full-term pregnancy and breast cancer of subgroup analysis by country in N/S America, the '20-30 years' ***vs.*** '< 20 years' [reference] risks ratio was 1.09 (95% CI=1.03-1.17) and the category of the '≥ 30 years' ***vs.*** '< 20 years' [reference] risks ratio was 1.34 (95% CI=1.23-1.46). For the analysis of the association between age at first full-term pregnancy and breast cancer of subgroup analysis by country in Asia, the '20-30 years' ***vs.*** '< 20 years' [reference] risks ratio was 1.12 (95% CI=1.03-1.22) and the category of the '≥ 30 years' ***vs.*** '< 20 years' [reference] risks ratio was 1.36 (95% CI=1.23-1.51). Further analysis of secondary subgroups by study design from primary subgroup results, the result of Europe and Asia was significant in the cohort study design and the result of N/S America was significant in the case-control study design.

For the analysis of the association between duration of breastfeeding and breast cancer, the result of N/S America was significant. For the analysis of the association between duration of breastfeeding and breast cancer of subgroup analysis by country in N/S America, the '< 6 months' ***vs.*** 'Never' [reference] risks ratio was 0.91 (95% CI=0.88-0.95) and the category of the '≥ 6 months' ***vs.*** 'Never' [reference] risks ratio was 0.89 (95% CI=0.82-0.96). Further analysis of secondary subgroups by study design from primary subgroup results, the result of Asia was significant in the cohort study design and the result of N/S America was significant in the case-control study design.

For the analysis of the association between oral contraceptive use and breast cancer, none of the result was significant. However, further analysis of secondary subgroups by study design from primary subgroup results, the result of Europe was significant in the cohort study design and the result of Asia was significant in the case-control study design. For the analysis of the association between duration of oral contraceptives and breast cancer, the result of Europe was significant. For the analysis of the association between duration of oral contraceptive and breast cancer of subgroup analysis by country in N/S America, the '< 5 years' ***vs.*** 'Never' [reference] risks ratio was 1.13 (95% CI=1.04-1.23) and the category of the '≥ 5 years' ***vs.*** 'Never' [reference] risks ratio was 1.12 (95% CI=1.05-1.20). Further analysis of secondary subgroups by study design from primary subgroup results, the result of Europe was significant in the cohort study design.

For the analysis of the association between combination HRT use and breast cancer, all result was significant. For the analysis of the association between combination HRT and breast cancer of subgroup analysis by country in Europe, the 'Ever' ***vs.*** 'Never' [reference] risks ratio was 1.38 (95% CI=1.18-1.60). For the analysis of the association between combination HRT and breast cancer of subgroup analysis by

country in N/S America, the 'Ever' ***vs.*** 'Never' [reference] risks ratio was 1.18 (95% CI=1.03-1.34). For the analysis of the association between combination HRT and breast cancer of subgroup analysis by country in Asia, the 'Ever' ***vs.*** 'Never' [reference] risks ratio was 1.50 (95% CI=1.18-1.90). Further analysis of secondary subgroups by study design from primary subgroup results, the result of Europe and Asia was significant in the cohort study design and the result of Europe was significant in case-control study design. For the analysis of the association between estrogen only HRT use and breast cancer, the result of Europe and N/S America was significant. For the analysis of the association between estrogen only HRT and breast cancer of subgroup analysis by country in Europe, the 'Ever' ***vs.*** 'Never' [reference] risks ratio was 1.17 (95% CI=1.03-1.32). For the analysis of the association between estrogen only HRT and breast cancer of subgroup analysis by country in N/S America, the 'Ever' ***vs.*** 'Never' [reference] risks ratio was 1.07 (95% CI=1.01-1.14). Further analysis of secondary subgroups by study design from primary subgroup results, the result of Europe and N/S America was significant in the cohort study design (Table 8).

Table 8. Summary relative risks of breast cancer related to each reproductive factors in Global population of subgroup analysis by country (continents)

	Europe			N/S America			Asia		
Reproductive factors	**N**	**Summary RR (95% CI)[1]**	**Heterogeneity I^2 (%)**	**N**	**Summary RR (95% CI)[1]**	**Heterogeneity I^2 (%)**	**N**	**Summary RR (95% CI)[1]**	**Heterogeneity I^2 (%)**
Age at menarche									
≤ 14	14	1.00		18	1.00		12	1.00	
15-16		**0.94 (0.90-0.99)**	41%, p =0.05		**0.96 (0.93-0.99)**	10%, p =0.34		0.89 (0.76-1.03)	90%, p < 0.01
≥ 17		**0.89 (0.82-0.96)**	61%, p < 0.01		**0.87 (0.81-0.93)**	53%, p < 0.01		**0.78 (0.63-0.96)**	94%, p < 0.01
Cohort study									
≤ 14	4	1.00		7	1.00		7	1.00	
15-16		0.98 (0.89-1.08)	72%, p =0.01		0.96 (0.90-1.01)	38%, p =0.14		**0.82 (0.68-0.99)**	68%, p < 0.01
≥ 17		0.90 (0.77-1.06)	78%, p < 0.01		**0.90 (0.85-0.96)**	25%, p =0.24		**0.70 (0.65-0.88)**	61%, p =0.02
Case-control study									
≤ 14	10	1.00		11	1.00		5	1.00	
15-16		**0.93 (0.88-0.99)**	22%, p =0.24		0.97 (0.91-1.02)	0%, p =0.52		0.97 (0.80-1.17)	91%, p < 0.01
≥ 17		**0.88 (0.80-0.98)**	54%, p =0.02		**0.84 (0.74-0.96)**	60%, p < 0.01		0.86 (0.69-1.08)	95%, p < 0.01
Age at menopause*									
< 48	8	1.00		9	1.00		11	1.00	
48-52		**1.13 (1.08-1.19)**	0%, p =0.63		**1.23 (1.18-1.29)**	0%, p =0.63		**1.25 (1.16-1.34)**	22%, p=0.23
≥ 53		**1.18 (1.10-1.27)**	2%, p =0.41		**1.35 (1.23-1.48)**	36%, p =0.13		**1.38 (1.30-1.46)**	0%, p =0.55
Cohort study									
< 48	5	1.00		2	1.00		8	1.00	
48-52		**1.11 (1.03-1.19)**	0%, p =0.89		**1.19 (1.05-1.35)**	46%, p =0.18		**1.31 (1.13-1.52)**	0%, p =0.94
≥ 53		**1.17 (1.05-1.30)**	4%, p =0.39		**1.32 (1.10-1.58)**	80%, p =0.02		**1.73 (1.42-2.10)**	0%, p =0.93
Case-control study									
< 48	3	1.00		7	1.00		3	1.00	
48-52		**1.18 (1.06-1.31)**	43%, p =0.17		**1.25 (1.16-1.34)**	0%, p =0.65		**1.21 (1.06-1.39)**	81%, p < 0.01
≥ 53		**1.23 (1.07-1.41)**	30%, p =0.24		**1.36 (1.20-1.55)**	18%, p =0.29		**1.34 (1.26-1.43)**	0%, p =0.72
Family history of BC									
No	8	1.00		19	1.00		4	1.00	
Yes		**1.69 (1.49-1.92)**	88%, p < 0.01		**1.51 (1.42-1.60)**	70%, p < 0.01		**2.42 (1.64-3.57)**	36%, p=0.20
Cohort study									
No	4	1.00		10	1.00		2	1.00	
Yes		**1.76 (1.52-2.04)**	89%, p < 0.01		**1.48 (1.42-1.53)**	18%, p=0.28		**3.02 (1.93-4.73)**	0%, p=0.84
Case-control study	4								
No		1.00		9	1.00		2	1.00	
Yes		**1.57 (1.18-2.11)**	86%, p < 0.01		**1.51 (1.29-1.76)**	80%, p < 0.01		**2.04 (1.06-3.96)**	49%, p=0.16

Parity**									
Nulliparous	13	1.00		17	1.00		12	1.00	
Parous		**0.84 (0.77-0.91)**	80%, *p* < 0.01		**0.81 (0.74-0.88)**	88%, *p* < 0.01		**0.72 (0.55-0.93)**	93%, *p* < 0.01
Cohort study									
Nulliparous	7	1.00		5	1.00		8	1.00	
Parous		**0.81 (0.76-0.87)**	43%, *p*=0.01		0.92 (0.77-1.09)	95%, *p* < 0.01		0.80 (0.61-1.04)	57%, *p*=0.02
Case-control study									
Nulliparous	6	1.00		12	1.00		4	1.00	
Parous		0.85 (0.69-1.04)	90%, *p* < 0.01		**0.76 (0.68-0.84)**	79%, *p* < 0.01		**0.53 (0.46-0.61)**	28%, *p*=0.24
Number of childbirths**									
1	17	1.00		16	1.00		7	1.00	
2		**0.91 (0.88-0.95)**	37%, *p* =0.06		*0.95 (0.90-1.01)*	23%, *p* =0.19		0.78 (0.60-1.02)	83%, *p* < 0.01
≥ 3		**0.80 (0.74-0.86)**	56%, *p* < 0.01		**0.80 (0.72-0.89)**	84%, *p* < 0.01		**0.58 (0.48-0.71)**	59%, *p* =0.02
Cohort study									
1	**7**	1.00		4	1.00		5	1.00	
2		**0.88 (0.83-0.94)**	17%, *p* =0.30		1.04 (0.96-1.14)	7%, *p* =0.36		0.78 (0.53-1.16)	77%, *p* < 0.01
≥ 3		**0.78 (0.74-0.82)**	0%, *p* =0.51		1.03 (0.92-1.15)	57%, *p* =0.07		**0.53 (0.33-0.84)**	72%, *p* < 0.01
Case-control study									
1	10	1.00		12	1.00		2	1.00	
2		**0.94 (0.91-0.97)**	8%, *p* =0.37		**0.91 (0.86-0.97)**	0%, *p* =0.54		***0.75 (0.56-1.00)***	66%, *p* =0.09
≥ 3		**0.79 (0.70-0.90)**	67%, *p* < 0.01		**0.74 (0.68-0.81)**	58%, *p* < 0.01		**0.59 (0.56-0.62)**	0%, *p* =0.80
Age at first-full term pregnancy**									
< 20	16	1.00		22	1.00		15	1.00	
20-30		**1.09 (1.02-1.17)**	79%, *p* < 0.01		**1.09 (1.03-1.17)**	72%, *p* < 0.01		**1.12 (1.03-1.22)**	43%, *p* =0.04
≥ 30		**1.26 (1.15-1.38)**	83%, *p* < 0.01		**1.34 (1.23-1.46)**	57%, *p* < 0.01		**1.36 (1.23-1.51)**	28%, *p* =0.15
Cohort study									
< 20	6	1.00		6	1.00		10	1.00	
20-30		**1.16 (1.11-1.22)**	0%, *p* =0.58		1.02 (0.86-1.21)	84%, *p* < 0.01		**1.28 (1.10-1.48)**	14%, *p* =0.31
≥ 30		**1.34 (1.17-1.53)**	59%, *p* =0.03		**1.23 (1.02-1.49)**	61%, *p* =0.03		**1.60 (1.34-1.91)**	0%, *p* =0.78
Case-control study									
< 20	10	1.00		16	1.00		5	1.00	
20-30		1.06 (0.95-1.19)	87%, *p* < 0.01		**1.12 (1.06-1.20)**	56%, *p* < 0.01		1.05 (0.98-1.13)	43%, *p* =0.13
≥ 30		**1.22 (1.05-1.43)**	86%, *p* < 0.01		**1.38 (1.25-1.52)**	56%, *p* < 0.01		**1.25 (1.07-1.46)**	64%, *p* =0.03
Duration of breastfeeding									
Never	4	1.00		12	1.00		4	1.00	
< 6 months		1.00 (0.85-1.17)	78%, *p* < 0.01		**0.91 (0.88-0.95)**	0%, *p* =0.71		0.59 (0.30-1.16)	99%, *p* < 0.01
≥ 6 months		0.96 (0.81-1.15)	80%, *p* < 0.01		**0.89 (0.82-0.96)**	68%, *p* < 0.01		0.56 (0.22-1.38)	99%, *p* < 0.01

Cohort study									
Never	2	1.00		3	1.00		1	1.00	
< 6 months		1.04 (0.94-1.15)	43%, p =0.19		**0.93 (0.89-0.97)**	0%, p =0.71		**0.80 (0.67-0.96)**	-
≥ 6 months		1.00 (0.92-1.08)	0%, p =0.81		0.94 (0.84-1.06)	79%, p < 0.01		**0.67 (0.48-0.93)**	-
Case-control study									
Never	2	1.00		9	1.00		3	1.00	
< 6 months		0.90 (0.51-1.58)	92%, p < 0.01		**0.87 (0.82-0.93)**	0%, p =0.75		0.54 (0.24-1.18)	100%, p < 0.01
≥ 6 months		0.90 (0.52-1.55)	93%, p < 0.01		**0.86 (0.78-0.95)**	45%, p =0.07		0.52 (0.18-1.52)	100%, p < 0.01
Oral contraceptives									
Never	19	1.00		16	1.00		10	1.00	
Ever		1.06 (0.96-1.18)	88%, p < 0.01		***1.07 (1.00-1.14)***	48%, p =0.02		1.04 (0.82-1.33)	92%, p < 0.01
Cohort study									
Never	11	1.00		2	1.00		7	1.00	
Ever		**1.09 (1.01-1.17)**	62%, p < 0.01		1.10 (0.94-1.29)	47%, p =0.17		0.93 (0.84-1.02)	0%, p =0.60
Case-control study									
Never	8	1.00		14	1.00		3	1.00	
Ever		1.01 (0.82-1.26)	93%, p < 0.01		*1.06 (0.99-1.14)*	50%, p =0.02		**1.37 (1.06-1.78)**	78%, p =0.01
Duration of OC use									
Never	11	1.00		15	1.00		3	1.00	
< 5 years		**1.13 (1.04-1.23)**	53%, p =0.22		1.04 (0.96-1.12)	54%, p < 0.01		0.86 (0.65-1.12)	0%, p =0.94
≥ 5 years		**1.12 (1.05-1.20)**	31%, p =0.15		**1.10 (1.01-1.20)**	65%, p < 0.01		1.08 (0.76-1.52)	30%, p =0.24
Cohort study									
Never	4	1.00		2	1.00		2	1.00	
< 5 years		**1.11 (1.02-1.22)**	33%, p =0.21		0.96 (0.76-1.22)	36%, p =0.21		0.90 (0.53-1.55)	0%, p =0.78
≥ 5 years		**1.18 (1.09-1.27)**	47%, p =0.13		**1.31 (1.08-1.58)**	0%, p =0.49		0.86 (0.53-1.39)	0%, p =0.34
Case-control study									
Never	7	1.00		13	1.00		1	1.00	
< 5 years		***1.16 (1.00-1.34)***	64%, p =0.01		1.05 (0.97-1.14)	57%, p < 0.01		0.84 (0.61-1.15)	-
≥ 5 years		1.05 (0.96-1.14)	0%, p =0.58		*1.08 (0.99-1.17)*	65%, p < 0.01		1.27 (0.97-1.67)	-
Hormone replacement therapy*									
Combination HRT									
Never	17	1.00		19	1.00		6	1.00	
Ever		**1.38 (1.18-1.60)**	87%, p < 0.01		**1.18 (1.03-1.34)**	80%, p < 0.01		**1.50 (1.18-1.90)**	71%, p < 0.01
Cohort study									
Never	11	1.00		10	1.00		3	1.00	
Ever		**1.48 (1.19-1.84)**	88%, p < 0.01		1.20 (0.98-1.46)	87%, p < 0.01		**1.81 (1.33-2.44)**	5%, p =0.35
Case-control study									

Never	6	1.00		9	1.00		3	1.00	
Ever		**1.21 (1.03-1.43)**	69%, $p < 0.01$		1.16 (0.98-1.37)	60%, $p = 0.01$		1.36 (0.97-1.92)	86%, $p < 0.01$
Estrogen only HRT									
Never	13	1.00		16	1.00		1	1.00	
Ever		**1.17 (1.03-1.32)**	67%, $p < 0.01$		**1.07 (1.01-1.14)**	20%, $p = 0.22$		1.40 (0.53-3.69)	-
Cohort study									
Never	7	1.00		7	1.00		1	1.00	
Ever		**1.19 (1.02-1.39)**	29%, $p = 0.21$		**1.13 (1.06-1.21)**	0%, $p = 0.75$		1.40 (0.53-3.69)	-
Case-control study									
Never	6	1.00		9	1.00		0	-	-
Ever		1.14 (0.93-1.40)	82%, $p < 0.01$		1.01 (0.92-1.11)	34%, $p = 0.15$		-	-

*Corresponding variable was analysis only in postmenopausal women.

**Corresponding variable was analysis only in parous women.

Estimation of summary relative risk (RRs) are calculated by random effect model.

C. Publication date

As shown in Table 9, subgroup analysis by publication date was conducted. Most of the reproductive factors, which were collected for systematic review, were divided based on publication in 2010. For the analysis of the association between age at menarche and breast cancer of subgroup analysis by publication date after 2010, the '15-16 years' ***vs.*** '≤ 14 years' [reference] risks ratio was 0.94 (95% CI=0.90-0.98) and the category of '≥ 17years' ***vs.*** '≤ 14 years' [reference] risks ratio was 0.84 (95% CI=0.77-0.92). For the analysis of the association between age at menarche and breast cancer of subgroup analysis by publication date before 2010, the '15-16 years' ***vs.*** '≤ 14 years' [reference] risks ratio was 0.94 (95% CI=0.90-0.98) and the category of '≥ 17years' ***vs.*** '≤ 14 years' [reference] risks ratio was 0.85 (95% CI=0.79-0.91).

For the analysis of the association between age at menopause and breast cancer of subgroup analysis by publication date after 2010, the '48-52 years' ***vs.*** '< 48 years' [reference] risks ratio was 1.17 (95% CI=1.13-1.22) and the category of '≥ 53 years' ***vs.*** '< 48 years' [reference] risks ratio was 1.33 (95% CI=1.22-1.47). For the analysis of the association between age at menopause and breast cancer of subgroup analysis by publication date before 2010, the '48-52 years' ***vs.*** '< 48 years' [reference] risks ratio was 1.24 (95% CI=1.15-1.33) and the category of '≥ 53 years' ***vs.*** '< 48 years' [reference] risks ratio was 1.31 (95% CI=1.18-1.45).

For the analysis of the association between family history and breast cancer of subgroup analysis by publication date after 2010, the 'Yes' ***vs.*** 'No' [reference] risks ratio was 1.57 (95% CI=1.46-1.67). For the analysis of the association between family history and breast cancer of subgroup analysis by publication date before 2010, the 'Yes' ***vs.*** 'No' [reference] risks ratio was 1.58 (95% CI=1.40-1.78).

For the analysis of the association between parity and breast cancer of subgroup analysis by publication date after 2000, the 'Parous' ***vs.*** 'Nulliparous' [reference] risks ratio was 0.82 (95% CI=0.77-0.87). For the analysis of the association between

parity and breast cancer of subgroup analysis by publication date before 2000, the 'Parous' ***vs.*** 'Nulliparous' [reference] risks ratio was 0.77 (95% CI=0.60-1.00).

For the analysis of the association between number of childbirths and breast cancer of subgroup analysis by publication date after 2010, the '2 children' ***vs.*** '1 child' [reference] risks ratio was 0.93 (95% CI=0.89-0.97) and the category of '≥ 3 children' ***vs.*** '1 child' [reference] risks ratio was 0.80 (95% CI=0.72-0.89). For the analysis of the association between number of childbirths and breast cancer of subgroup analysis by publication date before 2010, the '2 children' ***vs.*** '1 child' [reference] risks ratio was 0.91 (95% CI=0.87-0.95) and the category of '≥ 3 children' ***vs.*** '1 child' [reference] risks ratio was 0.77 (95% CI=0.71-0.83).

For the analysis of the association between age at first full-term pregnancy and breast cancer of subgroup analysis by publication date after 2010, the '20-30 years' ***vs.*** '< 20 years' [reference] risks ratio was 1.12 (95% CI=1.07-1.18) and the category of '≥ 30 years' ***vs.*** '< 20 years' [reference] risks ratio was 1.24 (95% CI=1.12-1.37). For the analysis of the association between age at first full-term pregnancy and breast cancer of subgroup analysis by publication date before 2010, the '20-30 years' ***vs.*** '< 20 years' [reference] risks ratio was 1.08 (95% CI=1.02-1.15) and the category of '≥ 30 years' ***vs.*** '< 20 years' [reference] risks ratio was 1.34 (95% CI=1.25-1.44).

For the analysis of the association between duration of breastfeeding and breast cancer of subgroup analysis by publication date after 2010, the '< 6 months' ***vs.*** 'Never' [reference] risks ratio was 0.88 (95% CI=0.78-1.00) and the category of '≥ 6 months' ***vs.*** 'Never' [reference] risks ratio was 0.92 (95% CI=0.86-0.99). For the analysis of the association between duration of breastfeeding and breast cancer of subgroup analysis by publication date before 2010, the '< 6 months' ***vs.*** 'Never' [reference] risks ratio was 0.89 (95% CI=0.80-0.98) and the category of '≥ 6 months' ***vs.*** 'Never' [reference] risks ratio was 0.86 (95% CI=0.75-0.98).

For the analysis of the association between oral contraceptive use and breast cancer

of subgroup analysis by publication date before 2005, the 'Ever' ***vs.*** 'Never' [reference] risks ratio was 1.07 (95% CI=0.99-1.15) which was only marginally significant. For the analysis of the association between duration of oral contraceptive and breast cancer of subgroup analysis by publication date after 2005, the '< 5 years' ***vs.*** 'Never' [reference] risks ratio was 1.09 (95% CI=1.02-1.16) and the category of '≥ 5 years' ***vs.*** 'Never' [reference] risks ratio was 1.14 (95% CI=1.05-1.24).

For the analysis of the association between combination HRT use and breast cancer of subgroup analysis by publication date after 2010, the 'Ever' ***vs.*** 'Never' [reference] risks ratio was 1.13 (95% CI=1.15-1.49). For the analysis of the association between combination HRT use and breast cancer of subgroup analysis by publication date before 2010, the 'Ever' ***vs.*** 'Never' [reference] risks ratio was 1.20 (95% CI=1.04-1.38). For the analysis of the association between estrogen only HRT use and breast cancer of subgroup analysis by publication date before 2010, the 'Ever' ***vs.*** 'Never' [reference] risks ratio was 1.15 (95% CI=1.05-1.27) which was only significant (Table 9).

Table 9. Summary relative risks of breast cancer related to each reproductive factors in Global population of subgroup analysis by publication date

	Publication date 1			Publication date 2		
Reproductive factor	**Studies N**	**Summary RR (95% CI)[1]**	**Heterogeneity I^2 (%)**	**Studies N**	**Summary RR (95% CI)[1]**	**Heterogeneity I^2 (%)**
Age at menarche		**After 2010**			**Before 2010**	
≤ 14	23	1.00		19	1.00	
15-16		**0.94 (0.90-0.98)**	54%, $p < 0.01$		**0.94 (0.90-0.98)**	30%, $p = 0.11$
≥ 17		**0.84 (0.77-0.92)**	81%, $p < 0.01$		**0.85 (0.79-0.91)**	40%, $p = 0.04$
Age at menopause*		**After 2010**			**Before 2010**	
< 48	14	1.00		8	1.00	
48-52		**1.17 (1.13-1.22)**	13%, $p = 0.31$		**1.24 (1.15-1.33)**	0%, $p = 0.61$
≥ 53		**1.33 (1.21-1.47)**	60%, $p < 0.01$		**1.31 (1.18-1.45)**	16%, $p = 0.31$
Family history of BC		**After 2010**			**Before 2010**	
No	20	1.00		11	1.00	
Yes		**1.57 (1.46-1.67)**	71%, $p < 0.01$		**1.58 (1.40-1.78)**	88%, $p < 0.01$
Parity		**After 2000**			**Before 2000**	
Nulliparous	28	1.00		9	1.00	
Parous		**0.82 (0.77-0.87)**	83%, $p < 0.01$		***0.77 (0.60-1.00)***	89%, $p < 0.01$
Number of childbirths		**After 2010**			**Before 2010**	
1	19	1.00		18	1.00	
2		**0.93 (0.89-0.97)**	29%, $p = 0.12$		**0.91 (0.87-0.95)**	10%, $p = 0.34$
≥ 3		**0.80 (0.72-0.89)**	77%, $p < 0.01$		**0.77 (0.71-0.83)**	67%, $p < 0.01$
Age at first-full term pregnancy		**After 2010**			**Before 2010**	
< 20	19	1.00		29	1.00	
20-30		**1.12 (1.07-1.18)**	53%, $p < 0.01$		**1.08 (1.02-1.15)**	76%, $p < 0.01$
≥ 30		**1.24 (1.12-1.37)**	76%, $p < 0.01$		**1.34 (1.25-1.44)**	60%, $p < 0.01$
Duration of breastfeeding		**After 2010**			**Before 2010**	
Never	9	1.00		10	1.00	
< 6 months		***0.88 (0.78-1.00)***	84%, $p < 0.01$		**0.89 (0.80-0.98)**	71%, $p < 0.01$
≥ 6 months		**0.92 (0.86-0.99)**	64%, $p < 0.01$		**0.86 (0.75-0.98)**	78%, $p < 0.01$
Oral contraceptives		**After 2005**			**Before 2005**	
Never	26	1.00		15	1.00	
Ever		1.05 (0.97-1.14)	84%, $p < 0.01$		***1.07 (0.99-1.15)***	62%, $p < 0.01$
Duration of OC use		**After 2005**			**Before 2005**	
Never	14	1.00		14	1.00	
< 5 years		**1.09 (1.02-1.16)**	17%, $p = 0.26$		1.07 (0.98-1.16)	67%, $p < 0.01$
≥ 5 years		**1.14 (1.05-1.24)**	57%, $p < 0.01$		1.06 (0.97-1.16)	64%, $p < 0.01$
Hormone replacement therapy*						
Combination HRT		**After 2010**			**Before 2010**	
Never	21	1.00		17	1.00	
Ever		**1.31 (1.15-1.49)**	87%, $p < 0.01$		**1.20 (1.04-1.38)**	73%, $p < 0.01$
Estrogen only HRT		**After 2010**			**Before 2010**	
Never	16	1.00		14	1.00	
Ever		1.07 (0.98-1.17)	61%, $p < 0.01$		**1.15 (1.05-1.27)**	42%, $p = 0.05$

Abbreviation: OC; oral contraceptive, HRT; hormone replacement therapy

1. Estimation of summary relative risks (RRs) are calculated by random effect model.

*Corresponding variables are evaluated only in postmenopausal women.

