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Association between reproductive factors and breast cancer subtypes: A meta-analysis

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Dr. Tomi Akinyemiju, Committee Chair

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Association between reproductive factors and breast cancer subtypes: A meta-analysis

Xihua Mao, BM

CAPSTONE PROJECT PAPER

University of Kentucky College of Public Health

Lexington, Kentucky
November 21, 2018 (Presentation date)

Committees

Tomi Akinyemiju, Ph.D., chair

Tisha K. Johnson, MD, MPH

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Abstract

Introduction: Hormone-related reproductive factors have been reported to be associated with breast cancer subtypes. However, the direction and magnitude of these associations were inconsistent. Additionally, for breast cancer defined by estrogen receptor (ER) and progesterone receptor (PR): ER+PR+, ER+PR-, ER-PR+, and ER-PR- subtypes, no meta-analysis was available for ER+PR-and ER-PR+ subtypes. For ER+PR+ and ER-PR- subtypes, only a few reproductive risk factors have been examined in meta-analyses.

Methods: Primary studies published from 2011 to 2017 were retrieved from PubMed, Embase, and Scopus. Following PRISMA guidelines, a total of 98 eligible studies investigated the association between reproductive factors and breast cancer subtypes. Among these 98 studies, 27 were included in the meta-analysis regarding the association between reproductive factors and ERPR subtypes. Odds ratios (OR), relative risks (RR), and hazard ratios (HR) were extracted for reproductive factors, including age at menarche, age at menopause, menopausal status, pregnancy, age at first birth, parity, breastfeeding, years since last birth, OC use, and HRT. OR and HR were converted to RR to ensure consistency. A meta-analysis with a random effect model was separately conducted for each combination of a reproductive factor and a BC subtype defined by ERPR status. Heterogeneity across studies was examined by I^2-statistic, publication bias was examined utilizing Egger and Begg's test.

Results: This meta-analysis observed that late age at menarche was associated with a reduced risk for ER+PR+ (RR:0.79, 95% CI: 0.72, 0.85), ER+PR- (RR:0.75, 95% CI:0.58, 0.92), ER-PR+ (RR: 0.79, 95% CI:0.63, 0.95), and ER-PR- subtypes (RR:0.85, 95% CI: 0.79, 0.91). Ever versus never pregnancy was associated with a statistically significant reduced risk of ER+PR+ (RR: 0.62, 95% CI: 0.47, 0.78), ER+PR- (RR: 0.70, 95% CI: 0.57, 0.83), and ER-PR+ subtypes

(RR: 0.68, 95% CI: 0.49, 0.87). Ever versus never breastfeeding was associated with a statistically significant reduced risk of ER+PR+ (RR: 0.87, 95% CI: 0.79, 0.96), ER+PR- (RR: 0.67, 95% CI: 0.52, 0.83), and ER-PR- subtypes (RR: 0.81, 95% CI: 0.69, 0.93). No significant results were observed for years since last birth and oral contraceptive use. Additionally, results were relatively less consistent for age at menopause, menopausal status, age at first birth, parity, and hormone replacement therapy. There was no evidence of publication bias for pregnancy and parity. For the rest reproductive factors, there is some evidence of publication bias.

Conclusion: The patterns of reproductive factors differ by ERPR status. Most significant associations were observed for ER+PR+ and ER+PR- subtypes. Moreover, strongest associations were mostly observed in ER+PR- subtype. Thus, breast cancer preventive guideline regarding reproductive factors probably should be revised by subtypes. Moreover, ever breastfeeding and pregnancy could probably be added to breast cancer risk calculation model, although more prospective studies with a large sample size are needed to confirm the findings.