IV. Discussion

1. Summary of the results

A. Korean meta-analysis: 1st objective

In the case of the Korean meta-analysis, we set the reference in the direction of larger than 1 to calculate the population attributable risk (PAF) later. Thus, we used different or reverse reproductive variables criteria in the Korean meta-analysis. As a result, we newly re-calculated the risk factor when we aggregated the Korean meta-analysis results and the global population meta-analysis. The reproductive variables which were parity, age at first full-term pregnancy (the category of '20-30' ***vs.*** '< 20' [reference]), duration of breastfeeding (the category of 'Never' ***vs.*** '≥ 6 months' [reference]) and oral contraceptives were not significant. However, the trend of the breast cancer and reproductive factors was the same as the global trend.

For the analysis of mortality and breast cancer, all reproductive factors were not significant due to the lack of raw data. Reproductive factors, which are age at menopause, duration of breastfeeding, and use of HRT, got the reverse results compared between Global trends. To make matter worse, the relation of the duration of breastfeeding and breast cancer study had only one paper.

For the subgroup analysis of the study design, the cohort design was reliable. The corresponding variables, which were age at menarche, age at menopause, parity, number of childbirths, age at first full-term pregnancy, breastfeeding, and use of HRT, had lower heterogeneity (approximately 10% or less). In the process of changing the risk reference, *Lee SY et al. (2003)* with an indicator of number of childbirths was excluded. During the calculation of the number of presented in paper, the calculated risk excluding the adjusting factors was too different to use in the meta analysis.

This research will be further used in the PAF project by calculating the representative exposure rate of Koreans according to each reproductive factors.

B. Global population meta-analysis: 2nd & 3rd objective

The trend of the results showed earlier menarche age, later menopause age, having a family history of breast cancer, later age of first-full term pregnancy, lower number of children, short breastfeeding duration, ever use of an oral contraceptives (OC) or HRT, and the longer use of HRT duration. For total estimation of Global population, reproductive factors except for the duration of breastfeeding and oral contraceptive use, were significant.

For the subgroup analysis by study design in Global population, the cohort study design was reliable for the results because of the lower heterogeneity than the case-control study design (Table 7).

For the subgroup analysis by the country (continent) in Global population, we analyzed the results based on Asian countries including Korea. The association between age at menarche and breast cancer, the risk of Asia was more protective than Europe and N/S America. The category of '15-16 years' ***vs.*** '≤ 14 years' [reference] had 0.89 (95% CI=0.76-1.03) risk ratio and the category of '≥ 17 years' ***vs.*** '≤ 14 years' [reference] had 0.78 (95% CI=0.63-0.96) risk ratio, which indicate that later the menarche is protective to the risk of breast cancer. The reason is that women of East Asian ancestry are reported to have a lower circulation level of sex steroid hormone, such as an estrogen, compared to their age matching those of European/Western women (10). The association between age at menopause and breast cancer, the risk of Asia was similar with N/S America. It can be interpreted that the pattern of Asia becomes similar to the pattern of the United States over time is the influx of the Western culture. If you look at the other papers published in Asia,

such as *Liu R. et al. (2019), Kawai M et al. (2010) or Shin AS. et al. (2011)*, has the risk above 1.72 in the menopause. The association between family history and breast cancer, the risk of Asia was the highest ('Yes' ***vs.*** 'No' [reference]: 2.42 (95% CI=1.64-3.57)). Also the association between parity and breast cancer, the risk of Asia was most protective ('Parous' ***vs.*** 'Nulliparous' [reference]: 0.72 (95% CI=10.55-0.93)). The association between age at first full-term pregnancy and breast cancer, the risk of Asia was the highest. Combination of HRT use was all significant in three continents and Asia had the highest risk of breast cancer. In the case of estrogen only HRT use, Asians are relatively less likely to use than Westerns, judging from the small number of papers. Comparing within the cohort study design, the risk of breast cancer in Europeans was higher than in N/S Americans (Table 8).

For the subgroup analysis by the publication date in Global population, most of the studies were divided in the publication of 2010. The three reproductive factors, which are under genetic control and are known as unmodifiable factors, such as 'age at menarche', 'age at menopause', and 'family history of BC', did not differ depending on the year of publication of the paper. Pregnancy/ parity variables, which act as a protective factor for breast cancer risk, tend to decrease as of 2000, which can be inferred that they reflect fewer children over the years (Publication date before 2000: 0.77 (95% CI=0.60-1.00), publication date after 2000: 0.82 (95% CI=0.77-0.87)). In the case of use of oral contraceptives, the meta-analysis before 2005 suggested that is has been used in the past. In the case of HRT use, the combination of HRT was more reliable risk than estrogen only HRT (11) (Table 9).

After interpreting the result of the subgroup analysis, it seems that the risk of breast cancer is different depending on the density of breast, the race/ethnicity and the type of breast cancer rather than the reproductive factors (12).

2. Biological plausible mechanism

Except for the genetic effects in the family history of breast cancer, the rest of the reproductive variables are affected by the female hormones, especially for estrogen and progesterone that remain in the human body. It was mentioned that the large number of undifferentiated cells in the breast might increase the breast cancer risk and that estrogen increases cell proliferation, which increases the mutation risk during DNA replications (13). As a result, because of early menarche, late menopause and using an OC or HRT, the estrogen might affect the DNA replication step and increase the chance of acquiring breast cancer. Among many of the reproductive variables, age at first-full term pregnancy and the number of childbirths are correlated. If parous women had a delivery, the protection of breast cancer works due to the pregnancy. Also, previous research found that the transient increase in risk shortly after birth was strongest after a late first birth. The differentiation of breast cells after first full-term births is assumed to develop breast tissue less vulnerable to cancer and thus result in a less pronounced or even no adverse effect of subsequent births (14). For breastfeeding, lactation inhibits ovulation and decreases the hormones effect on the breast cells. As a result, during the breastfeeding to children, breast cells were less exposed to hormones. Thus, the longer the duration of breastfeeding, the less exposed of hormones to the breast cells and the reduced chance of cell mutations (15).

In regard to the reason of different risk ratios of countries, the difference between breast density in ethnicity or many other types of hormone replacement for each country might be considered. Having a dense breast can increase the breast cancer risk as shown in the World Cancer Research Fund (WCRF) report. However, some research suggested that breast density is not a major cancer risk. Cancer risk for 40% of women with heterogeneously dense breasts is only about 1.2 times greater than

women with non-dense breasts, and the risk for 10% of women with extremely dense breasts is only about 2 times greater than women with none dense breasts. For the corresponding studies, the research proposed that breast density might depend on the race or where the population inhabits (16). Also, the type of HRT in Korea has only the combination of estrogen and progesterone, but in Europe the type of HRT varies. Therefore, the sub-analysis by country might be inconsistent because of the lack of studies in the Asian population and the type of hormone therapy in Western countries.

3. Limitations and strengths of our study

This study had several limitations. First, we only searched the literature of general breast cancer. Breast cancer can be categorized into many subtypes. For example, there have been many ongoing studies that are analyzed using hormone receptors such as the estrogen receptor (ER) and the progesterone receptor (PR). Second, there was a shortage of Korean and Asian population research because the exclusion type of study was a hospital-based case-control study.

There are the strengths of this studies. First, we re-evaluated the Korean representative meta-analysis by using the literature and the raw data analysis. Second, due to the additional cohort, the heterogeneity of each reproductive factors were reduced. Therefore, the quality of the study was upgraded.

V. Conclusion

This study summarized the modifiable factors and unmodifiable factors of breast cancer and confirmed the trend of the risk of breast cancer. In order to calculate the Korean PAF model, we conducted a Korean meta-analysis to produce the latest indicators. Furthermore, we confirmed the association between publication date and the biological age in each reproductive variable.

This study is based on the meta analysis, so it can produce high level evidence of the link between breast cancer and reproductive factors in the clinical trial. Furthermore, based on the above evidence, the medical staff can recommend women's life style, which are related to the modifiable factors. This results can also calculate Korean's population attributable risk fractions (PAF) and guess the contribution of reproductive factors to breast cancer and further produce the preventive indicators.

Supplementary table 1. Search strategies for each reproductive factor and breast cancer in PubMed

Reproductive factors	Reproductive factors key words	Cancer key words	Study design	Publication year
Age at menarche	Reproductive factor*[Text words] OR Risk factor*[Text words] OR "menarche"[Mesh terms] OR age at menarche[Text words] OR age of menarche[Text words]	"Breast neoplasms"[Mesh terms] OR Breast cancer*[Text words] OR Breast tumor*[Text words] OR Breast malignant neoplasm*[Text words]	"Cohort studies"[Mesh terms] OR Cohort*[Text words] OR "Case-Control Studies"[Mesh terms] OR Case-control*[Text words]	"1990/01/01"[Date-Publication] : "2020/04/30" [Date-Publication]
Age at menopause	Reproductive factor*[Text words] OR Risk factor*[Text words] OR "Menopause.Premature"[Mesh terms] OR age at menopause[Text words] OR age of menopause[Text words]	"Breast neoplasms"[Mesh terms] OR Breast cancer*[Text words] OR Breast tumor*[Text words] OR Breast malignant neoplasm*[Text words]	"Cohort studies"[Mesh terms] OR Cohort*[Text words] OR "Case-Control Studies"[Mesh terms] OR Case-control*[Text words]	"1990/01/01"[Date-Publication] : "2020/04/30"[Date-Publication]
Family history	Family history[Text words] OR first-degree relative[Text words] OR second-degree relatives[Text words] OR third-degree relatives[Text words]	"Breast neoplasms"[Mesh terms] OR Breast cancer*[Text words] OR Breast tumor*[Text words] OR Breast malignant neoplasm*[Text words]	"Cohort studies"[Mesh terms] OR Cohort*[Text words] OR "Case-Control Studies"[Mesh terms] OR Case-control*[Text words]	"1990/01/01"[Date-Publication] : "2020/04/30"[Date-Publication]
Breastfeeding/ Duration	"Breastfeeding"[Mesh terms] OR "Lactation"[Mesh terms] OR duration of breastfeeding[Text words] OR breastfeeding duration[Text words] OR period of breastfeeding[Text words]	"Breast neoplasms"[Mesh terms] OR Breast cancer*[Text words] OR Breast tumor*[Text words] OR Breast malignant neoplasm*[Text words]	"Cohort studies"[Mesh terms] OR Cohort*[Text words] OR "Case-Control Studies"[Mesh terms] OR Case-control*[Text words]	"1990/01/01"[Date-Publication] : "2020/04/30"[Date-Publication]
Parity/ age at first full-term pregnancy	"parity"[Mesh terms] OR nulliparous[Text words] OR "pregnancy"[Mesh terms] OR age at first full-term pregnancy[Text words] OR FTTP[Text words] OR age at first childbirth[Text words]	"Breast neoplasms"[Mesh terms] OR Breast cancer*[Text words] OR Breast tumor*[Text words] OR Breast malignant neoplasm*[Text words]	"Cohort studies"[Mesh terms] OR Cohort*[Text words] OR "Case-Control Studies"[Mesh terms] OR Case-control*[Text words]	"1990/01/01"[Date-Publication] : "2020/04/30"[Date-Publication]
Parity/ number of children	"parity"[Mesh terms] OR nulliparous[Text words] OR "pregnancy"[Mesh terms] OR number of children[Text words] OR number of live birth[Text words]	"Breast neoplasms"[Mesh terms] OR Breast cancer*[Text words] OR Breast tumor*[Text words] OR Breast malignant neoplasm*[Text words]	"Cohort studies"[Mesh terms] OR Cohort*[Text words] OR "Case-Control Studies"[Mesh terms] OR Case-control*[Text words]	"1990/01/01"[Date-Publication] : "2020/04/30"[Date-Publication]

Oral contraceptives	Oral contraceptive*[Text word] OR Oral contraceptive Agent*[Text word] OR oral contraceptive pill*[Text word] OR combined oral contraceptive*[Text word]	"Breast neoplasms"[Mesh terms] OR Breast cancer*[Text words] OR Breast tumor*[Text words] OR Breast malignant neoplasm*[Text words]	"Cohort studies"[Mesh terms] OR Cohort*[Text words] OR "Case-Control Studies"[Mesh terms] OR Case-control*[Text words]	"1990/01/01"[Date-Publication] : "2020/04/30"[Date-Publication]
Hormone replacement therapy	"Hormone replacement therapy"[Mesh terms] OR HRT[Text words] OR MRT[Text words] OR Menopausal hormone therap*[Text words] OR Postmenopausal hormone therapy[Text words] OR replacement therap*[Text words] OR hormone therap*[Text words] OR estrogen replacement therapy[Text words] OR estrogen-progestin therapy[Text words]	"Breast neoplasms"[Mesh terms] OR Breast cancer*[Text words] OR Breast tumor*[Text words] OR Breast malignant neoplasm*[Text words]	"Cohort studies"[Mesh terms] OR Cohort*[Text words] OR "Case-Control Studies"[Mesh terms] OR Case-control*[Text words]	"1990/01/01"[Date-Publication] : "2020/04/30"[Date-Publication]

1. For Korean population research, we included extra key words in the search strategies. ("Korea"[Mesh terms] OR Korea*[All fields])
2. For other countries, which are East Asia (China, Japan), South/West Asia, North America (United States), Central/South America, Europe, Australia/New Zealand, and Africa, we use search strategies in corresponding table.

Supplementary table 2. Systematic review of association with age at menarche on breast cancer risk in Global population

Author (year)	Country	Study design	Study period	Category of reproductive factors	Control Cohort/PY	Cases	RR/OR/HR (95% CI)
Cohort studies							
Azam S. et al. (2020) (17)	Europe	Cohort	2011-2013	<13	14,666	174	1.00
				≥13	27,470	372	1.06 (0.88-1.27)
Peila R. et al. (2020)(18)	Europe	Cohort	2006-2010	≤11	50,854	175	1.00
				12-13	118,210	484	1.21 (1.01-1.43)
				≥14	93,708	357	1.12 (0.94-1.34)
Sandvei M. S. et al. (2019)(19)	Europe	Cohort	2006-2013	≤12	102,842	1,809	1.00
				13	95,616	1,570	0.92 (0.86-0.98)
				14	84,951	1,388	0.90 (0.84-0.96)
				≥15	63,210	1.027	0.90 (0.84-0.98)
Mullolly M. et al. (2017)(20)	United States	Cohort	1995-1996	≤12	ND	ND	1.00
				13-14	ND	ND	0.85 (0.62-1.16)
				≥15	ND	ND	0.94 (0.56-1.58)
Bertrand K.A. et al. (2017)(21)	United States	Cohort	1995	≤11	/300,514	553	1.30 (1.12-1.50)
				12-13	/546,800	965	1.22 (1.07-1.39)
				≥14	/198,945	308	1.00
Dartois et al. (2016)(22)	Europe	Cohort	1990-1993	<10	205	2	1.43 (0.35-5.81)
				10-12	12,758	98	1.26 (0.95-1.66)
				12-14	33,177	291	1.36 (1.09-1.70)
				≥14	17,859	106	1.00
Warner E.T. et al. (2013)(23)	United States	Cohort	1976 1989	<12	/507,748	732	1.10 (0.99-1.23)
				12	/636,302	849	1.00
				13	/622,504	839	0.92 (0.73-1.16)
				≥14	/391,196	487	0.87 (0.78-0.98)
Ritte R. et al. (2013)(24)	Europe	Cohort	1992-2000	<13	ND	1,749	1.00
				14	ND	2,198	0.96 (0.90-1.03)
				≥15	ND	574	0.78 (0.71-0.86)
Poynter J. N et al. (2013)(25)	United States	Cohort	1986-2008	≤12	/175,292	725	1.00
				>12	/232,907	855	0.90 (0.81-1.00)
Setiawan V.W. et al. (2009)(26)	United States	Cohort	1993-1996	≤12	42,213	1,700	1.00*
				13-14	32,082	1,242	0.96 (0.85-1.09)
				≥15	10,132	328	0.80 (0.64-1.00)
Lacey J.V. et al. (2009)(27)	United States	Cohort	1993-2001	<12	/76,987	457	1.00
				12-13	/209,082	1,099	0.86 (0.77-0.97)
				14-15	/84,595	439	0.85 (0.74-0.97)
				≥16	/17,874	88	0.81 (0.65-1.02)
Henderson K.D. et al. (2008)(28)	United States	Cohort	1993-1996	<11	ND	ND	1.00
				11-12	ND	ND	0.96 (0.92-0.99)
				13-14	ND	ND	0.95 (0.91-0.98)
				15-16	ND	ND	0.93 (0.89-0.97)
				≥17	ND	ND	0.92 (0.86-0.99)
Heuch I. et al. (2008)(29)	Europe	Cohort	1956-1959	≤12	ND	42	1.06 (0.75-1.50)
				13	ND	82	1.15 (0.87-1.52)
				14	ND	131	1.00
				15	ND	102	1.08 (0.83-1.40)
				≥16	ND	73	1.02 (0.77-1.36)
Li C.I. et al. (2007)(30)	United States	Cohort	2000-2002	≤11	ND	136	1.40 (1.10-1.70)
				12	ND	167	1.10 (0.90-1.40)
				13	ND	165	1.10 (0.90-1.40)
				≥14	ND	117	1.00
Ha M. et al. (2007)(31)	United States	Cohort	1983-1998	≤11	/113,250	165	1.00
				12	/154,745	243	1.15 (0.94-1.40)
				13	/172,570	268	1.12 (0.92-1.36)
				≥14	/120,264	202	1.09 (0.89-1.34)
Stahlberg C et al. (2005)(32)	Europe	Cohort	1993-1999	≤12	2,039	51	1.00
				>12	8,555	188	0.85 (0.62-1.16)

Liu R. et al. (2019) (33)	Asia (Japan)	Cohort	1984-1992 1985-2000	≤13	/73,925	75	1.00
				14	/69,044	57	0.84 (0.59-1.18)
				15	/68,959	71	1.06 (0.76-1.47)
				≥16	/91,023	59	0.69 (0.48-0.99)
Sepandi M. et al. (2014)(34)	Asia	Cohort	2004-2012	<12	896	33	1.00
				12-15	10,028	155	0.34 (0.21-0.55)
				>15	729	9	0.40 (0.16-0.95)
Kawai M et al. (2010)(35)	Asia (Japan)	Cohort	1990-2003	≤13	/66,211	69	1.00
				14	/64,547	66	1.02 (0.73-1.43)
				15	/58,406	58	1.03 (0.72-1.48)
				≥16	/73,495	56	0.89 (0.61-1.32)
Iwasaki M. et al. (2007)(36)	Asia (Japan)	Cohort	1990-1993	<14	/145,749	134	1.00
				14	/129,722	111	0.92 (0.71-1.18)
				15	/116,264	87	0.79 (0.60-1.05)
				≥16	/155,064	96	0.69 (0.51-0.93)
Tamakoshi K. et al. (2005)(37)	Asia (Japan)	Cohort	1988-1997	≤12	/17,524	9	1.00
				13-14	/99,163	51	1.05 (0.51-2.15)
				15-16	/102,068	51	1.15 (0.55-2.41)
				≥17	/50,030	23	1.27 (0.56-2.85)
Yoo T.K. et al. (2020)(38)	Korea	Cohort	2009-2014	<14	ND	ND	1.25 (1.21-1.29)
				≥14	ND	ND	1.28 (1.15-1.42)
Lee SY et al. (2003)(39)	Korea	Cohort	1992-2000	<14	465,340	264	1.00
				≥14	117,012	96	0.80 (0.70-1.00)
Shin AS et al. (2011)(40)	Korea	Cohort	1993-2004	≤14	93,321	819	1.52 (1.36-1.70)
				15-16	187,703	1,272	1.24 (1.13-1.36)
				≥17	162,885	762	1.00
Case-control studies							
Figueroa J.D. et al. (2020)(41)	Europe	PCCS	2013-2015	<15	568	266	1.00
				15	548	255	0.88 (0.70-1.10)
				16	383	223	1.13 (0.89-1.44)
				≥17	395	228	1.08 (0.85-1.37)
Hamdi-Cherif M. et al. (2020)(42)	Africa	PCCS	2012-2017	<13	225	213	1.00
				13-14	276	271	1.06 (0.82-1.37)
				≥15	103	115	1.20 (0.56-1.66)
Bravi F. et al. (2018)(43)	Europe	NCCS	2003-2007	≤11	2,355	827	1.00
				12-13	4,750	1,641	1.00 (0.90-1.10)
				≥14	2,552	755	0.88 (0.78-0.98)
Al-Ajmi K. et al. (2018)(4)	Europe	PCCS	2006-2010	>13	20,785	198	1.00
				≥13	24,501	407	1.23 (1.04-1.45)
Banegas M.P. et al. (2017)(44)	United States	PCCS	1995-2002	<12	140	186	1.68 (1.26-2.25)
				12-13	248	391	1.30 (1.12-1.50)
				≥14	165	370	1.00
Ellingjord-Dale M. et al. (2017)(45)	Europe	NCCS	2006-2014	9-12	7,615	1,681	1.00
				13	7,157	1,471	0.93 (0.86-1.01)
				14	6,439	1,265	0.89 (0.82-0.97)
				15-18	4,721	935	0.90 (0.82-0.98)
Veisy A. et al. (2015)(46)	Europe	PCCS	1983-1984	<13	247	307	1.00
				13	292	374	1.05 (0.84-1.32)
				14	346	389	0.90 (0.71-1.12)
				15	217	197	0.73 (0.57-0.95)
				≥16	175	161	0.75 (0.57-0.98)
Sisti J.S. et al. (2015)(47)	United States	PCCS	1985-2009	≤11	305	437	1.00
				12	419	528	1.16 (0.93-1.44)
				13	404	589	0.96 (0.77-1.19)
				≥14	387	650	0.82 (0.65-1.03)
Warren Anderson S. et al. (2013)(23)	United States	PCCS	1995-2000	<12	355	317	1.00
				12-13	668	799	0.96 (0.79-1.17)
				≥14	374	350	0.75 (0.60-0.94)
Barnes B.B et al. (2011)(48)	Europe	PCCS	2001-2005	<12	259	512	1.16 (0.97-1.39)
				12-14	1,996	4,050	1.11 (1.00-1.23)
				≥15	819	1,824	1.00

Hines L.M. et al. (2010)(49)	United States	PCCS	2000-2005	≤11	138	160	1.38 (1.02-1.88)
				12-13	416	476	1.39 (1.10-1.76)
				≥14	262	180	1.00
Phillips L.S. et al. (2009)(50)	United States	PCCS	1993-2001	<11	393	503	1.00**
				12	549	647	0.93 (0.78-1.11)
				13	562	589	0.80 (0.63-1.01)
				≥14	510	512	0.80 (0.60-1.06)
Sprague B.L. et al. (2008)(51)	United States	PCCS	1996-2000	<12	863	770	1.37 (1.15-1.63)
				12	924	822	1.33 (1.12-1.58)
				13-14	1,820	1,480	1.20 (1.02-1.40)
				≥15	531	355	1.00
Li C.I. et al. (2008)(30)	United States	PCCS	1994-1998	<12	1,108	1,184	1.00
				13-14	757	740	0.92 (0.74-1.13)
				≥15	174	160	0.90 (0.71-1.14)
Shantakumar S. et al. (2007)(52)	United States	PCCS	1996-1997	<12	412	382	1.00
				12	390	412	1.10 (0.90-1.36)
				13	345	368	1.07 (0.84-1.37)
				≥14	340	304	0.94 (0.76-1.17)
Li C.I. et al. (2003)(53)	United States	PCCS	1997-1999	8-11	173	182	1.00
				12-13	520	525	1.00 (0.80-1.20)
				≥14	313	261	0.80 (0.60-1.00)
Mangusson C.M. et al. (1999)(54)	Europe	PCCS	1993-1995	≤11	156	199	1.33 (1.06-1.67)
				12	445	429	1.00 (0.86-1.17)
				13-14	1,627	1,484	1.00
				15-16	609	551	1.00 (0.87-1.15)
				≥17	99	68	0.74 (0.54-1.03)
Rockhill B. et al. (1998)(55)	United States	PCCS	1993-1996	<12	81	108	1.24 (0.83-1.86)
				12-13	260	294	1.08 (0.78-1.49)
				≥14	104	111	1.00
Rockhill B. et al. (1998)(56)	United States	PCCS	1993-1996	<11	51	62	1.40 (0.90-2.10)
				11	107	131	1.30 (1.00-1.90)
				12	205	229	1.20 (0.90-1.60)
				13	196	225	1.30 (1.00-1.70)
				≥14	199	183	1.00
McCredie M. et al. (1998)(57)	New Zealand	PCCS	1983-1987	<12	289	154	1.00
				12	388	185	0.93 (0.70-1.20)
				13	549	243	0.80 (0.61-1.00)
				14	332	161	0.80 (0.59-1.10)
				≥15	302	146	0.79 (0.59-1.10)
Bouchardy C. et al. (1990)(58)	Europe	PCCS	1976-1980	<12	208	121	1.30 (0.90-1.90)
				12	364	194	1.20 (0.90-1.70)
				13	479	282	1.30 (1.00-1.80)
				14	474	236	1.10 (0.80-1.50)
				15	212	83	0.90 (0.60-1.30)
				≥16	189	85	1.00
Ewertz M. et al. (1988)(59)	Europe	PCCS	1983-1984	<13	247	307	1.00
				13	292	374	1.05 (0.84-1.32)
				14	346	389	0.90 (0.71-1.12)
				15	217	197	0.73 (0.57-0.95)
				≥16	175	161	0.75 (0.57-0.98)
Bergkvist L. et al. (1988)(60)	Europe	NCCS	1977-1980	≤11	43	25	1.20 (0.70-2.30)
				12	146	88	1.20 (0.70-1.90)
				13	220	175	1.50 (1.00-2.40)
				14	269	184	1.30 (0.90-2.10)
				15	125	96	1.50 (0.90-2.40)
				≥16	81	41	1.00
Brignone G. et al. (1987)(61)	Europe	PCCS	1972-1983	<11	27	29	1.00**
				11-15	777	780	0.95 (0.55-1.64)
				>15	45	44	0.78 (0.21-2.92)
Bruzzi P. et al. (1985)(62)	United States	PCCS	1973-1977	<12	138	175	1.00*
				12-13	521	515	0.78 (0.58-1.05)

				≥14	289	258	0.70 (0.50-1.00)
Wang J.M. et al. (2020)	Asia (China)	PCCS	2012-2017	≤13	1,505	1,291	1.00
				14	931	784	0.91 (0.82-1.01)
				≥15	1,746	1,722	0.98 (0.90-1.06)
Gao Y.T. et al. (2000)(63)	Asia (China)	PCCS	1996-1998	≤12	133	139	1.00
				13	281	323	1.20 (0.90-1.60)
				14	337	309	0.90 (0.70-1.20)
				15	305	304	1.00 (0.70-1.30)
				16	276	231	0.80 (0.60-1.10)
				≥17	224	153	0.70 (0.50-0.90)
Park BY et al. (2018)(64)	Korea	PCCS	2007-2015	≤13	470	163	1.00
				14-16	3,258	871	0.77 (0.62-0.96)
				≥17	2,113	454	0.62 (0.48-0.80)

Abbreviation: PCCS; Population-based case-control study, NCCS; Nested case-control study, SeBCS; Seoul Breast Cancer Society, KBCS; Korean Breast Cancer Study, KMCC; Korean Multi-center cancer cohort

*Calculated RR; Calculation of crude RR (95% CI) by the population of each data set.

**Summary RR; Recalculation of adjusted RR (95% CI) by the meta-analysis.

Supplementary table 3. Systematic review of association with age at menopause on breast cancer risk in postmenopausal women in Global population

Author (year)	Country	Study design	Study period	Category of reproductive factors	Control Cohort/PY	Cases	RR/OR/HR (95% CI)
Cohort studies							
Peila R. et al. (2020)(18)	Europe	Cohort	2006-2010	≤44	/27,192	94	1.00
				45-54	/35,391	540	1.10 (0.89-1.37)
				≥55	/22,215	100	1.20 (0.90-1.59)
Xu X. et al. (2020) (65)	Australia	Cohort	1996-2016	≤40	35	84	1.98 (1.31-2.98)
				41-45	190	266	1.15 (0.92-1.42)
				46-49	313	427	1.11 (0.92-1.34)
				50-51	545	662	1.00
				52-53	483	526	0.89 (0.75-1.05)
				≥54	727	849	0.95 (0.82-1.11)
Sandvei M. S. et al. (2019)(19)	Europe	Cohort	2006-2013	≤45	ND	316	0.99 (0.87-1.12)
				46-48	ND	359	0.92 (0.81-1.04)
				49-51	ND	865	1.00
				52-54	ND	647	1.12 (1.01-1.24)
				≥55	ND	341	1.22 (1.07-1.39)
Mullolly M. et al. (2017)(20)	United States	Cohort	1995-1996	<45	ND	ND	0.71 (0.37-1.34)
				45-49	ND	ND	0.61 (0.39-0.96)
				50-54	ND	ND	1.00
				≥55	ND	ND	0.70 (0.37-1.33)
Tamimi et al. (2016)(66)	United States	Cohort	1980	<45	ND	ND	1.00
				45-52	ND	ND	1.24 (1.17-1.32)
				≥52	ND	ND	1.43 (1.34-1.53)
Dartois et al. (2016)(22)	Europe	Cohort	1990-1993	<48	10,426	489	1.00
				48-50	10,275	548	1.09 (0.97-1.23)
				50-52	18,587	993	1.11 (1.00-1.24)
				52-54	13,251	623	1.03 (0.92-1.16)
				≥54	9,673	485	1.17 (1.03-1.34)
Poynter J. N et al. (2013) (25)	United States	Cohort	1986-2008	<50	/215,226	778	1.00
				≥50	/197,407	815	1.15 (1.04-1.27)
Horn L. et al. (2013)(67)	Europe	Cohort	1961-1980	<45	28,642	26	1.00
				45-49	65,173	84	1.26 (0.80-1.98)
				50-54	60,909	90	1.38 (0.87-2.19
				≥55	3,617	8	2.16 (0.95-4.89)
Lacey J.V. et al.(2009)(27)	United States	Cohort	1993-2001	<45	/25,254	123	1.00
				45-49	/64,113	340	1.07 (0.87-1.31)
				50-54	/126,080	700	1.12 (0.92-1.35)
				≥55	/32,192	211	1.29 (1.03-1.62)
Heuch I. et al.(2008)(29)	Europe	Cohort	1956-1959	≤47	ND	57	1.00
				48-49	ND	33	1.05 (0.68-1.63)
				50-51	ND	58	1.47 (1.02-2.14)
				≥52	ND	44	1.37 (0.92-2.06)
Chang-Claude et al. (2007)(68)	Europe	Cohort	1997-2002	Pre-meno	57,459	665	1.00
				<35	274	8	0.60 (0.25-1.44)
				35-44	525	36	1.02 (0.65-2.04)
				45-54	1,000	62	1.15 (0.65-1.60)
				>55	58	4	1.12 (0.25-5.02)
Stahlberg C. et al. (2004) (69)	Europe	Cohort	1996-2001	<44	1,334	25	1.00
				45-49	3,886	76	1.02 (0.65-1.61)
				50-54	4,368	102	1.16 (0.74-1.82)
				≥55	514	19	1.70 (0.92-3.14)
Liu R. et al. (2019) (33)	Asia (Japan)	Cohort	1984-1992 1985-2000	≤47	ND	42	1.00
				48-50	ND	34	1.18 (0.79-1.77)
				51-53	ND	53	1.14 (0.72-1.81)
				≥54	ND	45	1.72 (0.98-3.02)
Kawai M et al. (2010) (35)	Asia (Japan)	Cohort	1990-2003	≤47	/22,914	10	1.00
				48-50	/40,518	28	1.40 (0.67-2.93)
				51-53	/29,193	31	2.46 (1.19-5.08)
				≥54	/8,939	8	1.96 (0.73-5.27)
Shin AS et al.(2011)(40)	Korea	Cohort	1993-2004	<45	23,311	69	1.00
				45-49	59,556	239	1.27 (1.22-2.05)
				50-54	79,872	404	1.58 (1.22-2.05)
				≥55	16,952	83	1.80 (1.31-2.49)
Case-control studies							

Hamdi-Cherif M. et al.(2020)(42)	Africa	PCCS	2012-2017	<46	83	135	1.00
				≥46	148	144	0.75 (0.51-1.11)
Ellingjord-Dale M. et al. (2017)(45)	Europe	NCCS	2006-2014	<47	4,595	817	1.00
				47-49	4,324	827	1.10 (0.99-1.22)
				50-52	8,218	1,613	1.13 (1.03-1.24)
				>52	5,508	1,155	1.15 (1.04-1.28)
Veisy A. et al.(2015)(46)	Europe	PCCS	1983-1984	<45	77	56	1.00
				45	194	185	1.30 (0.87-1.96)
				50	252	297	1.60 (1.08-2.38)
				≥55	41	57	1.67 (0.98-2.87)
Warren Anderson S. et al.(2013) (70)	United States	PCCS	1995-2000	<45	130	123	1.00
				45-49	173	171	1.04 (0.75-1.44)
				50-54	220	255	1.22 (0.89-1.66)
				≥55	59	91	1.60 (1.05-2.43)
Pfeiffer R.M. et al. (2013) (71)	United States	PCCS	1993-2001	<50	/459	2,850	1.00
				50-54	/388	4,069	1.18 (1.14-1.22)
				≥55	/570	876	-
Barnes B.B et al. (2011) (48)	Europe	PCCS	2001-2005	<45	727	300	1.00
				45-49	1,672	760	1.12 (0.95-1.33)
				50-54	1,992	1,013	1.28 (1.09-1.51)
				≥55	492	263	1.32 (1.07-1.64)
Hines L.M. et al. (2010) (49)	United States	PCCS	2000-2005	<50	1,124	913	1.00
				≥50	564	533	1.16 (0.98-1.38)
Berstad P. et al. (2010) (72)	United States	PCCS	1994-1998	<35	180	117	1.00*
				35-39	225	147	1.01 (0.66-1.53)
				40-44	369	288	1.20 (0.85-1.69)
Phillips L.S. et al. (2009) (50)	United States	PCCS	1993-2001	<40	280	232	0.66 (0.54-0.82)
				40-49	511	578	1.00**
				>50	317	401	1.09 (0.79-1.51)
Sprague B.L. et al. (2008) (51)	United States	PCCS	1997-2001	<45	1,176	780	1.00
				45-49	966	783	1.22 (1.06-1.40)
				50-54	1,279	1,124	1.25 (1.09-1.42)
				≥55	415	409	1.40 (1.18-1.68)
Shantakumar S. et al. (2007)(52)	United States	PCCS	1996-1997	<48	306	305	1.00**
				48-51	278	308	1.16 (0.86-1.56)
				≥52	246	260	1.06 (0.82-1.39)
Nelson D.A. et al. (2004) (73)	United States	PCCS	ND	<45	ND	ND	1.00
				45-49	ND	ND	1.40 (0.69-2.84)
				50-54	ND	ND	1.10 (0.57-2.12)
				≥55	ND	ND	2.70 (1.00-7.26)
Li C.I. et al. (2003)(53)	United States	PCCS	1997-1999	≤44	171	117	1.00
				45-49	191	187	1.50 (1.10-2.00)
				50-54	239	232	1.40 (1.00-1.90)
				≥55	98	92	1.50 (1.00-2.20)
Park BY et al.(2018)(64)	Korea	PCCS	2007-2015	Pre-meno	1,613	369	-
				<45	336	76	1.00
				45-54	3,316	868	1.16 (1.07-1.25)
				≥55	408	109	1.18 (0.78-1.49)

Abbreviation: PCCS; Population-based case-control study, NCCS; Nested case-control study, SeBCS; Seoul Breast Cancer Society, KBCS; Korean Breast Cancer Study, KMCC; Korean Multi-center cancer cohort

*Calculated RR; Calculation of crude RR (95% CI) by the population of each data set.

**Summary RR; Recalculation of adjusted RR (95% CI) by the meta-analysis.

Supplementary table 4. Systematic review of association with family history on breast cancer risk in Global population

Author (year)	Country	Study design	Study period	Category of reproductive factors	Control Cohort/PY	Cases	RR/OR/HR (95% CI)
Cohort studies							
Peila R. et al. (2020)(18)	Europe	Cohort	2006-2010	No	ND	ND	1.00
				Yes	ND	ND	1.63 (1.46-1.81)
Zhang D. et al. (2019)(74)	United States	Cohort	2003-2009	1st degree	/282,615	1,810	1.00
				2nd degree	/89,425.3	849	1.45 (1.34-1.58)
				3rd degree	/11,968.1	150	1.86 (1.58-2.20)
Mullolly M. et al. (2017)(20)	United States	Cohort	1995-1996	No	ND	ND	1.00
				Yes	ND	ND	1.63 (1.42-1.86)
Miller M.E. et al. (2017)(75)	United States	Cohort	1978-2011	No	1,661	271	1.00
				Yes	1,056	184	1.11 (0.78-1.57)
Tamimi et al. (2016)(66)	United States	Cohort	1980	No	ND	ND	1.00
				Yes	ND	ND	1.50 (1.42-1.51)
Dartois et al. (2016)(22)	Europe	Cohort	1990-1993	No	49,746	386	1.00
				Yes	4,587	46	1.37 (1.01-1.86)
Boggs D.A. et al. (2015)(76)	United States	Cohort	1995	No	/362,263	598	1.00
				Yes			
				1st degree	/43,709	153	1.85 (1.27-2.69)**
				2nd degree	/66,008	145	1.35 (1.12-2.08)
Beebe-Dimmer J.L. et al. (2015)(77)	United States	Cohort	1993-1998	No	63,776	2,787	1.00
				Yes			
				1st degree	9,796	636	1.42 (1.30-1.55)
				+2nd degree	1,093	83	1.66 (1.32-2.08)
Poynter J. N et al. (2013)(25)	United States	Cohort	1986-2008	No	/318,733	1,138	1.00
				Yes	/93,899	455	1.35 (1.21-1.51)
Welsh M.L. et al. (2009)(78)	United States	Cohort	2001-2005	No	44,421	558	1.00
				+1st degree	14,675	314	1.54 (1.34-1.77)
				1st only	8,355	181	1.52 (1.28-1.80)
				1st and 2nd	6,320	133	1.58 (1.30-1.90)
Lacey J.V. et al. (2009)(27)	United States	Cohort	1993-2001	No	/336,410	1,696	1.00
				Yes	/53,304	389	1.44 (1.29-1.60)
Granstorm C. et al. (2008)(79)	Europe	Cohort	1993-1995	No	ND	23,745	1.00
				1st degree**			1.75 (1.66-1.85)
				Mother	ND	2,222	1.64 (1.27-1.72)
				Sister	ND	1,276	1.77 (1.67-1.87)
Reinier K.S. et al. (2007)(80)	United States	Cohort	1996-2001	No	ND	ND	1.00
				Yes	ND	ND	1.48 (1.30-1.69)
Albrektsen G. et al (2006)(81)	Europe	Cohort	1955-1999	No	/18,446,000	6,549	1.00
				Yes	/927,000	828	2.14 (1.99-2.30)
				Mother only	/778,000	651	
				Sister	/149,000	177	
Liu R. et al. (2019) (33)	Asia (Japan)	Cohort	1984-1992 1985-2000	No	/323,338	280	1.00
				Yes (Mother)	/2,503	7	3.22 (1.52-6.84)
Kawai M. et al. (2010)(35)	Asia (Japan)	Cohort	1990-2003	No	/304,417	272	1.00
				Yes	/5,007	13	2.92 (1.67-5.10)
Case-control studies							
Hamdi-Cherif M. et al. (2020)(42)	Africa	PCCS	2012-2017	No	602	564	1.00
				Yes	13	48	4.15 (2.22-7.77)
Al-Ajmi K. et al. (2018)(4)	Europe	PCCS	2006-2010	No	51,547	520	1.00
				First degree	5,184	93	1.76 (1.41-2.19)
Baglia M.L. et al. (2018)(82)	United States	NCCS	1995-2013	No	729	365	1.00
				Yes	265	174	1.33 (1.05-1.69)

Engmann N.J. et al. (2017)(83)	United States	PCCS	1996-2015	No	40,020	4,181	1.00
				Yes	6,840	1,105	1.71 (1.59-1.84)
Banegas M.P. et al. (2017)(44)	United States	PCCS	1995-2002	No	396	445	1.00
				First degree	68	88	1.18 (0.83-1.68)
Masala G. et al. (2017)(84)	Europe	NCCS	1993-1998	No	583	699	1.00*
				Yes	52	72	0.87 (0.58-1.29)
Trentham-Dietz A. et al. (2014)(85)	United States	PCCS	1988-2008	No	24,285	18,737	1.00
				1st degree	3,255	4,145	1.61 (1.53-1.69)
				2nd degree	255	528	2.44 (2.10-2.84)
				+3rd degree	28	72	3.04 (1.97-4.69)
Petracci E. et al. (2011)(86)	Europe	PCCS	1991-1994	No	2,387	2,268	1.00
				+1st degree	117	255	2.35 (1.86-2.96)
Barnes B.B et al. (2011)(48)	Europe	PCCS	2002-2005	No	5,280	2,368	1.00
				Yes	746	534	1.49 (1.32-1.69)
Sprague B.L. et al. (2008)(51)	United States	PCCS	1997-2000	No	3,500	2,636	1.00
				Yes	585	746	1.66 (1.46-1.88)
Risendal B. et al. (2008)	United States	PCCS	1999-2002	No	2,106	1,793	1.00**
				Yes	346	164	1.70 (1.37-2.10)
Li C.I. et al. (2003)(53)	United States	PCCS	1997-1999	No	771	703	1.00*
				Yes	159	208	0.84 (0.59-1.19)
McCredie M. et al. (1997)(87)	Australia/ NZ	PCCS	1983-1987	No	1,563	645	1.00
				1st degree	86	101	2.60 (1.90-3.50)
				2nd degree	191	132	1.70 (1.30-2.20)
Siskind V. et al. (1989)(88)	Australia/ NZ	PCCS	1981-1985	No	942	347	1.00
				1st degree	66	54	2.20 (1.49-3.30)
				+2nd degree	83	58	1.90 (1.31-2.80)
McTiernan A. et al. (1986)(89)	United States	PCCS	1981-1982	No	786	789	1.00**
				Yes	67	63	0.96 (0.68-1.37)
Hislop T.G. et al. (1986)(90)	Canada	PCCS	1980-1982	No	501	449	1.00**
				Yes	39	63	1.81 (1.18-2.76)
Bain C. et al. (1980)(91)	United States	PCCS	1972-1976	No	ND	ND	1.00
				Mother	ND	106	1.80 (1.50-2.20)
				Sister	ND	65	2.50 (1.90-3.30)
				Either	ND	161	2.00 (1.70-2.40)
				Both	ND	10	5.60 (2.80-11.20)
Wang L. et al (2019)(92)	Asia (China)	PCCS	2008-2012	No	219	637	1.00
				Yes	9	19	3.25 (1.34-7.89)
Sanderson M. et al. (2001)(93)	Asia (China)	PCCS	1996-1998	No	1,459	1,333	1.00
				Yes	36	52	1.60 (1.00-2.40)

Abbreviation: PCCS; Population-based case-control study, NCCS; Nested case-control study, SeBCS; Seoul Breast Cancer Society, KBCS; Korean Breast Cancer Study, KMCC; Korean Multi-center cancer cohort, ND; No data

*Calculated RR; Calculated by the population of each data set.

**Summary RR; Recalculation of adjusted RR (95% CI) by the meta-analysis.

Supplementary table 5. Systematic review of association with parity on breast cancer risk in Global population

Author (year)	Country	Study design	Study period	Category of reproductive factors	Control Cohort/PY	Cases	RR/OR/HR (95% CI)
Cohort studies							
Fortner R.T. et al. (2019)(94)	United States	Cohort	1989-2013	Nulliparous	/742,502	1,498	1.00
				Parous	/4,540,107	10,954	0.84 (0.80-0.89)
Kullberg C. et al. (2017)(95)	Europe	Cohort	1991-1996	Nulliparous	1,896	132	1.00**
				Parous	11,973	743	0.88 (0.74-1.05)
Bertrand K.A. et al. (2017)(96)	United States	Cohort	1995-2013	Nulliparous	/248,039	431	1.00*
				Parous	/628,360	1,631	1.49 (1.30-1.71)
Horn J. et al. (2014)(97)	Europe	Cohort	1961-2008	Nulliparous	ND	154	1.00**
				Parous	ND	655	0.88 (0.54-1.42)
Warner E.T. et al. (2013)(23)	United States	Cohort	1976-1989	Nulliparous	/338,434	399	1.00**
				Parous	/1,882,333	2,382	0.91 (0.85-0.99)
Lacey J.V. et al. (2009)(27)	United States	Cohort	1993-2001	Nulliparous	/35,545	240	1.00**
				Parous	/353,497	1,842	0.72 (0.65-0.79)
Granstorm C. et al. (2009)(79)	Europe	Cohort	1993-1995	Nulliparous	/1,320,991	3,844	1.00*
				Parous	/9,745,986	23,399	0.83 (0.79-0.86)
Mellemkjaer L. et al. (2006)(98)	Europe	Cohort	1993-1997	Nulliparous	2,926	94	1.00**
				Parous	20,862	539	0.83 (0.62-1.11)
Clavel-Chapelon F. et al. (2002)(99)	Europe	Cohort	1988-1991 1992-1995	Nulliparous	/75,732	271	1.00**
				Parous	/503,793	1,177	0.71 (0.64-0.79)
de Vries E. et al. (2001)(100)	Europe	Cohort	1982-1985	Nulliparous	1,126	ND	1.00**
				Parous	7,575	ND	0.81 (0.74-0.89)
Mellemgaard A. et al. (1990)(101)	Europe	Cohort	1967-1984	Nulliparous	1,283	23	1.00*
				Parous	11,541	247	1.19 (0.74-1.93)
Wohlfahrt J. et al. (1999)(102)	United States	Cohort	1978-1994	Nulliparous	ND	ND	1.00**
				Parous	ND	ND	0.81 (0.71-0.92)
Liu R. et al. (2019)	Asia (Japan)	Cohort	1984-2000	Nulliparous	/38,122	47	1.00
				Parous	/283,679	239	0.72 (0.52-0.99)
Tamakochi K. et al. (2005)(37)	Asia (Japan)	Cohort	1988-1997	Nulliparous	/13,307	8	1.00
				Parous	/254,025	132	0.95 (0.38-2.32)
Gajalakshmi C.K et al. (1998)(103)	Asia (Japan)	Cohort	1960-1989	Nulliparous	/3,199	6	1.00**
				Parous	/13,993	32	1.82 (0.82-4.06)
Goodman M.T. et al. (1997)(104)	Asia (Japan)	Cohort	1979-1981	Nulliparous	/14,048	26	1.00
				Parous	/160,555	124	0.43 (0.28-0.65)
Case-control studies							
Hamdi-Cherif M. et al. (2020)(42)	Africa	PCCS	2012-2017	Nulliparous	86	106	1.00
				Parous	509	487	0.89 (0.72-1.09)
Figueroa J.D. et al. (2020)(41)	Europe	PCCS	2013-2015	Nulliparous	228	107	1.00
				Parous	1,870	1,015	0.85 (0.68-1.05)
Al-Ajmi K. et al. (2018)(4)	Europe	PCCS	2006-2010	Nulliparous	33,879	514	1.00**
				Parous	135,859	1,754	0.80 (0.72-0.88)
John E.M. et al (2018)(105)	United States	PCCS	1995-2002	Nulliparous	746	124	1.00**
				Parous	4,365	434	0.88 (0.66-1.19)
Ellingjord-Dale M. et al. (2017)(45)	Europe	NCCS	2006-2014	Nulliparous	2,144	586	1.00**
				Parous	23,590	4,766	0.72 (0.63-0.82)
Brinton L.A. et al. (2017)(106)	Africa	PCCS	2012	Nulliparous	232	111	1.00**
				Parous	1,921	1,085	0.85 (0.68-1.07)
O'Brien K.M. et	United	PCCS	2008-	Nulliparous	352	252	1.00**

al. (2015)(107)	States		2010	Parous	1,295	933	1.07 (0.92-1.24)
Work M.E. et al. (2014)(108)	United States	PCCS	1995-2004	Nulliparous	531	902	1.00**
				Parous	2,466	3,109	0.79 (0.71-0.89)
Li C.I. et al. (2013)(109)	United States	PCCS	2004-2010	Nulliparous	188	269	1.00**
				Parous	753	756	0.73 (0.60-0.88)
Barnes B.B. et al. (2011)(48)	Europe	PCCS	2002-2005	Nulliparous	1,007	525	1.00*
				Parous	5,379	2,549	0.91 (0.80-1.04)
Poynter J.N. et al. (2010)(110)	United States	PCCS	1985-1999	Nulliparous	225	133	1.00**
				Parous	1,171	572	0.79 (0.52-1.20)
Ma H. et al. (2010)(111)	United States	PCCS	1995-2007	Nulliparous	/92,927	493	1.00**
				Parous	/433,263	2,197	0.90 (0.84-0.96)
Sweeney C. et al. (2008)(112)	United States	PCCS	1999-2004	Nulliparous	312	337	1.00*
				Parous	2,117	1,804	0.79 (0.66-0.95)
Beaber E.F. et al. (2008)(113)	United States	PCCS	2000-2004	Nulliparous	36	143	1.00**
				Parous	433	901	0.50 (0.38-0.65)
Ursin G. et al. (2004)(114)	United States	PCCS	1994-1998	Nulliparous	481	588	1.00**
				Parous	3,865	3,680	0.73 (0.63-0.85)
Tavani A. et al. (1999)(115)	Europe	PCCS	1992-1995	Nulliparous	220	130	1.00**
				Parous	448	452	1.54 (1.25-1.91)
Mangusson C.M. et al. (1999)(54)	Europe	PCCS	1993-1995	Nulliparous	313	413	1.00**
				Parous	2,623	2,318	0.52 (0.39-0.69)
Wu A.H. et al. (1996)(116)	United States	PCCS	1983-1987	Nulliparous	94	91	1.00
				Parous	674	401	0.57 (0.41-0.80)
Mayberry R.M. et al. (1992)(117)	United States	PCCS	1980-1982	Nulliparous	558	327	1.00**
				Parous	3,828	4,097	0.65 (0.51-0.83)
Layde P.M. et al. (1989)(118)	United States	PCCS	1980-1982	Nulliparous	603	769	1.00**
				Parous	3,931	3,830	0.66 (0.56-0.78)
Wang J.M. et al. (2020)(119)	Asia (China)	PCCS	2012-2017	Nulliparous	109	86	1.00
				Parous	4,073	3,624	0.53 (0.43-0.65)

Abbreviation: PCCS; Population-based case-control study, NCCS; Nested case-control study, SeBCS; Seoul Breast Cancer Society, KBCS; Korean Breast Cancer Study, KMCC; Korean Multi-center cancer cohort

*Calculated RR; Calculation of crude RR (95% CI) by the population of each data set.