1. Background

Breast cancer (BC) is globally one of the most common cancers and one of the leading causes of cancers death among women[1]. The worldwide estimated incidence of female BC by 2050 is 3.2 million new cases per year[2]. Different patterns of reproductive factors, lifestyle-related factors, genetic factors, and BC screening have been reported to cause the BC incidence increase[3]. BC is widely recognized as a heterogeneous cancer due to its different risk factors, prognoses, and treatments by subtypes[4]. Common reproductive factors include age at menarche, age at menopause, menopausal status, pregnancy-related factors, age at first birth, parity, breastfeeding, years since last birth, OC use, and hormone replacement therapy (HRT). These factors probably impact BC subtypes through hormone such as estrogen[5]. Generally, age at first birth, pregnancy change hormone status. Some other factors such as age at menarche and age at menopause are markers for hormone status changes. Detailly, earlier age at menarche and later age at menopause might cause a longer duration of hormone exposure, which is generally believed to increase risk of BC[6]. According to estrogen receptor (ER) and progesterone receptor (PR), BC could be classified as ER+PR+ subtype, ER+PR- subtype, ER-PR+ subtype, and ER-PR- subtype. Among these four subtypes, ER+PR+ subtype is the most common one, and ER-PR+ subtype is least common, with ER-PR- and ER+PR- in the middle[7-9]. Associations have been investigated between reproductive factors and BC subtypes classified by ERPR status. However, the influences of many reproductive factors on these subtypes are controversial. For instance, according to a systematic review conducted by Anderson et al, lactation was inversely associated with hormone receptor positive BC only in five out of 18 studies[3]. According to expressions of ER, PR, and human epidermal growth factor receptor-2 (HER2), BC could be classified into luminal A, luminal B, HER2-overexpressing, and triple-negative (TN) BC[10, 11]. Associations

between reproductive factors and these subtypes, especially HER2-overexpressing and TN BC, have not been well established[3]. For example, Yang et al found higher parity was associated with an increased risk of HER2-overexpressing BC[12]; however, Ma et al found the opposite association[13].

It is unclear to what extent impacts of reproductive factors have on each subtype. To date, no thorough meta-analysis has summarized available studies about associations between reproductive factors and BC subtypes. Specifically, among four subtypes defined by ERPR status, associations between reproductive factors and ER-PR- BC has been summarized in a few meta-analysis[14-16]; however, ER+PR+ subtype has only been evaluated in one of them[16]. Additionally, no review is available for both the association between reproductive factors and ER+PR- subtype and the association between reproductive factors and ER-PR+ subtype. Similarly, for luminal A, luminal B, HER2-overexpressing, and TN BC, only a few meta-analyses summarized some of these subtypes with limited types of reproductive factors[4, 14, 15, 17]. The most recent meta-analysis published in 2017 only investigated the association between oral contraceptive (OC) use and TN BC[17]. Another meta-analysis conducted in 2016, focusing on associations between reproductive factors and BC subtypes, only researched parity, age at first birth, and breastfeeding[4].

Due to impacts reproductive factors have on BC incidence, prognoses, and treatment, inconsistent findings on associations between reproductive factors and BC subtypes, and no thorough meta-analysis of these associations, conducting a meta-analysis about these associations is crucial. It allows us to have a review of how papers researched all reproductive risk factors by different subtypes, to explore the magnitude and direction of these associations, to

better understand BC etiology based on subtypes, and to provide a theoretical foundation for future research, and to propose potential BC preventive strategies.

2. METHODS

PRISMA guidelines (**Fig. 1**) were followed for this systematic review and meta-analysis[18]. Primary studies with the subject as human and published in English from January 1st, 2000 to December 31st, 2017 were retrieved from PubMed, Scopus, and Embase. The search strategy utilized included MeSH and non-MeSH key terms: 1) “reproductive history” as a MeSH term in general as well as specific reproductive factors, including risk factors, menarche, menopause, menstruation, menstrual period, age at first birth, birth control, parity, family size, pregnancy, pregnan*, birth intervals, breastfeeding, contraceptives, and hormone replacement therapy, 2)“Breast Neoplasms” and its relevant permutations and abbreviations, 3) “subtypes”: receptors, estrogen; receptors, progesterone; receptors, androgen; pidermal growth factor; luminal A; luminal B; HER-2; basal-like; and triple negative breast neoplasms. The specific search strategy is the following:

((((((((((((((((("Reproductive History"[Mesh]) OR ((((("Contraceptive Agents, Female"[Mesh]) OR ((contraceptive*[Title/Abstract] OR "birth control"[Title/Abstract] OR contraception[Title/Abstract]))) OR (("birth control"[Title/Abstract]) AND pill*[Title/Abstract])) OR "family planning"[Title/Abstract])) OR ((((((("Gravidity"[Mesh]) OR "Parity"[Mesh]) OR parity[Title/Abstract]) OR gravidity[Title/Abstract]) OR "family size"[Title/Abstract]) OR "pregnan*"[Title/Abstract])) OR ((((((("pregnancy timing"[Title/Abstract]) OR "timing of pregnancies"[Title/Abstract])) OR "Birth Intervals"[Mesh])) OR "birth

intervals"[Title/Abstract])) OR (("Maternal Age"[Mesh]) OR "age at first birth"[Title/Abstract]))) OR ((("Breast Feeding"[Mesh]) OR ((breastfeed*[Title/Abstract] OR breastfed[Title/Abstract]))) OR (("breast feeding"[Title/Abstract] OR "breast feed"[Title/Abstract])))) OR ((((("Menarche"[Mesh]) OR "first period"[Title/Abstract]) OR menarche[Title/Abstract]) OR ((menstruation[Title/Abstract] OR menstrual[Title/Abstract] OR periods[Title/Abstract])))) OR (("Menopause"[Mesh]) OR menopaus*[Title/Abstract])) OR (("Hormone Replacement Therapy"[Mesh]) OR (("hormone replacement therapy"[Title/Abstract] OR HRT[Title/Abstract])))))) OR ((reproductive[Title/Abstract]) AND ((risk factors[MeSH Terms]) OR ((risks[Title/Abstract] OR "risk factors"[Title/Abstract] OR "risk factor"[Title/Abstract])))))) OR ((premenopaus*[Title/Abstract] OR postmenopaus*[Title/Abstract]))))

AND ((((((((((("Breast Neoplasms"[Mesh]) OR (("breast cancer"[Title/Abstract]) OR "breast neoplasms"[Title/Abstract])))

AND ((((((((((("Receptors, Estrogen"[Mesh]) OR (("estrogen receptor"[Title/Abstract] OR "estrogen receptors"[Title/Abstract])))) OR (("Receptors, Progesterone"[Mesh]) OR (("progesterone receptors"[Title/Abstract] OR "progesterone receptor"[Title/Abstract])))) OR (("Receptors, Androgen"[Mesh]) OR (("androgen receptors"[Title/Abstract] OR "androgen receptor"[Title/Abstract])))) OR "Epidermal Growth Factor"[Mesh]) OR "human epidermal growth factor receptor-2"[Title/Abstract]) OR "HER2"[Title/Abstract]) OR "ERB2"[Title/Abstract]) OR "luminal A"[Title/Abstract]) OR "luminal B"[Title/Abstract]) OR (("HER-2"[Title/Abstract] OR "HER 2"[Title/Abstract])) OR "basal-like"[Title/Abstract]))) OR (("Triple Negative Breast Neoplasms"[Mesh]) OR ((((("Breast Neoplasms"[Mesh]) OR (("breast

cancer"[Title/Abstract]) OR "breast neoplasms"[Title/Abstract]))) AND "triple negative"[Title/Abstract])))))) OR ((“estradiol receptor”[Title/Abstract] OR “estradiol receptors”[Title/Abstract]))) OR ((“Dihydrotestosterone Receptor”[Title/Abstract] OR “Dihydrotestosterone Receptors”[Title/Abstract] OR “Testosterone Receptor”[Title/Abstract] OR “Testosterone Receptors”[Title/Abstract]))) OR "Receptor, ErbB-2"[Mesh]))