**Summary RR; Recalculation of adjusted RR (95% CI) by the meta-analysis.

Supplementary table 6. Systematic review of association with age at first-full term pregnancy on breast cancer risk in Global population

Author (year)	Country	Study design	Study period	Category of reproductive factors	Control Cohort/PY	Cases	RR/OR/HR (95% CI)
Cohort studies							
Kullberg C. et al.(2017)(95)	Europe	Cohort	1991-1996	<20	1,457	83	1.00*
				20-24	4,683	301	0.75 (0.53-1.08)
				25-29	4,056	240	1.04 (0.74-1.46)
				30-34	1,341	85	1.11 (0.68-1.80)
				≥35	1,896	33	0.30 (0.14-0.63)
Crandall CJ. et al. (2017)(120)	United States	Cohort	1993-2005	Never	11,886	ND	1.00
				<20	10,458	ND	0.86 (0.62-1.20)
				20-29	54,529	ND	0.87 (0.71-1.07)
				≥30	7,195	ND	1.08 (0.82-1.42)
Bertrand K.A. et al.(2017)(96)	United States	Cohort	1995-2013	<20	/190,355	483	1.00**
				20-24	/205,055	522	1.00 (0.88-1.14)
				≥25	/221,970	602	1.24 (0.99-1.54)
Horn J. et al. (2014)(97)	Europe	Cohort	1961-2008	<25	ND	241	1.00**
				≥25	ND	372	1.13 (0.94-1.36)
Warner E.T. et al.(2013)(23)	United States	Cohort	1976-1989	<25	/760,507	978	0.86 (0.78-0.94)
				25-29	/742,025	1,013	1.00**
				≥30	/379,668	493	1.14 (1.02-1.28)
Horn J. et al. (2013)(97)	Europe	Cohort	1961-1980	<20	/27,340	87	1.00**
				20-24	/193,249	668	1.05 (0.84-1.31)
				25-29	/204,217	806	1.19 (0.90-1.56)
				30-34	/89,688	412	1.39 (0.93-2.08)
				≥35	/35,131	195	1.59 (1.23-2.05)
Lacey J.V. et al. (2009)(27)	United States	Cohort	1993-2001	Nulliparous	/35,545	240	1.00
				<20	/62,165	267	0.68 (0.53-0.86)
				20-24	/181,709	901	0.74 (0.59-0.91)
				25-29	/80,523	471	0.83 (0.66-1.03)
				30-35	/20,822	148	1.03 (0.81-1.31)
				≥35	/6,894	47	1.02 (0.74-1.41)
Granstorm C. et al. (2008)(79)	Europe	Cohort	1993-1995	13-20	ND	4,371	0.78 (0.74-0.81)
				21-24	ND	7,501	0.80 (0.77-0.83)
				25-29	ND	7,454	0.86 (0.83-0.90)
				≥30	ND	3,713	1.00
Reinier K.S. et al. (2007)(80)	United States	Cohort	1996-2001	<21	4,526	ND	1.00
				21-30	11,686	ND	1.05 (0.86-1.27)
				>30	3,464	ND	1.44 (1.09-1.89)
				Nulliparous	4,512	ND	1.25 (0.92-1.71)
Li C.I. et al. (2007)(30)	United States	Cohort	2000-2002	≤19	4,990	86	1.00
				20-24	11,518	236	1.20 (1.00-1.50)
				25-29	5,419	116	1.30 (1.00-1.70)
				30-34	1,899	39	1.50 (1.00-2.10)
				≥35	586	17	2.10 (1.30-3.30)
				Nulliparous	3,484	91	1.70 (1.30-2.30)
Mellemkjaer L. et al. (2006)(98)	Europe	Cohort	1993-1997	≤19	3,163	72	1.00*
				20-24	9,929	243	1.12 (0.93-1.35)
				25-29	5,963	166	1.21 (0.98-1.49)
				30-34	1,420	46	1.50 (1.00-2.10)
				≥35	386	12	2.10 (1.30-3.30)
Clavel-Chapelon F. et al. (2002)(99)	Europe	Cohort	1988-1991	<22	/94,468	232	1.00
				22-24	/171,850	461	1.07 (0.91-1.25)
			1992-1995	25-27	/129,234	382	1.16 (0.98-1.38)
				28-30	/62,741	201	1.25 (1.03-1.52)
				≥31	/45,500	171	1.46 (1.18-1.81)
Vatten L.J. et al. (1992)(121)	Europe	Cohort	1974-1978	<25	15,350	141	1.00
				25-29	8,270	111	1.17 (1.02-1.34)
				30-34	2,458	26	0.96 (0.76-1.22)
				≥35	900	16	1.20 (0.86-1.67)

Mellemgaard A. et al.(1990)(101)	Europe	Cohort	1967-1984	≤19	2,508	39	0.82 (0.58-1.12)
				20-24	6,452	109	0.87 (0.71-1.05)
				25-29	3,185	76	1.20 (0.94-1.50)
				≥30	956	23	1.20 (0.76-1.78)
Liu R. et al. (2019)(33)	Asia (Japan)	Cohort	1984-1992	≤21	/44,677	30	1.00
				22-25	/144,724	111	1.07 (0.71-1.61)
			1985-2000	26-29	/65,507	67	1.30 (0.83-2.04)
				≥30	/22,495	25	1.27 (0.73-2.21)
Kawai M et al. (2010)(35)	Asia (Japan)	Cohort	1990	≤21	/46,518	27	1.00
				22-25	/160,129	142	1.43 (0.94-2.16)
				26-29	/56,433	58	1.53 (0.96-2.44)
				≥30	/13,859	13	1.21 (0.61-2.44)
Tamakoshi K. et al. (2005)(37)	Asia (Japan)	Cohort	1988-1997	<25	/105,682	48	1.00
				25-30	/105,347	51	1.02 (0.67-1.56)
				30-35	/15,527	17	1.99 (1.09-3.66)
				>35	/3,228	4	2.12 (0.72-6.21)
Gajalakshmi C.K. et al. (1998)(103)	Asia	Cohort	1960-1989	<21	/6,448	11	1.00
				21-25	/3,660	15	2.80 (1.20-6.70)
				>25	/1,714	2	0.50 (0.10-2.60)
				Nulliparous	/3,199	6	0.50 (0.00-40.00)
Goodman M.T. et al. (1997)(104)	Asia (Japan)	Cohort	1979-1981	<21	/14,384	8	1.00
				21-23	/42,679	27	1.12 (0.51-2.40)
				24-26	/46,639	44	1.82 (0.84-3.91)
				27-29	/20,593	12	1.14 (0.46-2.83)
				≥30	/12,228	13	1.89 (0.78-4.60)
Lee SY et al. (2003)(39)	Korea	Cohort	1992-2000	<26	/99,968	55	1.00
				26-28	/312,409	170	1.20 (0.80-1.60)
				≥29	/169,975	135	1.60 (1.10-2.20)
Case-controls studies							
Figueroa J.D. et al. (2020)(41)	Europe	PCCS	2013-2015	<19	555	235	1.00
				19-21	510	265	1.14 (0.90-1.43)
				22-25	412	260	1.27 (1.00-1.62)
				≥26	322	197	1.18 (0.91-1.54)
Troisi R. et al. (2018)(122)	Europe	PCCS	1967-2013	<20	54,485	4,588	0.83 (0.80-0.86)
				20-29	477,222	48,678	1.00
				30-39	157,058	19,564	1.22 (1.19-1.24)
				≥40	8,259	1,074	1.26 (1.18-1.34)
Ma H. et al. (2017)(123)	United States	PCCS	1998-2003	≤20	799	1,392	1.00**
				21-24	510	487	1.14 (0.98-1.32)
				25-29	348	449	1.30 (1.03-1.64)
				≥30	333	442	1.03 (0.85-1.25)
Engmann N.J. et al. (2017)(83)	United States	PCCS	1996-2015	Nulliparous	11,729	1,240	1.14 (1.05-1.22)
				≤30	29,060	2,615	1.00
				>30	12,071	1,431	1.28 (1.19-1.37)
Banegas M.P. et al. (2017)(44)	United States	PCCS	1995-2002	<20	134	124	1.00
				20-29	242	280	1.26 (1.05-1.52)
				≥30	88	129	1.59 (1.10-2.31)
Hajiebrahimi M. et al.(2016)(124)	Europe	NCCS	1973-2010	<25	827	797	0.79 (0.70-0.90)
				25-29	2,591	2,618	0.89 (0.82-0.97)
				30-34	2,998	3,122	1.00
				35-39	1,575	1,540	1.05 (0.95-1.15)
				≥40	336	250	0.92 (0.76-1.10)
Sisti J.S. et al. (2015)(47)	United States	PCCS	1985-2009	<20	276	175	1.00
				20-24	667	444	1.19 (0.90-1.58)
				25-29	550	355	1.01 (0.75-1.35)
				≥30	317	234	1.20 (0.84-1.70)
O'Brien K.M. et al. (2015)(107)	United States	PCCS	2008-2010	<25	465	324	1.00
				25-29	456	393	1.28 (0.98-1.66)
				30-34	233	254	1.65 (1.20-2.28)
				≥35	100	86	1.22 (0.80-1.87)
Li C. et al.	United	PCCS	2004-	<20	82	59	1.56 (1.32-1.84)

(2013)(109)	States		2010	20-24	166	162	1.00**
				25-29	243	228	0.89 (0.58-1.37)
				30-34	181	204	0.65 (0.47-0.92)
				≥35	84	100	0.58 (0.40-0.84)
Ma H. et al. (2010)(111)	United States	PCCS	1995-2007	<21	/48,165	203	1.00
				21-24	/150,692	727	1.07 (0.92-1.25)
				25-29	/163,749	888	1.22 (1.05-1.43)
				30-34	/52,784	281	1.22 (1.01-1.47)
				≥35	/16,644	94	1.27 (0.99-1.65)
Sweeney C. et al.(2008)(112)	United States	PCCS	1999-2004	<20	240	179	1.00
				20-24	362	317	1.16 (0.90-1.51)
				25-29	167	135	1.15 (0.83-1.58)
				≥30	62	88	1.99 (1.32-3.00)
				Nulliparous	88	77	1.30 (0.88-1.92)
Sprague B.L. et al. (2008)(51)	United States	PCCS	1997-2000	<20	827	597	1.00
				20-24	2,010	1,568	1.02 (0.89-1.16)
				25-29	740	654	1.15 (0.98-1.36)
				≥30	202	236	1.42 (1.11-1.80)
Beaber E.F. et al. (2008)(113)	United States	PCCS	2000-2004	≤19	87	189	1.00**
				20-24	216	423	0.86 (0.69-1.08)
				25-29	100	191	0.89 (0.67-1.18)
				≥30	28	95	1.02 (0.84-2.39)
Ursin G. et al. (2004)(114)	United States	PCCS	1994-1998	≤19	1,493	1,044	1.00**
				20-24	1,460	1,367	1.04 (0.92-1.18)
				25-29	718	777	1.22 (0.98-1.53)
				≥30	497	492	1.15 (0.95-1.38)
Chie W.C. et al. (2000)(125)	United States	PCCS	1992-1995	<20	1,607	1,087	1.00
				20-24	4,969	3,741	1.00 (0.90-1.10)
				25-29	2,396	2,038	1.03 (0.90-1.18)
				30-34	523	530	1.16 (0.96-1.18)
				≥35	92	105	1.19 (0.86-1.66)
Newcomb P.A. et al. (1999) (126)	United States	PCCS	1992-1995	<20	655	468	1.00
				20-24	1,935	1,763	1.27 (1.10-1.47)
				25-29	891	972	1.45 (1.24-1.71)
				≥30	301	420	1.69 (1.38-2.08)
Mangusson C.M. et al. (1999)(54)	Europe	PCCS	1993-1995	<20	299	229	1.00
				20-24	1,138	906	1.01 (0.83-1.23)
				25-29	841	766	1.08 (0.88-1.33)
				30-34	258	295	1.37 (1.06-1.76)
				≥35	87	122	1.49 (1.06-2.11)
Rockhill B. et al. (1998)(55)	United States	PCCS	1993-1996	<20	94	95	1.00
				20-24	163	167	1.08 (0.74-1.56)
				25-29	97	99	1.02 (0.67-1.54)
				≥30	42	61	1.35 (0.81-2.25)
				Nulliparous	49	91	1.53 (0.96-2.46)
Lambe M. et al. (1998)(127)	Europe	NCCS	1943-1960	<20	953	162	1.00
				20-24	2,600	465	0.96 (0.79-1.18)
				25-29	1,675	358	1.12 (0.90-1.38)
				30-34	511	108	1.10 (0.83-1.45)
				≥35	149	37	1.42 (0.93-2.17)
Kroman N. et al. (1998)(128)	Europe	PCCS	1978-1994	Nulliparous	ND	ND	0.92 (0.80-1.06)
				<20	ND	ND	1.00
				20-24	ND	ND	0.87 (0.78-0.98
				25-29	ND	ND	0.79 (0.70-0.90)
				≥30	ND	ND	0.94 (0.80-1.11)
Enger S.M. et al. (1997)(129)	United States	PCCS	1987-1989	<20	141	146	1.00
				20-24	499	448	0.90 (0.68-1.19)
				25-29	236	248	1.03 (0.75-1.43)
				≥30	97	132	1.20 (0.81-1.77)
Wu A.H. et al. (1996)(116)	United States	PCCS	1983-1987	Nulliparous	94	91	1.00
				≤19	40	14	0.24 (0.12-0.50)
				20-24	227	112	0.44 (0.30-0.66)

				25-29	238	143	0.58 (0.40-0.84)
				30-34	117	70	0.58 (0.37-0.89)
				≥35	34	34	1.06 (0.59-1.90)
Alberktsen G. et al. (1995)(130)	Europe	PCCS	1960-1991	≤19	ND	ND	1.00
				20-24	ND	ND	1.05 (0.96-1.14)
				25-29	ND	ND	1.19 (1.06-1.34)
				≥30	ND	ND	1.26 (1.05-1.51)
Mayberry R.M. et al.(1992)(117)	United States	PCCS	1980-1982	<20	994	876	1.00**
				20-24	1,842	1,946	1.17 (1.09-1.24)
				25-29	775	917	1.35 (1.19-1.54)
				≥30	206	352	1.57 (1.30-1.90)
Lund E (1989) (131)	Europe	PCCS	1984-1985	<19	ND	ND	1.00
				20-24	ND	ND	1.10 (0.50-2.30)
				≥25	ND	ND	2.10 (1.00-4.40)
				Nulliparous	ND	ND	1.40 (0.60-3.30)
Siskind V. et al. (1989)	Australia	PCCS	1981-1985	<20	132	46	1.00
				20-24	517	196	1.07 (0.70-1.63)
				25-29	333	137	1.15 (0.74-1.79)
				30-34	76	62	2.30 (1.33-3.90)
				35-44	30	18	1.57 (0.73-3.40)
Layde P.M. et al. (1989)(118)	United States	PCCS	1980-1982	<18	342	268	1.00
				18-19	680	566	1.02 (0.83-1.24)
				20-21	845	766	1.01 (0.83-1.23)
				22-23	727	716	1.06 (0.87-1.30)
				24-25	353	574	1.09 (0.88-1.34)
				26-27	212	383	1.04 (0.83-1.31)
				28-29	94	245	1.20 (0.93-1.55)
				30-31	34	130	1.41 (1.02-1.94)
				32-34	82	130	1.51 (1.08-2.11)
				≥35	43	76	1.58 (1.03-2.42)
Ewertz M. et al. (1988)(59)	Europe	PCCS	1983-1984	<20	136	144	1.00
				20-24	565	538	0.92 (0.71-1.20)
				25-29	358	423	1.12 (0.85-1.48)
				30-34	114	125	1.04 (0.74-1.78)
				≥35	29	25	0.77 (0.43-1.39)
Brignone G. et al. (1987)(61)	Europe	PCCS	1974-1983	<20	103	70	1.00**
				20-24	312	226	1.02 (0.72-1.46)
				25-29	197	208	1.52 (1.06-2.17)
				>29	129	141	1.61 (1.09-2.38)
Wang J.M. et al. (2020)(119)	Asia (China)	PCCS	2012-	<25	1,987	1,809	1.00
				25-29	1,793	1,545	0.96 (0.85-1.10)
				≥30	293	270	0.96 (0.74-1.25)
Huang Z. et al. (2014)(132)	Asia (China)	PCCS	1996-1998 2002-2005	<25	1,246	1,067	1.00
				25-29	1,721	1,732	1.04 (0.92-1.17)
				30-34	326	400	1.22 (1.01-1.47)
				≥35	48	70	1.49 (1.00-2.20)
Liu Y.T. et al. (2011)(133)	Asia (China)	PCCS	2004-2007	≤25	530	454	1.00
				26-29	127	169	1.46 (1.10-1.94)
				≥30	18	30	1.68 (0.90-3.14)
				Nulliparous	7	16	2.61 (1.05-6.50)

Abbreviation: PCCS; Population-based case-control study, NCCS; Nested case-control study, SeBCS; Seoul Breast Cancer Society, KBCS; Korean Breast Cancer Study, KMCC; Korean Multi-center cancer cohort

*Calculated RR; Calculation of crude RR (95% CI) by the population of each data set.

**Summary RR; Recalculation of adjusted RR (95% CI) by the meta-analysis.

Supplementary table 7. Systematic review of association with number of childbirths among parous women on breast cancer risk in Global population

Author (year)	Country	Study design	Study period	Category of reproductive factors	Control Cohort/PY	Cases	RR/OR/HR (95% CI)
Cohort studies							
Kullberg C. et al. (2017)(95)	Europe	Cohort	1991-1996	Nulliparous	1,896	132	1.00*
				1	3,065	172	0.81 (0.57-1.14)
				2	5,802	393	0.97 (0.75-1.27)
				3	2,275	140	0.88 (0.61-1.29)
				≥4	831	38	0.66 (0.34-1.28)
Bertrand K.A. et al. (2017)(106)	United States	Cohort	1995-2013	Nulliparous	/248,039	431	1.04 (0.88-1.23)
				1	/217,057	525	1.00**
				2	/224,278	584	0.96 (0.85-1.09)
				≥3	/187,025	522	1.00 (0.70-1.44)
Tamimi et al. (2016)(66)	United States	Cohort	1980	Nulliparous	ND	ND	1.23 (1.12-1.35)
				<1	ND	ND	1.00
				1-4	ND	ND	1.13 (1.07-1.19)
				≥5	ND	ND	1.06 (0.96-1.18)
Palmer J.R. et al. (2014)(134)	United States	Cohort	1995-2001	1	2,948	844	1.00**
				2	3,541	1,113	1.13 (0.94-1.35)
				3	2,140	723	1.14 (1.01-1.28)
				≥4	2,842	900	1.11 (0.87-1.42)
Horn J. et al. (2014)(97)	Europe	Cohort	1961-2008	1	ND	124	1.00
				2	ND	159	0.76 (0.60-0.96)
				3	ND	122	0.73 (0.57-0.94)
				≥4	ND	101	0.53 (0.40-0.70)
Horn J. et al. (2013)(67)	Europe	Cohort	1961-1980	1	/233,128	529	1.00**
				2	/377,763	778	0.94 (0.84-1.05)
				3	/249,219	481	0.90 (0.79-1.02)
				4	/129,564	220	0.79 (0.66-0.95)
				≥5	/116,434	160	0.69 (0.57-0.82)
Lacey J.V. et al. (2009)(27)	United States	Cohort	1993-2001	0	/35,545	240	1.00
				1	/28,296	160	0.70 (0.55-0.89)
				2	/88,510	524	0.76 (0.62-0.92)
				3	/96,130	526	0.75 (0.62-0.91)
				4	/66,673	331	0.72 (0.59-0.88)
				≥5	/73,888	301	0.65 (0.53-0.80)
Granstorm C. et al. (2008)(79)	Europe	Cohort	1993-1995	0	/1,320,991	3,844	1.10 (1.04-1.16)
				1	/1,781,455	4,977	1.20 (1.16-1.25)
				2	/4,828,863	11,808	1.11 (1.08-1.15)
				≥3	/3,135,668	6,614	1.00
Mellemkjaer L. et al. (2006)(98)	Europe	Cohort	1993-1997	Nulliparous	2,926	94	1.00*
				1	3,632	126	1.08 (0.72-1.62)
				2-3	15,582	383	0.77 (0.57-1.02)
				≥4	1,648	30	0.57 (0.27-1.19)
Clavel-Chapelon F. et al. (2002)(99)	Europe	Cohort	1988-1991 1992-1995	0	/75,732	271	1.00
				1	/92,361	265	0.76 (0.61-0.95)
				2	/245,718	705	0.73 (0.60-0.89)
				3	/121,610	326	0.68 (0.55-0.83)
				≥4	/44,104	121	0.68 (0.53-0.87)
de Vries E. et al. (2001)(100)	Europe	Cohort	1982-1985	Nulliparous	1,126	ND	1.00
				1-2	3,961	ND	0.85 (0.78-0.93)
				≥3	3,614	ND	0.77 (0.70-0.85)
Mellemgaard A. et al. (1990)(101)	Europe	Cohort	1967-1984	0	1,283	23	0.96 (0.61-1.44)
				1	1,738	37	1.06 (0.75-1.46)
				2	3,991	78	1.02 (0.81-1.27)
				3	3,286	62	0.98 (0.75-1.26)
				4	2,024	38	0.96 (0.68-1.31)
				5	1,026	17	0.83 (0.49-1.34)
				≥6	1,036	15	0.70 (0.39-1.16)

Liu R. et al. (2019)(33)	Asia (Japan)	Cohort	1984-1992 1985-2000	1	/18,008	22	1.00
				2	/66,708	57	0.70 (0.42-1.17)
				3	/48,581	33	0.57 (0.33-1.00)
				4	/20,724	9	0.37 (0.16-0.83)
				≥5	/24,320	12	0.43 (0.19-0.97)
Kawai M. et al. (2010)(35)	Asia (Japan)	Cohort	1990	1	/20,317	25	1.00
				2	/117,058	116	0.80 (0.51-1.26)
				3	/99,686	80	0.70 (0.43-1.12)
				4	/30,648	16	0.50 (0.26-0.96)
				≥5	/11,124	4	0.35 (0.12-1.04)
Tamakoshi K. et al. (2005)(37)	Asia (Japan)	Cohort	1988-1990	1	/18,984	17	1.00
				2	/96,954	59	0.78 (0.42-1.44)
				3	/86,679	45	0.68 (0.36-1.31)
				≥4	/51,408	11	0.31 (0.13-0.76)
Gajalakshmi C.K. et al. (1998)(103)	Asia	Cohort	1960-1989	Nulliparous	/3,199	6	1.00
				1-3	/7,686	15	1.50 (0.50-4.90)
				≥4	/6,307	17	2.20 (0.70-6.60)
Lee SY et al. (2003)(39)	Korea	Cohort	1992-2000	1	/227,953	95	1.00
				2	/309,641	224	1.30 (1.00-1.60)
				≥3	/44,758	41	1.10 (0.70-1.70)
Case-control studies							
Figueroa J.D. et al. (2020)(41)	Europe	PCCS	2013-2015	Nulliparous	228	107	1.00
				1-2	533	319	1.04 (0.72-1.51)
				3-4	685	365	0.80 (0.55-1.15)
				≥5	652	331	0.73 (0.50-1.07)
Troisi R. et al. (2018)(122)	Europe	PCCS	1967-2013	1	155,946	17,811	1.06 (1.04-1.08)
				2	479,498	51,854	1.00
				3	315,014	30,594	0.89 (0.88-0.91)
				≥4	196,574	15,937	0.74 (0.72-0.75)
John E.M. et al. (2018)(105)	United States	PCCS	1995-2002	Nulliparous	746	124	1.00**
				1	743	99	1.17 (0.36-3.81)
				2	1,458	151	0.78 (0.54-1.14)
				3	992	110	1.26 (0.58-2.71)
				≥4	1,172	74	0.94 (0.43-2.05)
Ellingjord-Dale M. et al. (2017) (45)	Europe	NCCS	2006-2014	0	2,144	586	1.00
				1	2,911	673	0.83 (0.73-0.94)
				2	11,000	2,301	0.76 (0.68-0.84)
				3	6,956	1,351	0.71 (0.63-0.79)
				≥4	2,723	441	0.59 (0.51-0.68)
Brinton L.A. et al. (2017)(106)	Africa	PCCS	2012	Nulliparous	232	111	1.00
				1-2	565	342	1.05 (0.79-1.40)
				3-4	698	392	0.81 (0.60-1.08)
				≥5	658	351	0.71 (0.52-0.97)
Hajiebrahimi M. et al. (2016) (124)	Europe	NCCS	1973-2010	1	1,209	1,439	1.00
				2	3,986	4,210	0.87 (0.79-0.95)
				3	2,214	2,066	0.74 (0.67-0.82)
				≥4	918	612	0.54 (0.47-0.62)
Sisti J.S. et al. (2015)(47)	United States	PCCS	1985-2009	1	314	264	1.00
				2	847	572	0.97 (0.75-1.25)
				3	390	260	0.87 (0.65-1.17)
				≥4	232	112	0.60 (0.41-0.88)
O'Brien K.M. et al. (2015)(107)	United States	PCCS	2008-2010	Nulliparous	352	252	1.00
				1	256	186	0.91 (0.69-1.22)
				2	613	458	1.12 (0.88-1.42)
				≥3	426	289	1.15 (0.88-1.50)
Li C. et al. (2013)(109)	United States	PCCS	2004-2010	1	192	208	1.00**
				2	363	373	0.91 (0.74-1.10)
				≥3	198	175	0.69 (0.54-0.89)
Barnes B.B. et al. (2011)(48)	Europe	PCCS	2002-2005	0	1,007	525	1.10 (0.91-1.32)
				1	1,624	890	1.30 (1.13-1.50)
				2	2,453	1,121	1.08 (0.95-1.23)

				≥3	1,302	538	1.00
Poynter J.N. et al. (2010)(110)	United States	PCCS	1985-1999	Nulliparous	225	133	1.00
				1-2	749	388	0.97 (0.73-1.29)
				≥3	422	184	0.63 (0.45-0.87)
Ma H. et al. (2010)(111)	United States	PCCS	1995-2007	Nulliparous	/92,927	493	1.00
				1	/70,615	355	0.95 (0.83-1.09)
				2	/170,385	878	0.94 (0.84-1.04)
				3	/115,629	591	0.88 (0.78-0.99)
				≥4	/76,634	373	0.82 (0.72-0.94)
Sweeney C. et al. (2008)(112)	United States	PCCS	1999-2004	Nulliparous	312	337	1.07 (0.88-1.29)
				1-2	880	1,016	1.00**
				3-4	888	759	0.86 (0.75-0.99)
				≥5	349	209	0.62 (0.49-0.77)
Sprague B.L. et al. (2008)(51)	United States	PCCS	1997-2000	0-1	756	767	1.35 (1.12-1.65)
				2	948	854	1.26 (1.10-1.44)
				3	1,020	810	1.13 (0.99-1.28)
				≥4	1,475	1,051	1.00
Beaber E.F. et al. (2008)(113)	United States	PCCS	2000-2004	1	42	119	1.00**
				2	160	308	0.66 (0.49-0.89)
				3	117	249	0.67 (0.49-0.92)
				≥4	112	222	0.67 (0.48-0.93)
Ursin G. et al. (2004)(114)	United States	PCCS	1994-1998	Nulliparous	481	588	1.00**
				1	717	770	0.88 (0.75-1.03)
				2	1,355	1,371	0.83 (0.72-0.96)
				3	905	841	0.73 (0.63-0.86)
				4	443	381	0.65 (0.49-0.87)
				≥5	445	317	0.55 (0.44-0.68)
Tavani A. et al. (1999)(115)	Europe	PCCS	1983-1994	Nulliparous	220	130	1.00
				1	180	181	1.53 (1.09-2.13)
				2	196	215	1.70 (1.21-2.40)
				3	55	46	1.42 (0.86-2.36)
				≥4	17	10	1.13 (0.47-2.71)
Newcomb P.A. et al. (1999)(126)	United States	PCCS	1992-1995	1	351	434	1.00
				2	895	967	0.91 (0.76-1.09)
				3	954	888	0.81 (0.67-0.97)
				≥4	1,590	1,344	0.75 (0.63-0.89)
Mangusson C.M. et al. (1999)(54)	Europe	PCCS	1993-1995	Nulliparous	313	413	1.00
				1	536	573	0.69 (0.53-0.90)
				2	1,065	1,032	0.63 (0.49-0.81)
				3-4	891	655	0.50 (0.40-0.64)
				5-6	106	56	0.39 (0.26-0.58)
				≥7	25	2	0.06 (0.01-0.26)
Kroman N. et al. (1998)(128)	Europe	PCCS	1978-1994	Nulliparous	ND	ND	1.04 (0.90-1.19)
				1	ND	ND	1.00
				2	ND	ND	0.96 (0.86-1.07)
				3	ND	ND	0.99 (0.88-1.12)
				≥4	ND	ND	1.07 (0.90-1.28)
Enger S.M. et al. (1998)(135)	United States	PCCS	1987-1989	1	106	152	1.00
				2	298	332	0.80 (0.59-1.09)
				3	273	263	0.69 (0.50-0.95)
				≥4	296	227	0.54 (0.39-0.75)
Mayberry R.M. et al. (1992)(117)	United States	PCCS	1980-1982	0	ND	ND	1.00**
				1-2	ND	ND	0.84 (0.65-1.08)
				3-4	ND	ND	0.61 (0.50-0.76)
				≥5	ND	ND	0.45 (0.38-0.54)
Layde P.M. et al. (1989)(118)	United States	PCCS	1980-1982	Nulliparous	603	769	1.00
				1	485	566	0.92 (0.78-1.09)
				2	1,134	1,273	0.83 (0.73-0.95)
				3	1,029	994	0.70 (0.61-0.81)
				4	622	520	0.55 (0.44-0.67)
				5	308	243	0.52 (0.40-0.67)
				6	172	124	0.41 (0.31-0.53)

				≥7	181	110	0.73 (0.65-0.83)
Ewertz M. et al. (1988)(59)	Europe	PCCS	1983-1984	1	185	217	1.00
				2	505	568	0.98 (0.78-1.23)
				3	299	304	0.89 (0.69-1.15)
				≥4	221	117	0.71 (0.54-0.95)
Brignone G. et al. (1987)(61)	Europe	PCCS	1974-1983	1-2	326	264	1.00**
				3-4	289	276	1.19 (0.86-1.66)
				>4	126	105	1.25 (0.53-2.96)
Wang J.M. et al. (2020)(119)	Asia (China)	PCCS	2012-2017	1	2,121	1,914	1.00
				≥2	1,952	1,710	0.88 (0.80-0.97)
Park BY et al. (2018)(64)	Korea	PCCS	2007-2015	0	271	106	1.64 (1.10-2.45)
				1	581	208	1.50 (1.12-2.01)
				≥2	5,065	1,208	1.00

Abbreviation: PCCS; Population-based case-control study, NCCS; Nested case-control study, SeBCS; Seoul Breast Cancer Society, KBCS; Korean Breast Cancer Study, KMCC; Korean Multi-center cancer cohort

*Calculated RR; Calculation of crude RR (95% CI) by the population of each data set.

**Summary RR; Recalculation of adjusted RR (95% CI) by the meta-analysis.

Supplementary table 8. Systematic review of association with duration of breastfeeding on breast cancer risk in Global population

Author (year)	Country	Study design	Study period	Category of reproductive factors	Control Cohort/PY	Cases	RR/OR/HR (95% CI)
Cohort studies							
Fortner R.T. et al. (2019)(94)	United States	Cohort	1989-2013	Never	/2,100,966	5,101	1.00
				≤6 months	/1,255,908	3,242	0.93 (0.88-0.97)
				7-11	/535,074	1,203	0.96 (0.90-1.03)
				≥12	/1,390,661	2,906	0.96 (0.91-1.01)
Kwan M.L. et al. (2015)(136)	United States	Cohort	1997-2000	Never	ND	192	1.00
				<6 months	ND	77	0.81 (0.58-1.14)
				≥6	ND	116	0.63 (0.46-0.87)
Butts S. et al. (2014)(137)	Europe	Cohort	1991-1996	<4 months	270	80	1.00
				4-8	288	108	1.04 (0.77-1.40)
				8-13	304	109	1.09 (0.80-1.48)
				≥13	293	103	1.10 (0.78-1.54)
Ritte R. et al. (2013)(24)	Europe	Cohort	1992-2000	<1 months	ND	321	1.00
				1-3	ND	757	1.01 (0.89-1.15)
				4-6	ND	597	0.97 (0.85-1.12)
				7-12	ND	619	0.96 (0.83-1.10)
				13-17	ND	244	0.97 (0.81-1.15)
				≥18	ND	370	1.10 (0.94-1.30)
Ma H. et al. (2010)(111)	United States	Cohort	1995-2007	Never	/131,753	688	1.00
				<6 months	/117,111	571	0.94 (0.84-1.05)
				6-11	/75,315	402	1.05 (0.93-1.19)
				12-23	/69,112	352	1.02 (0.90-1.17)
				≥24	/38,744	180	0.99 (0.84-1.18)
Andrieu N. et al. (2006)(138)	Europe	Cohort	1997-2002	0 months	/6,843	197	1.00
				1-5	/6,039	202	1.10 (0.82-1.47)
				6-12	/4,430	150	1.05 (0.76-1.46)
				13-24	/2,778	70	0.83 (0.56-1.23)
				>24	/1,093	28	1.08 (0.62-1.89)
				Nulliparous	/42,135	150	0.80 (0.53-1.21)
Lee SY et al. (2003)(39)	Korea	Cohort	1992-2000	Never	/263,472	161	1.00
				1-12 months	/256,199	149	0.80 (0.70-1.00)
				13-24	/39,125	32	0.70 (0.50-1.10)
				>24	/23,556	18	0.60 (0.30-1.00)
Case-control studies							
Chollet-Hinton L. et al. (2017)(139)	United States	PCCS	1993-2013	Never	1,832	668	1.00
				<3 months	429	126	0.92 (0.61-1.38)
				≥3	1,423	452	0.91 (0.78-1.08)
Ambrosone C.B. et al.(2014)(140)	United States	PCCS	2002-2006	Never	442	412	1.00
				<6 months	138	110	0.83 (0.60-1.13)
				≥6	265	249	0.87 (0.69-1.11)
Li C.I. et al. (2013)(109)	United States	PCCS	2004-2010	Never	60	76	1.00
				<6 months	190	202	0.92 (0.66-1.28)
				6-11	111	119	0.94 (0.60-1.47)
				>12	389	357	0.77 (0.45-1.31)
Palmer J.R. et al. (2011)(141)	United States	PCCS	1995-2001	Never	/808,893	410	1.00
				<6 months	/335,876	163	1.02 (0.77-1.34)
				≥6	/273,266	129	1.02 (0.77-1.34)
Peterson N.B. et al. (2008)(142)	United States	PCCS	1996-1997	Never	680	649	1.00
				≤3 months	406	357	0.85 (0.70-1.04)
				>3	415	426	1.10 (0.91-1.34)
Tryggvadottir L. et al. (2001)(143)	Europe	NCCS	1979-1995	0-4 weeks	483	80	1.00
				5-26	3,606	373	0.67 (0.51-0.89)
				27-52	2,688	292	0.79 (0.59-1.05)
				53-104	1,917	180	0.70 (0.51-0.97)

				≥105	755	48	0.48 (0.31-0.74)
Newcomb P.A. et al. (1999)(126)	United States	PCCS	1992-1994	Never	1,988	1,925	1.00
				<3 months	775	719	0.89 (0.78-1.02)
				3-6	367	322	0.77 (0.64-0.93)
				7-12	275	305	1.06 (0.87-1.28)
				13-23	182	175	0.81 (0.63-1.04)
				≥24	170	151	0.73 (0.56-0.94)
Furberg H. et al. (1999)(144)	United States	PCCS	1993-1996	Never	387	441	1.00
				1-3 months	99	90	0.70 (0.50-0.90)
				4-12	115	95	0.60 (0.40-0.90)
				≥13	100	103	0.80 (0.50-1.10)
Enger S.M. et al. (1998)(135)	United States	PCCS	1987-1989	Never	433	504	1.00
				1-3 months	208	207	0.86 (0.68-1.09)
				4-6	95	81	0.77 (0.55-1.07)
				7-15	128	102	0.75 (0.55-1.01)
				≥16	109	80	0.73 (0.52-1.01)
Negri E. et al. (1996)(145)	Europe	PCCS	1991-1994	Never	500	486	1.00
				1-5 months	472	537	1.19 (1.00-1.40)
				6-11	574	579	1.15 (1.00-1.40)
				12-17	337	355	1.34 (1.10-1.70)
				18-23	160	114	1.10 (0.80-1.50)
				≥24	131	68	0.86 (0.50-1.30)
Layde P.M. et al. (1989)(118)	United States	PCCS	1980-1982	Never	2,134	2,318	1.00
				<6 months	1,228	1,198	0.92 (0.82-1.02)
				6-12	612	562	0.85 (0.73-0.98)
				13-24	381	304	0.75 (0.62-0.90)
				≥25	244	154	0.67 (0.52-0.85)
Gao Y.T. et al. (2000)(63)	Asia (Shanghai)	PCCS	1996-1998	Never	300	302	1.00
				<12 months	638	593	0.90 (0.80-1.10)
				12-23	307	275	0.90 (0.70-1.10)
				≥24	250	215	1.00 (0.70-1.40)
Park BY et al. (2018)(64)	Korea	PCCS	2007-2015	Never	715	247	1.00
				<12 months	1,777	410	0.67 (0.61-0.73)
				≥12	3,433	876	0.74 (0.63-0.87)

Abbreviation: PCCS; Population-based case-control study, NCCS; Nested case-control study, SeBCS; Seoul Breast Cancer Society, KBCS; Korean Breast Cancer Study, KMCC; Korean Multi-center cancer cohort

*Calculated RR; Calculation of crude RR (95% CI) by the population of each data set.

**Summary RR; Recalculation of adjusted RR (95% CI) by the meta-analysis.

Supplementary table 9. Systematic review of association with use of oral contraceptives on breast cancer risk in Global population

Author (year)	Country	Study design	Study period	Category of reproductive factors	Control Cohort/PY	Cases	RR/OR/HR (95% CI)
Cohort studies							
Al Ajmi K. et al. (2020)(146)	Europe	Cohort	2006-2010	Never	17,240	561	1.00
				Ever	71,149	2,165	1.02 (0.93-1.12)
Arriaga M.E. et al. (2019)(147)	Australia	Cohort	1990-2009	Never	ND	ND	1.00
				Ever	ND	ND	1.29 (1.02-1.63)
Busund M. et al. (2018)(148)	Europe	Cohort	1991-2007	Never	ND	379	1.00
				Ever	ND	866	1.12 (0.99-1.26)
				Current	ND	129	1.36 (1.09-1.71)
				Former	ND	737	1.09 (0.96-1.24)
Iversen L. et al. (2017)(149)	Europe	Cohort	1968-1969	Never	ND	649	1.00
				Ever	ND	1,422	1.04 (0.91-1.17)
Hunter D.J. et al. (2010)(150)	United States	Cohort	1989-2001	Never	/176,581	162	1.00
				Ever	/1,070,386	1,182	1.19 (1.01-1.39)
Hannaford et al. (2007)(151)	Europe	Cohort	1996-2004	Never	ND	448	1.00
				Ever	ND	891	0.98 (0.87-1.10)
Vessey et al. (2007)(152)	Europe	Cohort	1968-2004	Never	ND	314	1.00
				Ever	ND	530	1.00 (0.80-1.10)
Dumeaux V et al. (2004)(153)	Europe	Cohort	1990-2000	Never	ND	951	1.00
				Ever	ND	454	0.91 (0.81-1.03)
Silvera S.A. et al. (2005)(154)	Canada	Cohort	1980-1985	Never	/182,112	745	1.00
				Ever	/266,497	962	0.88 (0.73-1.07)
				Former	/255,315	917	0.88 (0.72-1.07)
				Current	/10,968	45	1.01 (0.56-1.81)
Stahlberg C et al. (2004)(32)	Europe	Cohort	1996-2001	Never	6,687	138	1.00
				Ever	4,083	105	1.37 (1.04-1.80)
Dumeaux V. et al. (2003)(155)	Europe	Cohort	1991-1997	Never	/212,487	305	1.00
				Ever	/324,692	483	1.25 (1.07-1.46)
Kumle M. et al. (2002)(156)	Europe	Cohort	1991-1992	Never	28,171	261	1.00
				Ever	74,856	747	1.30 (1.10-1.50)
				Former	65,557	656	1.20 (1.10-1.40)
				Current	9,299	91	1.60 (1.20-2.10)
Van Hoften C. et al. (2000)(157)	Europe	Cohort	1982-1984	Never	258	117	1.00
				Ever	352	192	1.19 (0.90-1.58)
Kay C.R. et al. (1988)(158)	Europe	Cohort	1968-1967	Never	ND	ND	1.00
				Former	ND	ND	1.21 (0.89-1.65)
				Current	ND	ND	1.25 (0.84-1.86)
Lipnick R.J. et al. (1986)(159)	United States	Cohort	1976-1978	Never	57,047	356	1.00**
				Ever	49,283	214	1.01 (0.85-1.20)
Kawai M et al. (2010)(35)	Asia (Japan)	Cohort	1990-2003	Never	/243,319	236	1.00
				Ever	/15,418	12	0.80 (0.45-1.44)
Dorjgochoo T. et al.(2009)(160)	Asia (China)	Cohort	1997-2000	Never	ND	448	1.00
				Ever	ND	110	1.05 (0.84-1.31)
Rosenblatt et al. (2009)	Asia (China)	Cohort	1998-1991	Never	/20,323,571	1,496	1.00
				Ever	/3,507,410	253	0.90 (0.78-1.03)
Lee SY et al. (2003)	Korea	Cohort	1992-2000	Never	/458,179	286	1.00
				Ever	/49,906	31	0.80 (0.60-1.00)
Case-control studies							
Hamdi-Cherif M. et al. (2020)(42)	Africa	PCCS	2012-	Never	222	202	1.00
				Ever	321	345	1.24 (0.96-1.60)

Al-Ajmi K. et al. (2018)(4)	Europe	PCCS	2006-2010	Never	6,297	53	1.00
				Ever	50,646	565	1.26 (0.95-1.67)
Brinton L.A. et al. (2018)(161)	United States	PCCS	1990-1992	Never	278	283	1.00
				Ever	641	748	1.14 (0.90-1.40)
Ellinjord-Dale M. et al. (2017)(45)	Europe	NCCS	2006-2014	Never	12,000	2,443	1.00
				Ever	11,562	2,386	1.02 (0.93-1.13)
Chollet-Hinton L. et al. (2017)(139)	United States	PCCS	1993-2013	Never	716	306	1.00**
				Ever	4,421	1,283	1.19 (1.00-1.41)
Elebro K. et al. (2014)(162)	Europe	PCCS	1991-1996	Never	ND	358	1.00
				Ever	ND	388	1.09 (0.93-1.28)
Beaber E.F. et al. (2014)(163)	United States	PCCS	2004-2010	Never	103	119	1.00
				Ever	779	866	1.00 (0.70-1.30)
Hayes J. et al. (2013)(164)	New Zealand	PCCS	2006-2009	Never	ND	ND	1.00
				Ever	ND	ND	1.20 (1.20-1.30)
Rosenberg L et al. (2010)(165)	United States	PCCS	1995	Never	/128,768	177	1.00**
				Ever	/445,824	597	1.23 (0.91-1.66)
Dolle J.M. et al. (2009)(166)	United States	PCCS	1983-1992	Never(<1yrs)	299	121	1.00
				Ever(≥1)	857	469	1.60 (1.10-2.10)
Nyante S.J. et al. (2008)(167)	United States	PCCS	1990-1992	Never	425	276	1.00
				Ever	1,076	888	1.21 (1.01-1.45)
				Former	911	750	1.17 (0.97-1.41)
				Recent	165	138	1.45 (1.08-1.96)
Lee E. et al. (2008)(168)	United States	PCCS	1998-2003	Never	48	184	1.00
				Ever	394	1,185	0.81 (0.57-1.14)
Sweeney C. et al. (2007)(169)	United States	PCCS	1999-2004	Never	1,011	809	1.00
				Ever	1,502	1,494	1.08 (0.94-1.24)
Nichols H.B. et al. (2007)(170)	United States	PCCS	1997-2001	Never	3,290	876	1.00
				Ever	3,995	977	1.11 (0.99-1.25)
				Former	3,748	941	1.13 (1.00-1.27)
				Current	247	36	0.75 (0.50-1.11)
Folger S.G. et al. (2007)(171)	United States	PCCS	1994-1998	Never	262	253	1.00
				Ever	194	244	1.13 (1.00-1.70)
				Current	3	4	1.20 (0.20-6.10)
				Former	191	239	1.30 (1.00-1.70)
Dinger J.G. et al. (2006)(172)	Europe	PCCS	2000-2004	Never	1,805	1,079	1.00*
				Ever	7,271	2,508	0.58 (0.52-0.64)
Newcomer L.M. et al. (2003)(173)	United States	PCCS	ND	Never	5,864	3,341	1.00
				Ever	3,447	1,676	1.00 (0.90-1.10)
				Former	3,306	1,629	1.00 (0.90-1.10)
				Current	141	47	1.20 (0.80-1.90)
Marchbanks P.A. et al. (2002)(174)	United States	PCCS	1994-1998	Never	980	1,032	1.00
				Ever	3,658	3,497	0.90 (0.80-1.00)
				Former	3,481	3,289	0.90 (0.80-1.00)
				Current	172	200	1.00 (0.80-1.30)
Ursin G. et al. (1999)(175)	United States	PCCS	1983-1987	Never	594	383	1.00
				Ever	351	207	0.91 (0.72-1.15)
Tavani A. et al. (1999)(115)	Europe	PCCS	1991-1994	Never	441	358	1.00
				Ever	227	221	1.05 (0.81-1.36)
Mangusson et al. (1999)(54)	Europe	PCCS	1993-1995	Never	1,938	1,733	1.00
				Ever	889	898	0.98 (0.86-1.12)
Tavani A. et al. (1993)(176)	Europe	PCCS	1983-1991	Never	1,663	1,938	1.00
				Ever	265	371	1.20 (1.00-1.40)
Lund E. (1989) (177)	Europe	PCCS	1984-1985	Never	ND	ND	1.00**
				Ever	ND	ND	1.27 (0.83-1.96)

Rosenbrerg L. et al. (1984)(178)	USA/ Canada	PCCS	1976-1981	Never	2,468	794	1.00**
				Ever	2,320	338	0.98 (0.80-1.18)
Park BY et al. (2018)(64)	Korea	PCCS	2007-2015	Never	4,061	866	1.00
				Ever	777	162	1.04 (0.69-1.56)

Abbreviation: PCCS; Population-based case-control study, NCCS; Nested case-control study, SeBCS; Seoul Breast Cancer Society, KBCS; Korean Breast Cancer Study, KMCC; Korean Multi-center cancer cohort, ND; No data
*Calculated RR; Calculated by the population of each data set.
**Summary RR; Recalculation of adjusted RR (95% CI) by the meta-analysis.

Supplementary table 10. Systematic review of association with duration of oral contraceptives on breast cancer risk in Global population

Author (year)	Country	Study design	Study period	Category of reproductive factors	Control Cohort/PY	Cases	RR/OR/HR (95% CI)
Cohort studies							
Arriaga M.E. et al. (2019)(147)	Australia	Cohort	1990-2009	Never	ND	ND	1.00
				Current			
				<5years	ND	ND	1.03 (0.57-1.88)
				≥5	ND	ND	1.34 (1.04-1.73
Busund M. et al. (2018)(148)	Europe	Cohort	1991-2007	Never	ND	379	1.00
				1-4years	ND	451	1.10 (0.96-1.26)
				5-9	ND	216	1.02 (0.86-1.21)
				≥10	ND	178	1.29 (1.09-1.54)
Boggs D.A. et al. (2015)(76)	United States	Cohort	1995-2005	<10	/312,506	663	1.00
				≥10	/159,474	233	1.19 (1.01-1.41)
Hunter D.J. et al. (2010)(150)	United States	Cohort	1989-2001	Never	/176,581	162	1.00
				0-8years	/55,333	34	1.16 (0.80-1.69)
				≥8	/57,899	57	1.42 (1.05-1.94)
Silvera S.A. et al. (2005)(154)	Canada	Cohort	1980-1985	Never	/182,112	745	1.00
				1-12months	/54,419	230	1.05 (0.79-1.42)
				12-36	/60,731	226	0.94 (0.70-1.26)
				36-84	/80,230	263	0.85 (0.64-1.12)
				≥84	/71,101	243	0.74 (0.55-0.99)
Dumeaux V. et al. (2003)(155)	Europe	Cohort	1991-1997	Never	/212,487	305	1.00
				0-4years	/173,321	261	1.25 (1.05-1.49)
				5-9	/75,261	104	1.19 (0.94-1.50)
				≥10	/51,055	86	1.40 (1.09-1.79)
Kumle M. et al. (2002)(156)	Europe	Cohort	1991-1992	Never	28,171	261	1.00
				<5years	38,742	384	1.20 (1.00-1.50)
				5-9	18,876	178	1.20 (1.00-1.50)
				10-14	10,803	113	1.40 (1.10-1.80)
				≥15	5,441	63	1.30 (1.00-1.80)
de Vries E. et al. (2001)(100)	Europe	Cohort	1982-1985	Never	4,185	ND	1.00
				1-2years	1,296	ND	0.98 (0.90-1.07)
				3-5	1,126	ND	1.08 (0.98-1.18)
				6-10	1,249	ND	1.08 (0.98-1.18)
				≥11	845	ND	1.13 (1.02-1.25)
Lipnick R.J. et al. (1986)(159)	United States	Cohort	1976-1978	Never	57,047	356	1.00
				1-11months	11,913	53	0.90 (0.70-1.30)
				12-35	13,187	41	0.80 (0.60-1.10)
				36-59	8,152	34	1.00 (0.71.40)
				60-119	12,149	59	1.20 (0.80-1.50)
				≥120	3,882	27	1.30 (0.90-1.90)
Kawai M et al. (2010)(35)	Asia (Japan)	Cohort	1990-2003	Never	/243,319	236	1.00
				<1years	/4,965	5	1.00 (0.41-2.45)
				1-5	/5,934	4	0.70 (0.26-1.89)
				≥5	/3,234	1	0.33 (0.05-2.33)
Dorjgochoo T. et al. (2009)(160)	Asia (China)	Cohort	1997-2000	Never	ND	448	1.00
				<2years	ND	59	1.18 (0.89-1.56)
				≥2	ND	51	0.93 (0.68-1.25)
Case-controls studies							
Brinton L.A. et al. (2018)(161)	United States	PCCS	1990-1992	Never	278	283	1.00
				<5years	310	344	1.11 (0.90-1.40)
				5-9	204	231	1.09 (0.80-1.40)
				≥10	127	173	1.27 (0.90-1.70)
Ellinjord-Dale M. et al. (2017) (45)	Europe	NCCS	2006-2014	Never	12,000	2,443	1.00
				<2years	3,405	614	0.89 (0.81-0.99)
				2-5	3,120	638	1.02 (0.92-1.13)
				6-10	2,834	619	1.10 (0.99-1.22)
				>10	2,203	515	1.11 (1.00-1.25)

Chollet-Hinton L. et al. (2017) (139)	United States	PCCS	1993-2013	Never/<1yrs	1,709	534	1.00**
				1-4	1,638	467	1.05 (0.89-1.23)
				≥5	1,494	590	1.27 (1.09-1.47)
Beaber E.F. et al. (2014) (163)	United States	PCCS	2004-2010	Never	103	119	1.00
				<5years	280	306	1.00 (0.70-1.30)
				5-10	219	213	0.90 (0.60-1.20)
				10-15	178	169	0.90 (0.60-1.20)
				≥15	100	174	1.50 (1.20-2.20)
Dolle J.M. et al. (2009)(166)	United States	PCCS	1983-1992	Never	299	121	1.00
				1-3years	242	126	1.50 (1.00-2.20)
				3-6	261	141	1.60 (1.10-2.40)
				≥6	354	202	1.50 (1.10-2.20)
Nyante S.J. et al. (2008)(167)	United States	PCCS	1990-1992	Never	425	276	1.00
				<1years	91	70	1.13 (0.80-1.61)
				1-3	395	295	1.11 (0.89-1.38)
				≥4	590	523	1.30 (1.06-1.59)
Lee E. et al. (2008)(168)	United States	PCCS	1998-2003	Never	48	184	1.00
				≤4years	181	558	0.80 (0.55-1.16)
				5-9	115	283	0.66 (0.45-0.98)
				≥10	97	331	0.95 (0.64-1.42)
Sweeney C. et al. (2008)(169)	United States	PCCS	1999-2004	Never	1,011	809	1.00
				<5years	688	685	1.13 (0.97-1.33)
				5-9	405	392	1.02 (0.84-1.22)
				10-19	351	330	0.97 (0.80-1.18)
				≥20	54	84	1.50 (1.04-2.17)
Nichols H.B. et al. (2007)(170)	United States	PCCS	1997-2001	Never	3,290	876	1.00
				1-2years	1,130	283	1.13 (0.96-1.33)
				2-4.5	1,126	297	1.22 (1.04-1.44)
				4.5-9	825	190	1.04 (0.86-1.25)
				≥9	914	207	0.96 (0.89-1.04)
Folger S.G. et al. (2007)(171)	United States	PCCS	1994-1998	Never	262	253	1.00
				<10years	21	25	1.20 (0.60-2.30)
				10-20	59	63	1.20 (0.80-1.80)
				≥20	114	155	1.30 (1.00-1.80)
Newcomer L.M. et al. (2003)(173)	United States	PCCS	ND	Never	5,864	3,341	1.00
				<1years	760	407	1.10 (1.00-1.30)
				1-4	1,344	591	1.00 (0.90-1.10)
				5-9	814	392	1.00 (0.90-1.20)
				10-14	407	222	1.00 (0.90-1.30)
				≥15	122	64	1.00 (0.70-1.30)
Marchbanks P.A. et al. (2002)(174)	United States	PCCS	1994-1998	Never	980	1,032	1.00
				<1years	822	782	0.90 (0.80-1.10)
				1-5	1,280	1,200	0.90 (0.80-1.00)
				5-10	882	848	0.90 (0.80-1.00)
				10-15	466	426	0.80 (0.70-1.00)
				≥15	202	234	1.00 (0.80-1.30)
Ursin G. et al. (1999)(175)	United States	PCCS	1983-1987	Never	594	383	1.00
				1-12months	111	83	1.20 (0.86-1.69)
				13-60	153	79	0.81 (0.58-1.12)
				>60	87	45	0.71 (0.47-1.07)
Tavani A. et al. (1999)(115)	Europe	PCCS	1991-1994	Never	441	358	1.00
				≤2years	120	128	1.19 (0.87-1.62)
				2-5	59	53	0.96 (0.63-1.48)
				>5	46	40	0.86 (0.53-1.40)
Mangusson et al. (1999) (54)	Europe	PCCS	1993-1995	Never	1,938	1,733	1.00
				<5years	492	509	1.00 (0.86-1.17)
				≥5	353	357	0.98 (0.82-1.18)
Tryggvadottir L. et al. (1997) (179)	Europe	PCCS	1991-1992	Never	ND	ND	1.00**
				0-4	ND	ND	0.96 (0.63-1.47)
				4-8	ND	ND	1.12 (0.54-2.33)
				>8years	ND	ND	1.46 (0.40-5.31)

Tavani A. et al. (1993)(176)	Europe	PCCS	1983-1991	Never	1,663	1,938	1.00
				<24months	109	185	1.50 (1.20-2.00)
				24-59	70	103	1.30 (0.90-1.80)
				≥60	84	82	0.80 (0.50-1.00)
Lund E. (1989) (177)	Europe	PCCS	1984-1985	Never	ND	ND	1.00
				1-3years	ND	ND	1.40 (0.80-2.50)
				4-7	ND	ND	1.20 (0.50-2.50)
				≥8	ND	ND	1.00 (0.30-2.80)
Kay C.R. et al. (1988)(158)	United Kingdom	PCCS	1968-1977	Never	ND	ND	1.00
				<2years	ND	ND	1.04 (0.69-1.58)
				2-3	ND	ND	1.60 (1.10-2.33)
				4-5	ND	ND	1.48 (0.98-2.23)
				6-7	ND	ND	0.80 (0.45-1.43)
				8-9	ND	ND	0.85 (0.46-1.59)
				≥10	ND	ND	1.44 (0.91-2.29)
Rosenberg L. et al. (1984)(178)	USA/ Canada	PCCS	1976-1981	Never	2,468	794	1.00
				<1years	717	98	0.90 (0.70-1.10)
				1-4	1,018	127	0.90 (0.80-1.20)
				5-9	457	88	1.30 (1.00-1.70)
				≥10	128	25	0.80 (0.50-1.30)
Park BY et al. (2018)(64)	Korea	PCCS	2007-2015	Never	4,061	866	1.00
				<12 months	519	92	0.84 (0.73-1.37)
				≥12	258	70	1.27 (0.84-1.45)

Abbreviation: PCCS; Population-based case-control study, NCCS; Nested case-control study, SeBCS; Seoul Breast Cancer Society, KBCS; Korean Breast Cancer Study, KMCC; Korean Multi-center cancer cohort

*Calculated RR; Calculation of crude RR (95% CI) by the population of each data set.

**Summary RR; Recalculation of adjusted RR (95% CI) by the meta-analysis.

Supplementary table 11. Systematic review of association with combination of HRT use on breast cancer risk in Global population

Author (year)	Country	Study design	Study period	Category of reproductive factors	Control Cohort/PY	Cases	RR/OR/HR (95% CI)
Cohort studies							
Al Ajmi K. et al. (2020)(146)	Europe	Cohort	2006-2010	Never	66,093	1,895	1.00
				Ever	22,244	826	1.23 (1.13-1.34)
Sandvei M.S. et al. (2019)(19)	Europe	Cohort	2006-2013	Never	/252,353	3,271	1.00
				Ever**			1.53 (0.77-3.05)
				Former	/80,173	1,471	1.08 (1.00-1.17)
				Current	/33,886	1,091	2.18 (2.01-2.37)
Holm M. et al. (2018)(180)	Europe	Cohort	1993-1997	Never	ND	ND	1.00
				Ever	ND	ND	1.98 (1.78-2.21)
Azam S. et al. (2018)(181)	Europe	Cohort	1993-1997	Never	/32,635	84	1.00**
				Ever	/13,034	85	2.62 (1.63-4.20)
Mullooly M. et al. (2017)(20)	United States	Cohort	1995-1996	Never	ND	ND	1.00
				Former	ND	ND	1.14 (0.93-1.39)
				Current**	ND	ND	1.59 (1.42-1.77)
Dartois et al. (2016)(22)	Europe	Cohort	1990-1993	Never	23,728	2,322	1.00
				E+P	4,621	296	1.20 (1.09-1.32)
				E+ other P	5,253	412	1.72 (1.57-1.88)
Thorbjarnardottir T. et al. (2014)(182)	Europe	Cohort	1987-2006	Never	4,390	ND	1.00
				Ever	4,344	ND	2.61 (2.00-3.41)
Fournier A. et al. (2014)(183)	Europe	Cohort	1992-2008	Never	ND	890	1.00
				Former	ND	552	0.96 (0.87-1.06)
				Current	ND	638	1.22 (1.11-1.35)
Saxena T. et al. (2010)(184)	United States	Cohort	1995	Never	/120,039	493	1.00
				Ever	/15,135	1,153	1.59 (1.42-1.78)
Lacey J.V. et al. (2009)(27)	United States	Cohort	1993-2001	Never	/134,329	571	1.00
				Former	/64,773	280	1.02 (0.88-1.18)
				Current**	/186,937	1,219	1.56 (1.35-1.80)
Calle E.E. et al. (2009)(185)	United States	Cohort	1992	Never	ND	780	1.00
				Former	ND	289	1.08 (0.86-1.35)
				Current	ND	364	1.75 (1.54-1.99)
Lund E. et al. (2007)(186)	Europe	Cohort	1991-1992 1998	Never	11,147	158	1.00
				Former	659	5	0.54 (0.22-1.33)
				Current	3,453	91	1.95 (1.49-2.56)
Brewster A.M. et al. (2007)(187)	Unites States	Cohort	1985-2000	Never	ND	1,301	1.00
				Ever	ND	735	0.63 (0.48-0.81)
Rosenberg L. et al. (2006)(188)	United States	Cohort	1995	Never	ND	ND	1.00
				Ever	/13,961	67	1.28 (0.97-1.70)
Lee S. et al. (2006) (189)	United States	Cohort	1993-1996	Never	ND	642	1.00**
				Former	ND	126	1.28 (0.74-2.22)
				Current	ND	467	2.08 (1.53-2.82)
Ewertz M. et al. (2005)(190)	Europe	Cohort	1989-1991	Never	/282.278	561	1.00**
				Ever	/10.913	19	0.81 (0.48-1.36)
Tjonneland A. et al. (2004)(191)	Europe	Cohort	1993-2000	Never	/11,801	144	1.00
				Ever	/1,929	24	1.08 (0.59-1.90)
de Lignieres B. et al. (2002)(192)	Europe	Cohort	1979-1984	Never	1,436	43	1.00
				Ever	1,545	59	1.10 (0.73-1.66)
Porch et al. (2002)(193)	United States	Cohort	1993-2000	Never	/38,762	146	1.00
				Ever	/32,885	164	1.37 (1.05-1.78)
Schairer C. et al. (2000)(194)	United States	Cohort	1980-1989	Never	/196,666	761	1.00
				Ever	/17,428	101	1.30 (1.00-1.60)
Gapstur S.M. et al. (1999)(195)	United States	Cohort	1986	Never	ND	ND	1.00
				Former	ND	ND	0.99 (0.87-1.14)
				Current	ND	ND	1.25 (1.03-1.51)

Yoo T.K. et al. (2020)	Korea	Cohort	2009-2014	Never	/18,771,852	21,262	1.00
				Ever	/3,420,942	5,535	1.25 (1.22-1.29)
				<2yrs	/2,014,117	2,792	1.08 (1.04-1.12)
				2-5yrs	/782,356	1,351	1.33 (1.25-1.40)
				≥5yrs	/624,468	1,392	1.72 (1.63-1.82)
Case-control studies							
Shieh M.S. et al. (2019)(196)	United States	NCCS	1996-2007	Never	2,089	734	1.00*
				Ever	689	339	1.40 (1.10-1.78)
Ellingjord-Dale M. et al. (2018)(197)	Europe	NCCS	2006-2014	Never	13,000	2,062	1.00
				Past	8,315	1,612	1.19 (1.10-1.29)
				E+P	661	224	2.23 (1.88-2.65)
Brinton L.A. et al. (2018)(161)	United States	PCCS	1990-1992	Never	671	783	1.00
				Ever	248	248	0.89 (0.70-1.20)
				E+P	124	148	0.99 (0.70-1.30)
Al-Ajmi K. et al. (2018)(4)	Europe	PCCS	2006-2010	Never	65,669	943	1.00
				Ever	46,830	811	1.14 (1.04-1.26)
Salagame U. et al. (2016)(198)	Australia	PCCS	2006-2014	Never	430	595	1.00
				Ever	23	76	2.62 (1.56-4.38)
Rosenberg L. et al. (2016)(199)	United States	PCCS	1993-2013	Never	3,509	949	1.00**
				Ever	1,293	321	1.32 (0.97-1.79)
Cui Y. et al. (2014) (200)	United States	PCCS	2001-2010	Never	ND	ND	1.00
				Ever	ND	ND	1.01 (0.88-1.16)
Fei C. et al. (2013) (201)	United States	NCCS	ND	Never	1,499	1,346	1.00*
				Ever	55	24	0.49 (0.21-1.13)
Cerne J.Z. et al. (2011)(202)	Europe	PCCS	2006-2008	Never	584	465	1.00
				Ever	147	162	0.89 (0.62-1.28)
Barnes B.B et al. (2011)(48)	Europe	PCCS	2002-2005	Never	2,596	1,020	1.01 (0.89-1.15)
				Former	1,647	637	1.00
				Current	19	14	1.92 (0.93-3.87)
Hines L.M. et al. (2010)(49)	United States	PCCS	2000-2005	Never	793	710	1.00
				Ever	287	390	1.19 (0.54-2.64)
Sprague B.L. et al. (2008)(51)	United States	PCCS	1997-2000	Never	2,125	1,583	0.92 (0.77-1.10)
				Former	364	283	1.00
				Current	638	741	1.31 (1.07-1.60)
Rosenberg L.U. et al. (2006)(203)	Europe	PCCS	1993-1995	Never	1,707	903	1.00
				Ever	350	320	1.60 (1.30-1.90)
Newcomb P.A. et al. (2002)(204)	United States	PCCS	1992-1994	Never	2,919	2,780	1.00
				Ever	245	279	1.51 (1.21-1.88)
Chen C.L. et al. (2002)(205)	United States	NCCS	1990-1995	Never	271	243	1.00
				Former	189	171	0.92 (0.70-1.22)
				Current	74	112	1.49 (1.04-2.12)
La Vecchia C. et al. (1995)(206)	Europe	PCCS	1991-1994	Never	2,395	2,376	1.00**
				Ever	31	36	1.32 (0.94-1.84)
Park BY et al. (2018)(64)	Korea	PCCS	2007-2015	Never	2,935	667	1.00
				Ever	660	169	1.13 (0.87-1.27)

Abbreviation: PCCS; Population-based case-control study, NCCS; Nested case-control study, SeBCS; Seoul Breast Cancer Society, KBCS; Korean Breast Cancer Study, KMCC; Korean Multi-center cancer cohort

*Calculated RR; Calculation of crude RR (95% CI) by the population of each data set.

**Summary RR; Recalculation of adjusted RR (95% CI) by the meta-analysis.

Supplementary table 12. Systematic review of association with estrogen only HRT use on breast cancer risk in Global population

Author (year)	Country	Study design	Study period	Category of reproductive factors	Control Cohort/PY	Cases	RR/OR/HR (95% CI)
Cohort studies							
Sandvei M.S. et al. (2019)(19)	Europe	Cohort	2006-2013	Never	/252,353	3,271	1.00
				Former	/90,633	1,623	1.06 (0.98-1.15)
				Current	/47,309	1,327	1.90 (1.76-2.06)
Holm M. et al. (2018)(180)	Europe	Cohort	1993-1997	Never	ND	ND	1.00
				Ever	ND	ND	1.40 (1.21-1.63)
Azam S. et al. (2018)(165)	Europe	Cohort	1993-1997	Never	/32,635	84	1.00
				Ever	/6,635	18	0.99 (0.59-1.65)
Dartois et al. (2016)(14)	Europe	Cohort	1990-1993	Never	23,728	2,322	1.00
				Ever	1,747	108	1.07 (0.92-1.23)
Saxena T. et al. (2010)(168)	United States	Cohort	1995	Never	/120,039	493	1.00
				Ever	/159,680	764	1.21 (1.07-1.36)
Calle E.E. et al. (2009)(169)	United States	Cohort	1992	Never	ND	780	1.00
				Former	ND	227	0.88 (0.75-1.04)
				Current	ND	365	0.99 (0.84-1.17)
Brinton L.A. et al. (2008)(145)	United States	Cohort	1995-1996	Never	/54,970.5	260	1.00
				Ever	/157,479.5	774	1.07 (0.93-1.24)
Espie et al. (2007) (207)	Europe	Cohort	2004-2006	Never	2,004	14	1.00*
				Ever	2,662	17	0.91 (0.31-2.71)
Lund E. et al. (2007) (170)	Europe	Cohort	1991-1992 1998	Never	11,147	158	1.00
				Former	211	8	0.88 (0.49-1.58)
				Current	938	12	2.38 (1.16-4.85)
Gertig et al. (2006) (208)	Australia	Cohort	1990-2002	Never	ND	209	1.00
				Former	ND	46	1.19 (0.86-1.64)
				Current	ND	81	1.51 (1.16-1.98)
Rosenberg L. et al. (2006)(172)	United States	Cohort	1995	Never	ND	ND	1.00
				Ever	/35,406	134	1.10 (0.85-1.41)
Lee S. et al. (2006)(173)	United States	Cohort	1993-1996	Never	ND	642	1.00
				Former	ND	237	0.97 (0.79-1.19)
				Current	ND	261	1.42 (1.19-1.70)
Olsson H.L. et al. (2003)(209)	Europe	Cohort	1990-2001	Never	ND	ND	1.00
				Ever	ND	ND	0.81 (0.34-1.96)
Porch et al. (2002) (177)	United States	Cohort	1993-2000	Never	/38,762	146	1.00
				Ever	/33,370	101	0.96 (0.65-1.42)
Schairer C. et al. (2000)(178)	United States	Cohort	1980-1989	Never	/196,666	761	1.00
				Ever	/179,401	805	1.10 (1.00-1.30)
Lai J.N. et al. (2011)(210)	Asia (Taiwan)	Cohort	1997-2008	Never	49,991	621	1.00
				Former	6,013	61	2.21 (1.54-3.17)
				Current	791	31	0.82 (0.43-1.57)
Case-control studies							
Shieh M.S. et al. (2019)(180)	United States	NCCS	1996-2007	Never	2,089	734	1.00**
				Ever	435	140	0.92 (0.64-1.31)
Ellingjord-Dale M. et al. (2018) (181)	Europe	NCCS	2006-2014	Never	13,000	2,062	1.00
				Former	8,315	1,612	1.19 (1.10-1.29)
				Current	1,120	183	1.08 (0.91-1.28)
DeBono N.L. et al. (2018)(211)	United States	PCCS	1993-2001	Never	853	988	1.00**
				Ever	299	251	0.88 (0.65-1.18)
Brinton L.A. et al. (2018)(145)	United States	PCCS	1990-1992	Never	671	783	1.00
				Ever	122	98	0.70 (0.50-0.90)
Salagame U. et al. (2016)(182)	Australia	PCCS	2006-2014	Never	430	595	1.00
				Ever	46	103	1.80 (1.21-2.68)
Rosenberg L. et al. (2016)(183)	United States	PCCS	1993-2013	Never	3,509	949	1.00**
				Ever	2,318	475	1.08 (0.93-1.25)
Thorbjarnardottir T. et al. (2014)(182)	Europe	PCCS	1987-2006	Never	4,390	ND	1.00
				Ever	2,722	ND	1.13 (0.85-1.49)

Fei C. et al. (2013)(185)	United States	NCCS	ND	Never	1,499	1,346	1.00*
				Ever	113	50	0.49 (0.27-1.89)
Cerne J.Z. et al. (2011) (186)	Europe	PCCS	2006-2008	Never	584	465	1.00
				Ever	53	82	0.51 (0.30-0.87)
Barnes B.B et al. (2011)(36)	Europe	PCCS	2002-2005	Never	2,596	1,020	1.01 (0.89-1.15)
				Former	1,647	637	1.00
				Current	739	341	1.19 (1.01-1.41)
Hines L.M. et al. (2010)(37)	United States	PCCS	2000-2005	Never	793	710	1.00**
				Ever	486	468	1.08 (0.87-1.34)
Sprague B.L. et al. (2008)(39)	United States	PCCS	1997-2000	Never	2,125	1,538	0.92 (0.77-1.10)
				Former	364	283	1.00
				Current	839	651	0.96 (0.791.17)
Rosenberg L.U. et al. (2006)(187)	Europe	PCCS	1993-1995	Never	1,707	903	1.00
				Ever	167	154	1.90(1.50-2.40)
Newcomb P.A. et al. (2002)(188)	United States	PCCS	1992-1994	Never	2,919	2,780	1.00
				Ever	303	308	1.11 (0.92-1.34)
Chen C.L. et al. (2002)(189)	United States	NCCS	1990-1995	Never	271	243	1.00
				Former	189	171	0.92 (0.70-1.22)
				Current	111	132	1.17 (0.85-1.60)
La Vecchia C. et al. (1995)(190)	Europe	PCCS	1991-1994	Never	2,395	2,376	1.00**
				Ever	68	62	1.08 (0.75-1.55)
Palmer J.R. et al. (1991)(212)	Canada	PCCS	1982-1986	Never	991	493	1.00
				Ever	185	94	1.00 (0.80-1.40)

Abbreviation: PCCS; Population-based case-control study, NCCS; Nested case-control study, SeBCS; Seoul Breast Cancer Society, KBCS; Korean Breast Cancer Study, KMCC; Korean Multi-center cancer cohort

*Calculated RR; Calculation of crude RR (95% CI) by the population of each data set.

**Summary RR; Recalculation of adjusted RR (95% CI) by the meta-analysis.

Supplementary table 13. Association between age at menarche and breast cancer in Korean women

Age at menarche	Age	RR (95% CI)
BC incidence		
Cohort study		
Korea multi-center cancer cohort (KMCC)[1]	-15	1.36 (0.75-2.45)
	16-17	1.24 (0.70-2.19)
	18+	1.00
Korean National Cancer Center (KNCC)	-13	*1.42 (0.99-2.05)*
	14-15	1.07 (0.78-1.46)
	16+	1.00
Korean Cancer Prevention Study (KCPS II)	-13	1.20 (0.96-1.49)
	14-15	1.07 (0.84-1.37)
	16+	1.00
Healthcare System Gangnam Center	-14	1.24 (0.65-2.33)
	15-16	1.09 (0.55-2.17)
	17+	1.00
Kangbuk Samsumg Hospital	-11	1.60 (0.81-3.16)
	12-13	1.22 (0.84-1.77)
	14+	1.00
Namwon cohort[1]	-14	1.61 (0.67-3.86)
	15-16	1.36 (0.68-2.72)
	17+	1.00
Shin AS et al. (2011)	-14	**1.52 (1.36-1.70)**
	15-16	**1.24 (1.13-1.36)**
	17+	1.00
Case-control study		
Korean Breast Cancer Study (KBCS)	-14	0.91 (0.88-0.94)
	15-16	0.99 (0.96-1.03)
	17+	1.00
Park BY et al. (2016)	-14	**1.94 (1.39-2.71)**
Seoul Breast Cancer Study (SeBCS)	15-16	**1.43 (1.21-1.70)**
	17+	1.00
Park BY et al. (2018) (NCSP)[2]	-13	**1.61 (1.15-2.26)**
	14-16	**1.24 (1.05-1.48)**
	17+	1.00
BC death		
Cohort study		
Korea multi-center cancer cohort (KMCC)[1]	-15	1.87 (0.46-7.54)
	16-17	1.15 (0.27-4.84)
	18+	1.00
Korean Genome and Epidemiology Study	-13	1.66 (0.86-3.19)
(KoGES)[1]	14-15	1.13 (0.66-1.96)
	16+	1.00
Korean National Health and Nutrition	-13	2.03 (0.21-19.50)
Examination Survey (KNHANES)[1]	14-16	1.79 (0.20-16.03)
	17+	1.00

1. Corresponding relative risks(RRs) and 95% CI were calculated in Poisson regression.
2. Mammographic breast cancer screening through the National Cancer Screening Program (NCSP)

Supplementary table 14. Association between age at menopause and breast cancer in Korean women

Age at menopause*	Age	RR (95% CI)
BC incidence		
Cohort study		
Korea multi-center cancer cohort (KMCC)[1]	-51	1.00
	52-53	1.68 (0.76-3.71)
	54+	1.15 (0.47-2.81)
Korean National Cancer Center (KNCC)	-49	1.00
	50-54	1.13 (0.63-2.03)
	55+	1.90 (0.89-4.07)
Korean Cancer Prevention Study (KCPS II)	-52	1.00
	53-54	1.06 (0.55-2.01)
	55+	1.46 (0.83-2.57)
Healthcare System Gangnam Center	-48	1.00
	48-52	1.37 (0.56-3.37)
	53+	1.77 (0.60-2.18)
Namwon cohort[1]	-48	1.00
	48-51	1.21 (0.52-2.77)
	52+	1.39 (0.63-3.05)
Shin AS et al. (2011)	-45	1.00
	45-54	**1.42 (1.14-1.75)**
	55+	**1.80 (1.31-2.49)**
Case-control study		
Korean Breast Cancer Study (KBCS)	-48	1.00
	48-53	**1.34 (1.26-1.42)**
	53+	**1.35 (1.27-1.45)**
Park BY et al. (2018) (NCSP)[2]	-45	1.00
	45-54	**1.16 (1.07-1.25)**
	55+	1.18 (0.78-1.49)
Park BY et al. (2016)	-44	1.00
Seoul Breast Cancer Study (SeBCS)	45-49	1.02 (0.76-1.37)
	50+	**1.36 (1.09-1.69)**
BC death		
Cohort study		
Korea multi-center cancer cohort (KMCC)[1]	-48	1.00
	48-53	0.48 (0.08-2.67)
	53+	0.47 (0.05-4.21)
Korean National Health and Nutrition	-44	1.00
Examination Survey (KNHANES)[1]	45-49	1.44 (0.15-13.82)
	50+	0.56 (0.05-6.13)

*Corresponding variable was calculated only in postmenopausal women.

1. Corresponding relative risks(RRs) and 95% CI were calculated in Poisson regression.

2. Mammographic breast cancer screening through the National Cancer Screening Program (NCSP)

Supplementary table 15. Association between parity and breast cancer in Korean women

Parity	Category	RR (95% CI)
BC incidence		
Cohort study		
Korea multi-center cancer cohort (KMCC)[1]	Nulliparous	1.21 (0.38-3.88)
	Parous	1.00
Korean National Cancer Center (KNCC)	Nulliparous	**1.12 (1.08-1.16)**
	Parous	1.00
Healthcare System Gangnam Center	Nulliparous	1.05 (0.53-2.10)
	Parous	1.00
Namwon cohort[1]	Nulliparous	1.65 (0.23-11.84)
	Parous	1.00
Case-control study		
Korean Breast Cancer Study (KBCS)	Nulliparous	**2.01 (1.83-2.20)**
	Parous	1.00
Park BY et al. (2018) (NCSP)[2,3]	Nulliparous	**1.56 (1.04-2.33)**
	Parous	1.00
Park BY et al. (2016)[4]	Nulliparous	0.82 (0.62-1.10)
Seoul Breast Cancer Study (SeBCS)	Parous	1.00
BC death		
Cohort study		
Korean Genome and Epidemiology Study	Nulliparous	2.22 (0.96-5.12)
(KoGES)[1]	Parous	1.00

1. Corresponding relative risks(RRs) and 95% CI were calculated in Poisson regression.
2. Mammographic breast cancer screening through the National Cancer Screening Program (NCSP).
3. Parity was recalculated using meta-analysis of two or three RRs (95% CIs) on each category of number of childbirths.
4. Parity was recalculated using meta-analysis of two or three RRs (95% CIs) on each category of age at first full-term pregnancy.

Supplementary table 16. Association between age at first-full term pregnancy and breast cancer in Korean women

Age at first full-term pregnancy*	Age	RR (95% CI)
BC incidence		
Cohort study		
Korea multi-center cancer cohort (KMCC)[1]	-19	1.00
	20-29	1.29 (0.61-2.70)
	30+	2.22 (0.77-6.42)
Korean National Cancer Center (KNCC)	-25	1.00
	26-28	1.04 (0.76-1.42)
	29+	**1.55 (1.10-2.18)**
Healthcare System Gangnam Center	-25	1.00
	26-28	1.56 (0.91-2.68)
	29+	1.80 (0.97-3.34)
Namwon cohort[1]	-26	1.00
	26-28	**2.52 (1.10-5.79)**
	29+	2.89 (0.88-9.46)
Lee SY et al. (2003)	-25	1.00
Korean Women's cohort[2]	26-28	1.20 (0.80-1.60)
	29+	**1.60 (1.10-2.20)**
Case-control study		
Korean Breast Cancer Study (KBCS)	-25	1.00
	26-28	*1.05 (1.00-1.10)*
	29+	**1.42 (1.34-1.51)**
Park BY et al. (2016)	-23	1.00
Seoul Breast Cancer Study (SeBCS)	24-30	1.06 (0.90-1.26)
	31+	1.14 (0.85-1.54)
BC death		
Cohort study		
Korea multi-center cancer cohort (KMCC)[1]	-22	1.00
	23-27	0.84 (0.27-2.64)
	28+	0.79 (0.10-6.44)
Korean Genome and Epidemiology Study	-19	1.00
(KoGES)[1]	20-29	1.33 (0.18-9.62)
	30+	1.38 (0.17-11.19)
Korean National Health and Nutrition	-22	1.00
Examination Survey (KNHANES)[1]	23-24	**2.47 (1.07-5.68)**
	25+	**3.76 (1.71-8.27)**

*Corresponding variable was calculated only in parous women.

1. Corresponding relative risks(RRs) and 95% CI were calculated in Poisson regression.

2. The Korean Women's Cohort (KWC) Study is an ongoing prospective cohort study designed to assess the effects of gender related variables on chronic disease in Korean women using the KMIC (the Korea Medical Insurance Corporation) sample.

Supplementary table 17. Association between number of childbirths and breast cancer in Korean women

Number of childbirths*	N	RR (95% CI)
BC incidence		
Cohort study		
Korea multi-center cancer cohort (KMCC)[1]	1	2.26 (0.88-5.77)
	2	**2.77 (1.67-4.60)**
	3+	1.00
Korean National Cancer Center (KNCC)	1	**3.47 (2.13-5.63)**
	2	**2.27 (1.51-3.41)**
	3+	1.00
Healthcare System Gangnam Center	1	2.05 (0.83-5.05)
	2	1.23 (0.55-2.76)
	3+	1.00
Namwon cohort[1]	1	**4.29 (1.31-14.05)**
	2	**2.51 (1.14-5.54)**
	3+	1.00
Lee SY et al. (2003)	1	**0.46 (0.27-0.75)**
Korean Women's cohort[2]	2	0.79 (0.53-1.18)
	3+	1.00
Case-control study		
Korean Breast Cancer Study (KBCS)	1	**1.79 (1.71-1.86)**
	2	**1.22 (1.19-1.26)**
	3+	1.00
Park BY et al. (2016)	Nulliparous	**1.64 (1.10-2.45)**
Seoul Breast Cancer Study (SeBCS)	1	**1.50 (1.12-2.01)**
	2+	1.00
BC death		
Cohort study		
Korea multi-center cancer cohort (KMCC)[1]	1-2	1.19 (0.37-3.85)
	3-4	1.15 (0.34-3.90)
	5+	1.00
Korean Genome and Epidemiology Study (KoGES)[1]	1	2.74 (0.31-23.95)
	2	**4.74 (1.42-15.82)**
	3+	1.00

*Corresponding variable was calculated only in parous women.

1. Corresponding relative risks(RRs) and 95% CI were calculated in Poisson regression.

2. The Korean Women's Cohort (KWC) Study is an ongoing prospective cohort study designed to assess the effects of gender related variables on chronic disease in Korean women using the KMIC (the Korea Medical Insurance Corporation) sample.

Supplementary table 18. Association between breastfeeding and breast cancer in Korean women

Breastfeeding	Category	RR (95% CI)
BC incidence		
Cohort study		
Korea multi-center cancer cohort (KMCC)[1]	Never	1.43 (0.70-2.89)
	Ever	1.00
Korean National Cancer Center (KNCC)	Never	1.36 (0.91-2.06)
	Ever	1.00
Namwon cohort[1]	Never	**3.34 (1.19-9.33)**
	Ever	1.00
Lee SY et al. (2003)	Never	**1.30 (1.11-1.52)**
Korean Women's cohort[2]	Ever	1.00
Case-control study		
Korean Breast Cancer Study (KBCS)	Never	**1.72 (1.03-1.77)**
	Ever	1.00
Park BY et al. (2016)	Never	**1.41 (1.20-1.64)**
Seoul Breast Cancer Study (SeBCS)	Ever	1.00
BC death		
Cohort study		
Korea multi-center cancer cohort (KMCC)[1]	Never	1.92 (0.41-8.98)
	Ever	1.00
Korean National Health and Nutrition	Never	1.29 (0.26-6.41)
Examination Survey (KNHANES)[1]	Ever	1.00

1. Corresponding relative risks(RRs) and 95% CI were calculated in Poisson regression.
2. The Korean Women's Cohort (KWC) Study is an ongoing prospective cohort study designed to assess the effects of gender related variables on chronic disease in Korean women using the KMIC (the Korea Medical Insurance Corporation) sample.

Supplementary table 19. Association between duration of breastfeeding and breast cancer in Korean women

Duration of breastfeeding	Months	RR (95% CI)
BC incidence		
Cohort study		
Korean National Cancer Center (KNCC)	Never	1.24 (0.79-1.94)
	6	**1.96 (1.25-3.07)**
	6+	1.00
Lee SY et al. (2003)	Never	0.77 (0.51-1.16)
Korean Women's cohort[2]	12	0.73 (0.48-1.11)
	12+	1.00
Case-control study		
Korean Breast Cancer Study (KBCS)	Never	**4.88 (4.70-5.07)**
	6	**1.29 (1.21-1.37)**
	6+	1.00
Park BY et al. (2018) (NCSP)[3]	Never	**1.35 (1.03-1.77)**
	12	0.90 (0.73-1.12)
	12+	1.00
Park BY et al. (2016)	Never	1.03 (0.87-1.21)
Seoul Breast Cancer Study (SeBCS)	6	**1.28 (1.07-1.53)**
	6+	1.00
BC death		
Cohort study		
Korean National Health and Nutrition	Never	0.91 (0.18-4.68)
Examination Survey (KNHANES)[1]	24	0.28 (0.03-2.42)
	24+	1.00

1. Corresponding relative risks(RRs) and 95% CI were calculated in Poisson regression.
2. The Korean Women's Cohort (KWC) Study is an ongoing prospective cohort study designed to assess the effects of gender related variables on chronic disease in Korean women using the KMIC (the Korea Medical Insurance Corporation) sample.
3. Mammographic breast cancer screening through the National Cancer Screening Program (NCSP).

Supplementary table 20. Association between use of oral contraceptives and breast cancer in Korean women

Oral contraceptive use	Months	RR (95% CI)
BC incidence		
Cohort study		
Korea multi-center cancer cohort (KMCC)[1]	Never	1.00
	Ever	0.99 (0.62-1.60)
Korean National Cancer Center (KNCC)	Never	1.00
	Ever	1.11 (0.81-1.53)
Healthcare System Gangnam Center	Never	1.00
	Ever	0.38 (0.17-0.82)
Namwon cohort[1]	Never	1.00
	Ever	0.72 (0.30-1.72)
Lee SY et al. (2003)	Never	1.00
Korean Women's cohort[2]	Ever	*0.80 (0.60-1.00)*
Case-control study		
Korean Breast Cancer Study (KBCS)	Never	1.00
	Ever	**1.65 (1.56-1.75)**
Park BY et al. (2018) (NCSP)[3]	Never	1.00
	Ever	1.04 (0.69-1.56)
Park BY et al. (2016)	Never	1.00
Seoul Breast Cancer Study (SeBCS)	Ever	**1.28 (1.01-1.60)**
BC death		
Cohort study		
Korea multi-center cancer cohort (KMCC)[1]	Never	1.00
	Ever	2.76 (0.95-8.00)
Korean Genome and Epidemiology Study	Never	1.00
(KoGES)[1]	Ever	0.46 (0.18-1.15)
Korean National Health and Nutrition	Never	1.00
Examination Survey (KNHANES)[1]	Ever	0.93 (0.11-7.73)

1. Corresponding relative risks(RRs) and 95% CI were calculated in Poisson regression.
2. The Korean Women's Cohort (KWC) Study is an ongoing prospective cohort study designed to assess the effects of gender related variables on chronic diseases in Korean women using the KMIC (the Korea Medical Insurance Corporation) sample.
3. Mammographic breast cancer screening through the National Cancer Screening Program (NCSP).

Supplementary table 21. Association between use of hormone replacement therapy (HRT) and breast cancer in Korean women

Hormone replacement therapy use*	Months	RR (95% CI)
BC incidence		
Cohort study		
Korea multi-center cancer cohort (KMCC)[1]	Never	1.00
	Ever	2.02 (0.99-4.10)
Healthcare System Gangnam Center	Never	1.00
	Ever	1.12 (0.55-2.29)
Kangbuk Samsung Hospital	Never	1.00
	Ever	**1.99 (1.40-2.81)**
Case-control study		
Korean Breast Cancer Study (KBCS)	Never	1.00
	Ever	**1.65 (1.56-1.75)**
Park BY et al. (2018) (NCSP)[2]	Never	1.00
	Ever	1.13 (0.87-1.27)
Park BY et al. (2016)	Never	1.00
Seoul Breast Cancer Study (SeBCS)	Ever	1.16 (0.36-3.78)
BC death		
Cohort study		
Korea multi-center cancer cohort (KMCC)[1]	Never	1.00
	Ever	1.17 (0.13-10.46)
Korean Genome and Epidemiology Study	Never	1.00
(KoGES)[1]	Ever	0.77 (0.36-1.64)
Korean National Health and Nutrition	Never	1.00
Examination Survey (KNHANES)[1]	Ever	1.67 (0.21-13.82)

* Corresponding variable was calculated only in postmenopausal women.

1. Corresponding relative risks(RRs) and 95% CI were calculated in Poisson regression.

2. Mammographic breast cancer screening through the National Cancer Screening Program (NCSP).

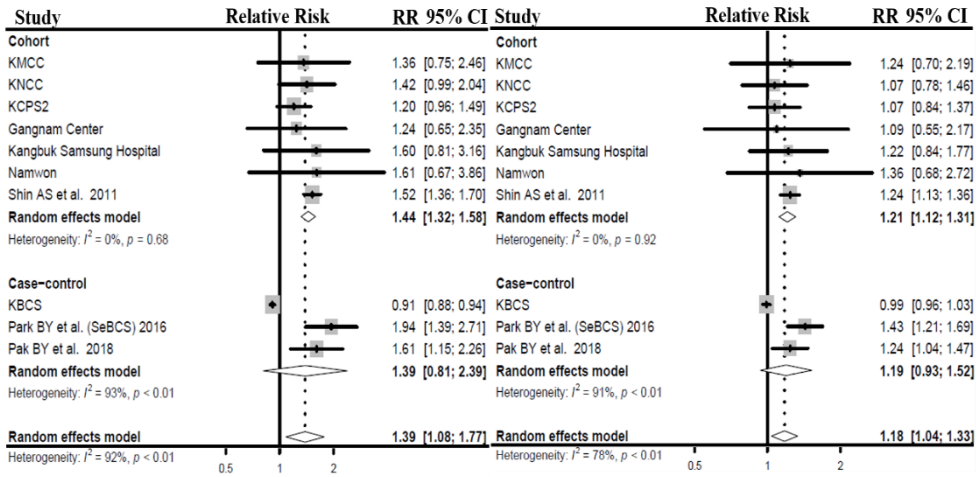


Figure 1. Association between age at menarche and breast cancer in Korea population. (Left: ≤ 14 *vs.* ≥ 17 [reference], Right: 15-16 *vs.* ≥ 17 [reference])

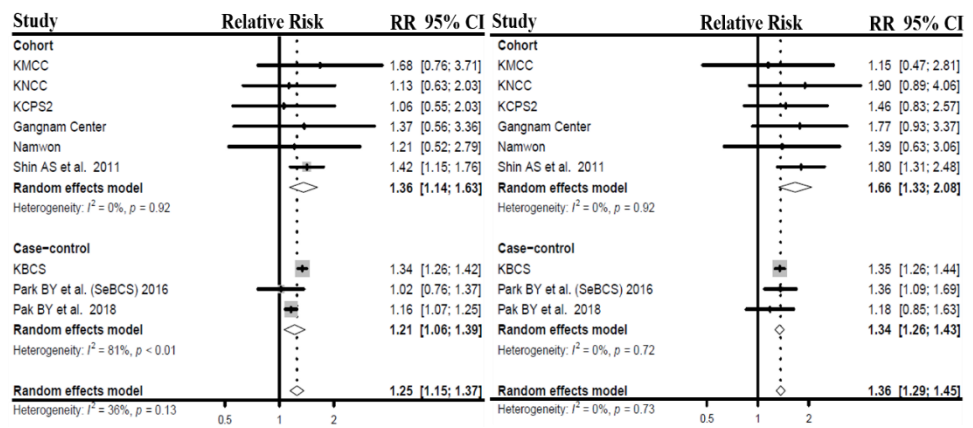


Figure 2. Association between age at menopause and breast cancer in Korean population. (Left: 48-52 *vs.* < 48 [reference], Right: ≥ 53 *vs.* < 48 [reference])

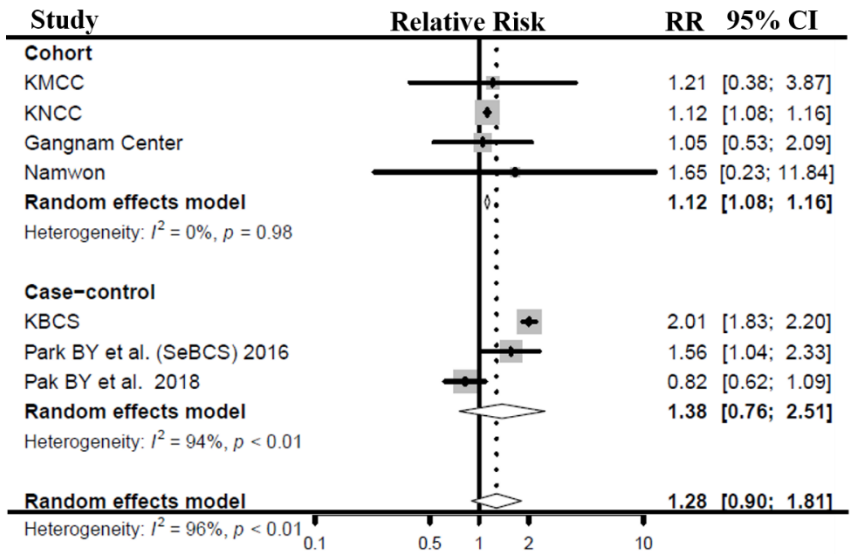


Figure 3. Association between parity and breast cancer in Korean population (Nulliparous *vs.* Parous [reference])

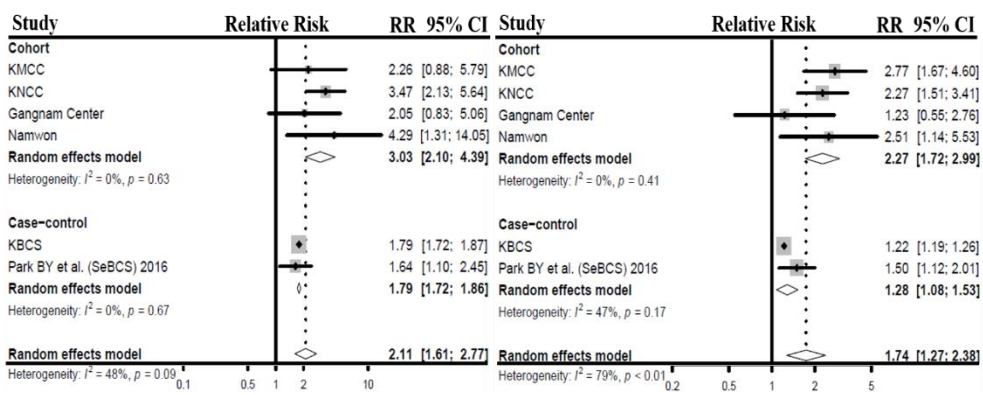


Figure 4. Association between number of childbirths and breast cancer among parous women in Korea population. (Left: 1 *vs.* ≥ 3 [reference], Right: 2 *vs.* ≥ 3 [reference])

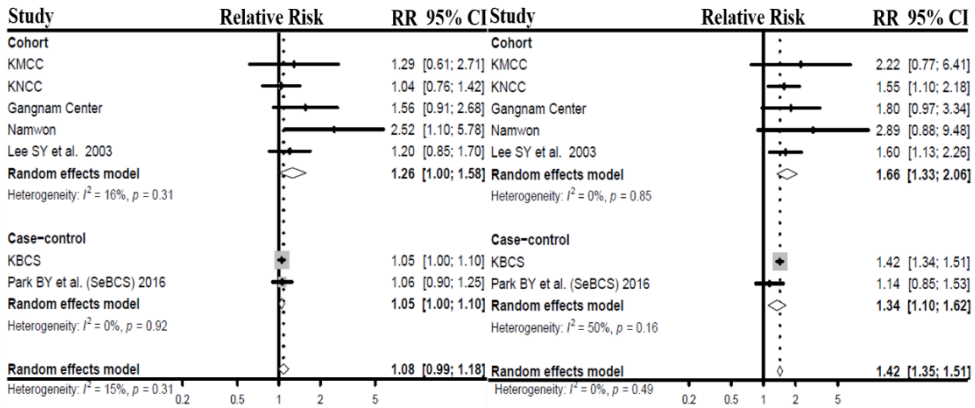


Figure 5. Association between age at first full-term pregnancy and breast cancer in Korean population. (Left: 20-30 *vs.* < 20 [reference], Right: ≥ 30 *vs.* < 20 [reference])

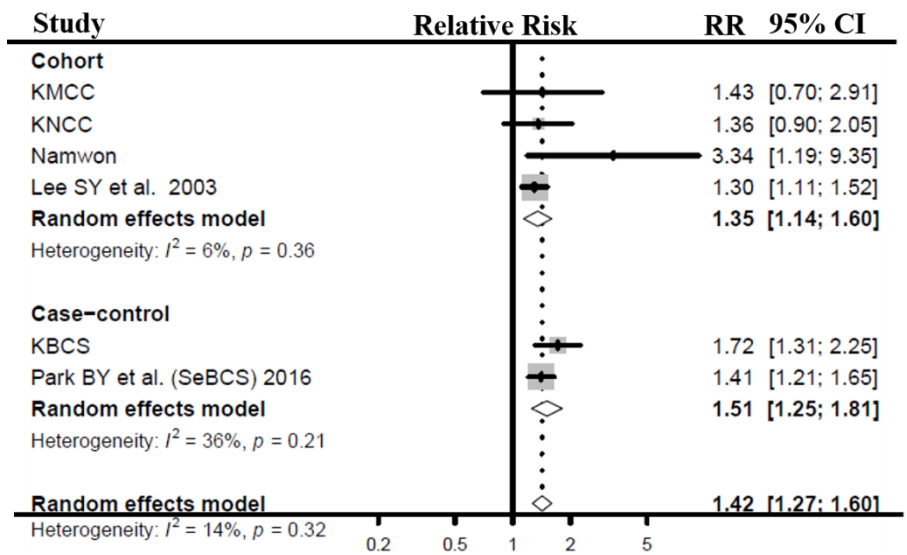


Figure 6. Association between breastfeeding and breast cancer in Korean population. (Never *vs.* Ever [reference])

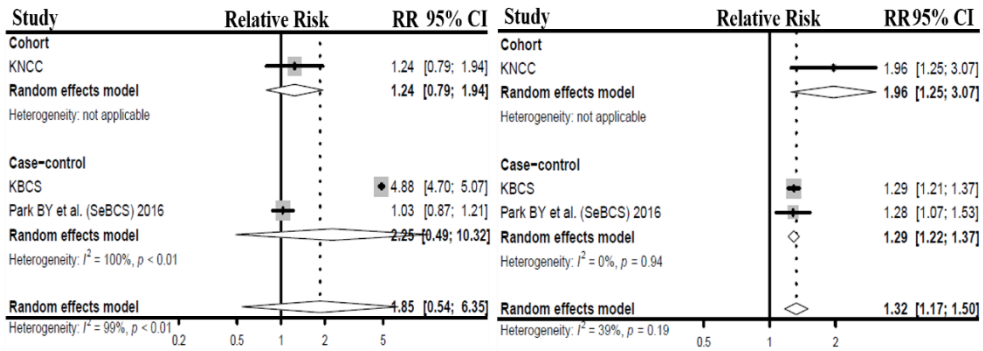


Figure 7. Association between duration of breastfeeding and breast cancer in Korean population. (Left: Never *vs.* ≥ 6 months [reference], Right: < 6 months *vs.* ≥ 6 months [reference])

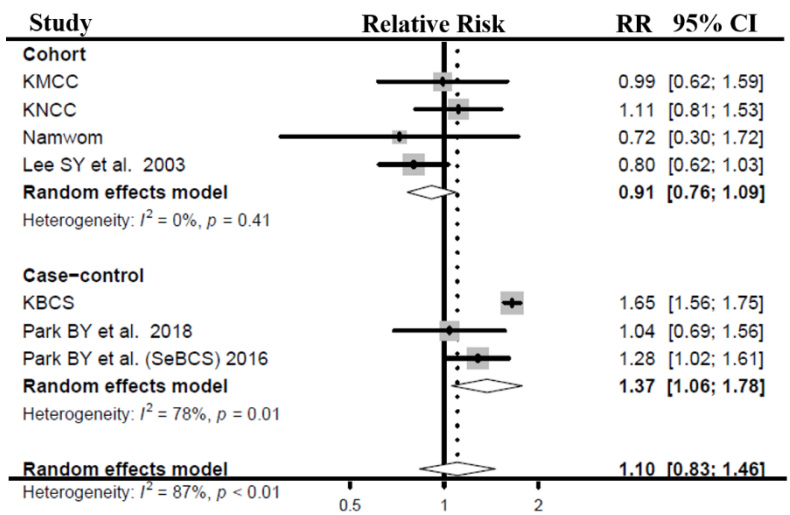


Figure 8. Association between oral contraceptives and breast cancer in Korean population. (Ever *vs.* Never [reference])

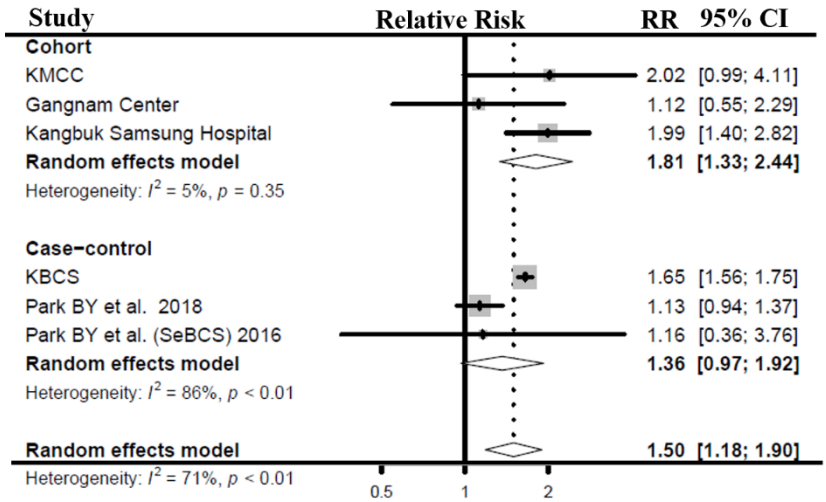


Figure 9. Association between hormone replacement therapy (combination) and breast cancer in Korean population. (Ever *vs.* Never [reference])

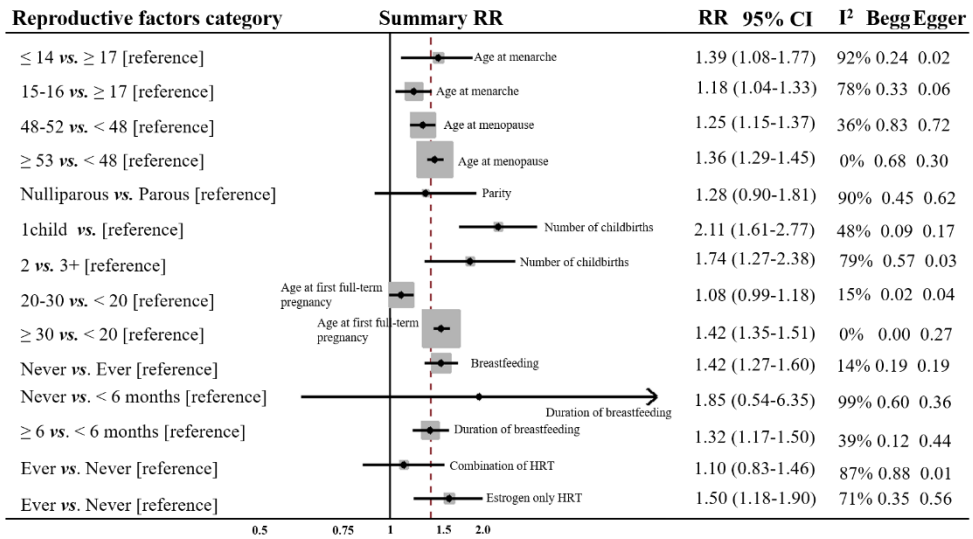


Figure 10. Summary relative risks of breast cancer related to each reproductive factors in Korean population.

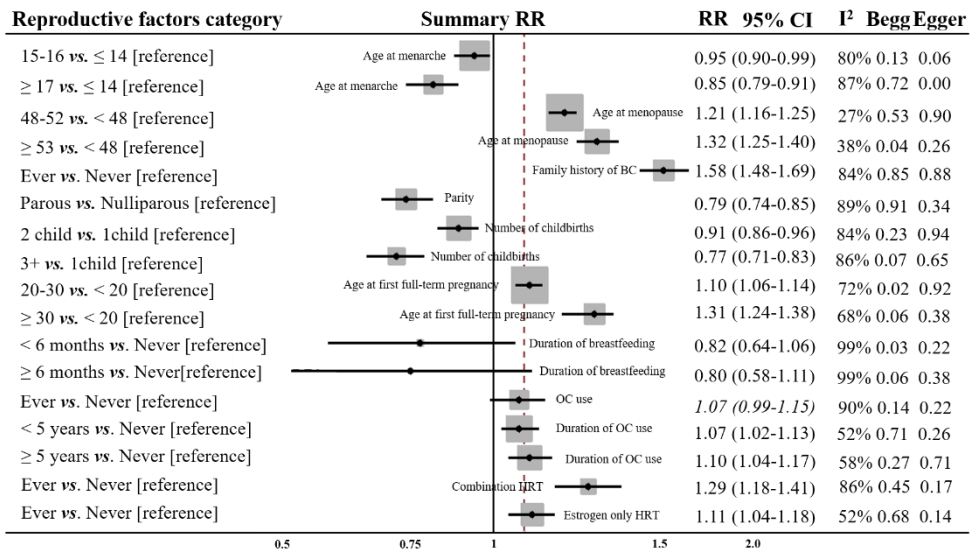
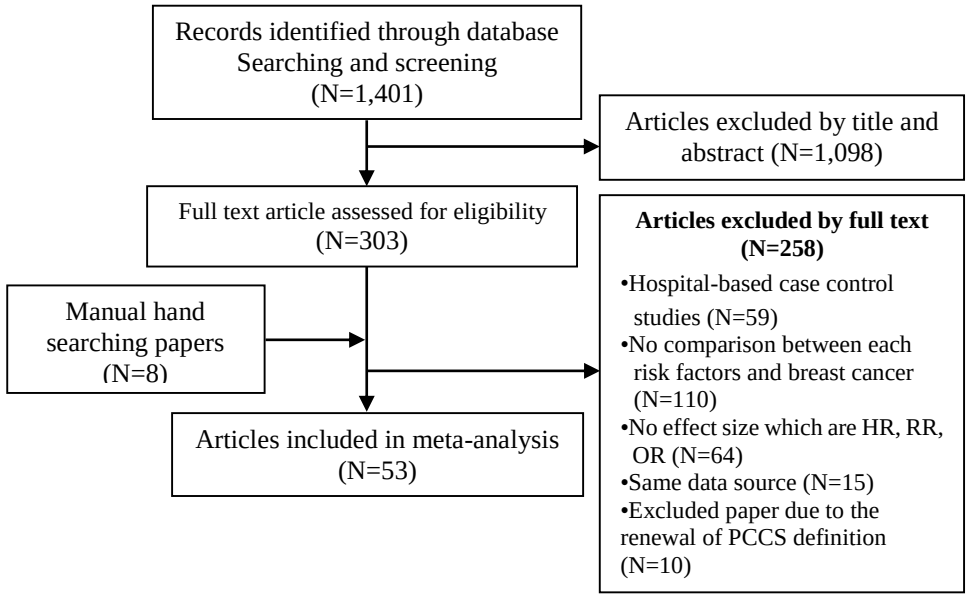
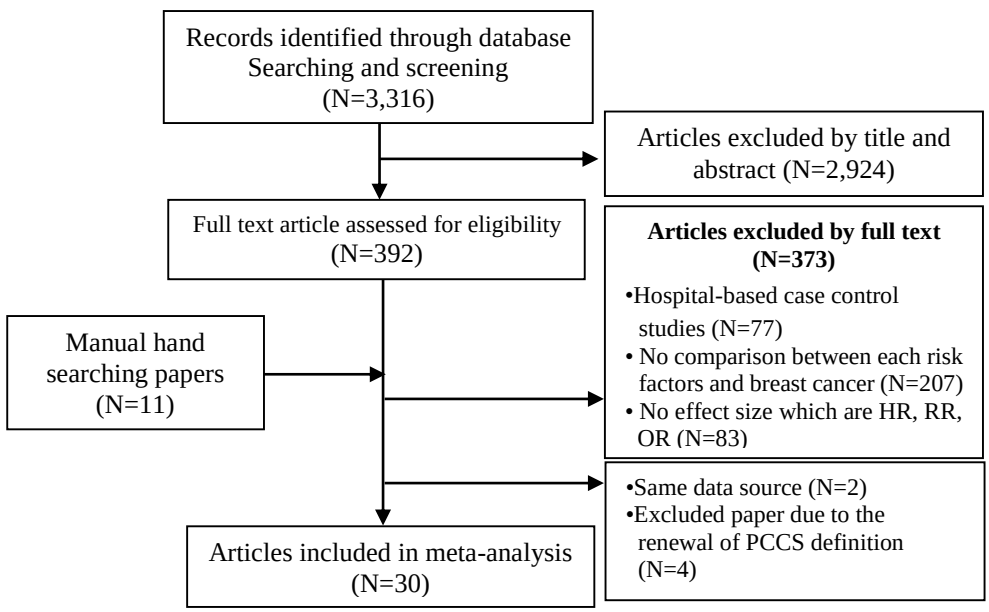


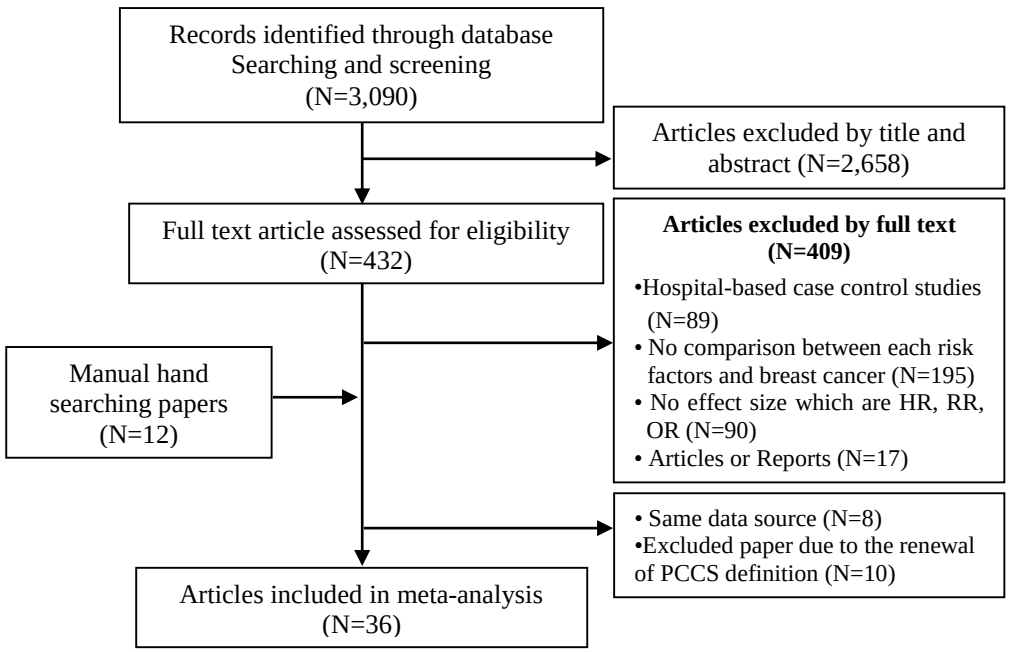
Figure 11. Summary relative risks of breast cancer related to each reproductive factors in Global population.



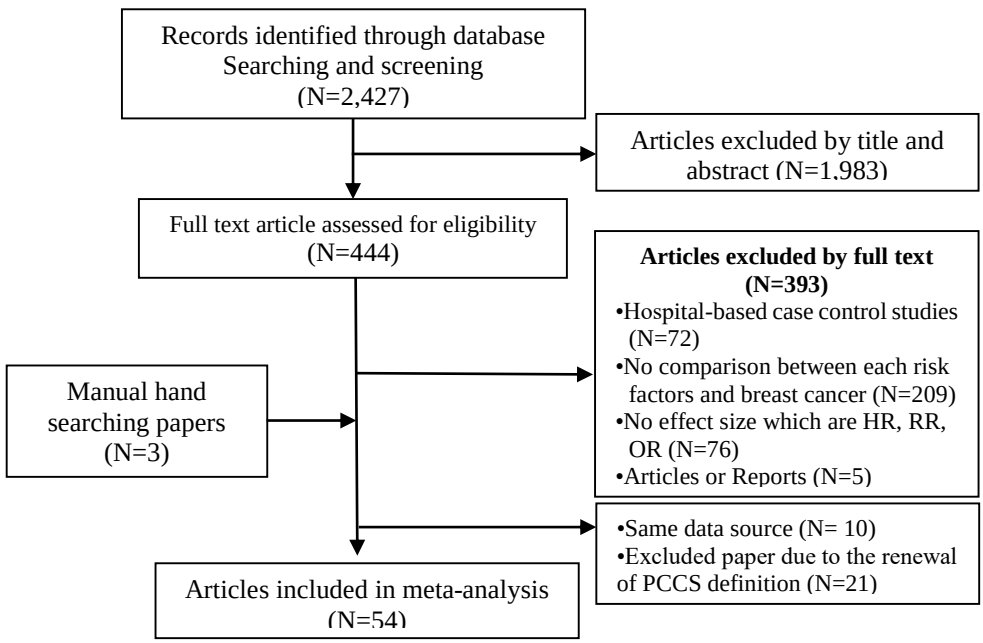
Supplementary figure 1. Flow chart for systematic review of association between age at menarche and breast cancer in Global population.



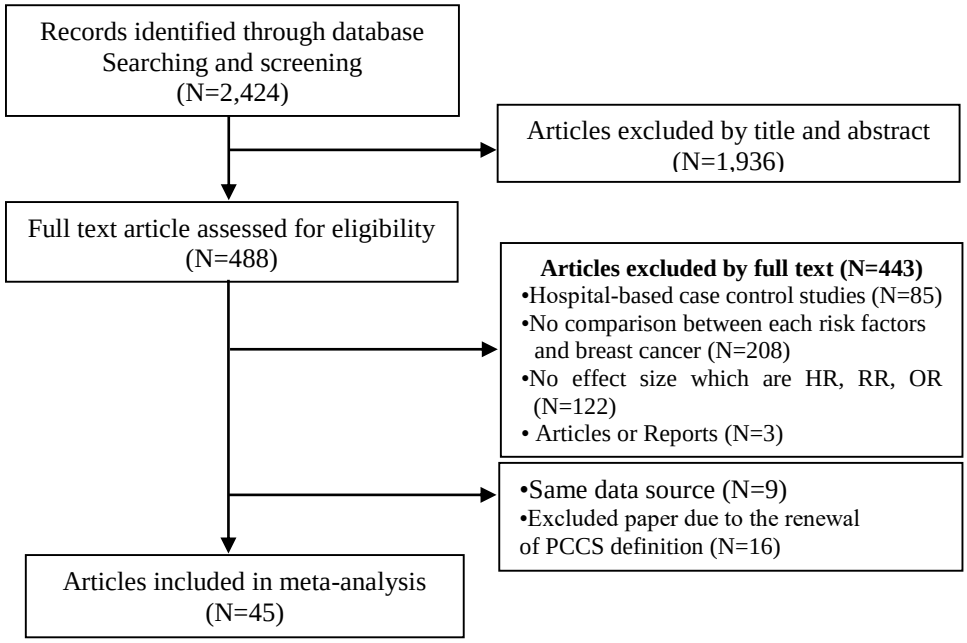
Supplementary Figure 2. Flow chart for systematic review of association between age at menopause and breast cancer in Global population.



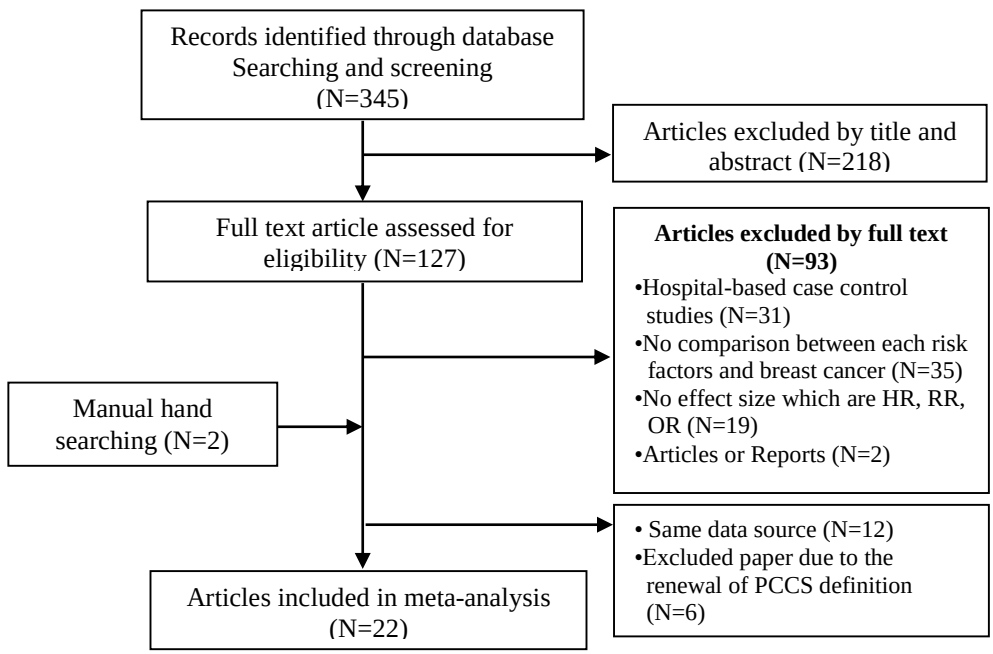
Supplementary figure 3. **Flow chart for systematic review of association between family history and breast cancer in Global population.**



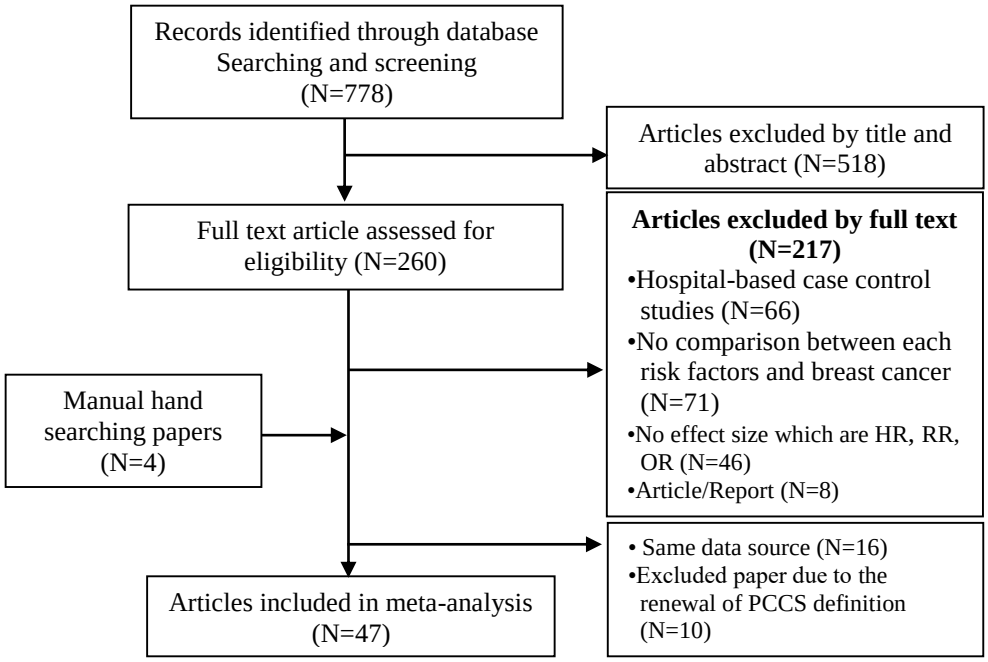
Supplementary figure 4. **Flow chart for systematic review of association between age at first-full term pregnancy and breast cancer in Global population.**



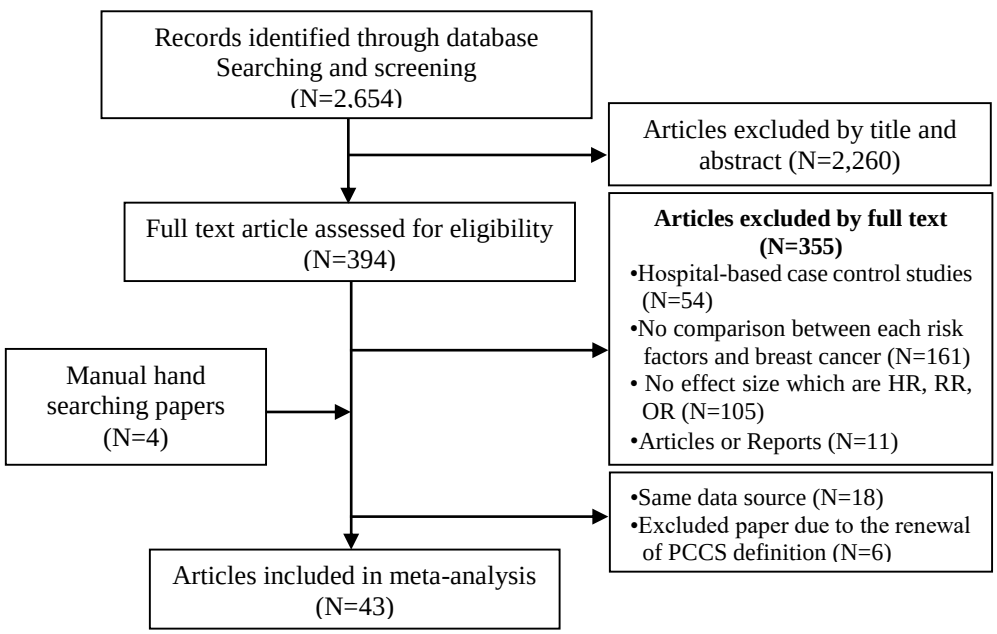
Supplementary figure 5. Flow chart for systematic review of association between the number of childbirths and breast cancer in Global population.



Supplementary figure 6. Flow chart for systematic review of association between the duration of breastfeeding and breast cancer in Global population.



Supplementary figure 7. Flow chart for systematic review of association between use of oral contraceptives and breast cancer in Global population.



Supplementary figure 8. Flow chart for systematic review of association between hormone replacement therapy use and breast cancer in Global population. (Combination of estrogen and progestin)

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초 록

서론: 유방암은 여성에게 가장 큰 위험을 주는 암이며 이에 따른 위험도는 생식 요인들과 외인성 호르몬에 기인한다는 것은 잘 알려져 있는 사실이다. 또한 유방암과 reproductive factors 간의 연관성에 대한 메타 분석 연구들은 많이 진행되어 있으나 아직까지 전체 reproductive factors 간의 최신 동향을 연구한 연구는 한국인을 포함하여 부족한 현실이다. 따라서 본 연구에서는 체계적 문헌 고찰 및 meta-analysis를 통하여 부족한 한국인의 메타 결과를 재 수립하고 한국인의 결과와 비교를 하기 위하여 전세계인의 결과를 비교 분석을 한 뒤 각 요인들에 걸맞는 범주를 수립하는 것이다.

방법: 연구를 수행하기 위하여 우선 체계적 문헌 고찰을 수행한 뒤, 통계적인 기법을 이용하여 메타 분석을 진행한다. PICO 기법을 이용하여 검색어 전략을 수행하며 검색원으로는 PubMed와 KoreaMed를 이용하였다. 연구논문 중 유방암과 그에 따른 위험 요인들의 위험도 산출 및 신뢰구간 산출에 관한 논문들을 선택하여 random effect model (변량효과 모형)을 이용하여 전체 summary RR을 산출한다. 또한 연구 디자인, 나라별 그리고 출판 연도로 subgroup analysis (하위 그룹 분석)을 수행한다.

결과: 한국 인구집단의 경우 각 요인들에 따른 유방암 한국인들의 메타 결과를 이용하여 각 요인들의 인구집단 기여율 (PAF)를 계산할 예정이기 때문에 모든 결과(RRs)들은 1보다 큰 방향으로 산출되었다. 결론적으로 대부분의 생식요인들이 유의함을 보였으나 임신 여부, 모유

수유 여부, 경구피임약 복용 여부에 대해서 유의하지 않음을 보였다. 또한 이 인구집단을 세계로 확장하였을 때, 경구피임약을 복용한 여성이 그렇지 않은 여성에 비해 약 10%정도의 유방암 위험도를 보이는 반면 호르몬치료제를 시행한 여성은 그렇지 않은 여성에 비해 약 30%정도 높은 유방암 위험도를 보인다. 더 나아가, 나라별 하위 그룹 분석을 시행하였을 경우 유럽과 미국 대륙을 서양이라고 하였을 때, 각 요인들에 따른 위험도가 증가한 경우 나라별로 위험도가 산발적이었으며 각 요인들이 보호 요인인 경우 아시아가 서양보다는 더 보호 요인을 보인다. 추가적인 출판 연도를 이용한 하위 그룹 분석 결과의 경우 출판 연도를 기준으로 한 생식요인들의 차이점을 발견하긴 하였지만 1990년도 이전의 논문들의 부족으로 인하여 유의한 근거를 수립하지는 못하였다.

고찰 및 결론: 본 연구는 modifiable과 unmodifiable 한 생식요인들의 변수를 모아 유방암과 그에 따른 생식요인들의 결과를 확인하며 더 나아가 한국형 PAF 값을 산출하기 위하여 한국인 메타 값을 재정립함이다. 또한 세계 인구로 확장하였을 때에도 각 생식 요인들의 위험도를 재 확인함에 있다.

주요어: 유방암, 생식 요인 및 외인성 호르몬 요인, 체계적 문헌 고찰, 메타 분석, 변량효과 모형

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