AND (((((“Case-Control Studies”[Mesh:noexp] OR "retrospective studies"[mesh:noexp] OR “Control Groups”[Mesh:noexp] OR (case[TIAB] AND control[TIAB]) OR (cases[TIAB] AND controls[TIAB]) OR (cases[TIAB] AND controlled[TIAB]) OR (case[TIAB] AND comparison*[TIAB]) OR (cases[TIAB] AND comparison*[TIAB]) OR “control group”[TIAB] OR “control groups”[TIAB])) OR (cohort studies[mesh:noexp] OR longitudinal studies[mesh:noexp] OR follow-up studies[mesh:noexp] OR prospective studies[mesh:noexp] OR retrospective studies[mesh:noexp] OR cohort[TIAB] OR longitudinal[TIAB] OR prospective[TIAB] OR retrospective[TIAB])) OR (Cross-Sectional Studies[Mesh:noexp] OR cross-sectional[TIAB] OR Prevalence[mesh:noexp] OR prevalence[tiab] OR transversal study[tiab])) OR ((systematic*[tiab] AND (bibliographic*[TIAB] OR literature[tiab] OR review[tiab] OR reviewed[tiab] OR reviews[tiab])) OR (comprehensive*[TIAB] AND (bibliographic*[TIAB] OR literature[tiab])) OR “cochrane database syst rev”[Journal] OR "Evidence report/technology assessment (Summary)"[journal] OR "Evidence report/technology assessment"[journal] OR "integrative literature review"[tiab] OR "integrative research review"[tiab] OR "integrative review"[tiab] OR “research synthesis”[tiab] OR “research integration”[tiab] OR cinahl[tiab] OR embase[tiab] OR medline[tiab] OR psyclit[tiab] OR (psycinfo[tiab] NOT “psycinfo database”[tiab]) OR pubmed[tiab] OR scopus[tiab] OR “web of science”[tiab] OR “data synthesis”[tiab] OR meta-analys*[tiab] OR meta-analyz*[tiab] OR

meta-analyt*[tiab] OR metaanalys*[tiab] OR metaanalyz*[tiab] OR metaanalyt*[tiab] OR "meta-analysis as topic"[MeSH:noexp] OR Meta-Analysis[ptyp] OR ((review[tiab] AND (rationale[tiab] OR evidence[tiab])) AND review[pt])))

2.1 Study Eligibility: Inclusion criteria were studies concentrating on BC subtypes and reproductive factors as mentioned above. Exclusion criteria included studies not published in English, not published within January 1st, 2000 to December 31st, 2017, study outcomes other than BC subtypes, studies without researching reproductive factors, and studies with unavailable main estimates.

2.2 Selection: A total of 7424 studies was retrieved from database searches, and 13 additional papers, including dissertation, were identified through other sources. Titles, abstracts, and full-texts were reviewed by 2 authors for 6505 de-duplicated retrieved studies. 6379 studies were excluded through title review, which left 126 studies. Through abstract review, 105 studies were kept for the full-text review, which eventually gave 98 eligible studies. Articles were excluded for irrelevant studies and studies with critical missing data.

2.3 Data extraction: Data was abstracted by one author. Each data entry was also independently reviewed and verified based on original full-texts by another author. Any discrepancies were discussed to reach consensus, and disagreements were resolved by consulting a third author. Specifically, author, year, study design (country of study, sample size, race, and data source, etc), BC subtypes (ER+PR+ BC, ER+PR- BC, ER-PR+ BC, ER-PR- BC, luminal A BC, luminal B BC, HER-2 overexpressing BC, and triple negative BC), reproductive factors, and corresponding estimates and their 95% confidence intervals were recorded.

2.4 Statistical analysis: Odds ratios (OR), relative risks (RR), and hazard ratios (HR) for reproductive factors comparing the most extreme (e.g. highest vs. lowest) categories were extracted. To ensure consistency in meta-analysis, if needed, ratio measures were inverted to ensure reference categories matched across studies. Odds and hazard ratios were converted to approximate RR. When at least 3 studies of the exposure-outcome combination are available, a meta-analysis was separately conducted for each combination of exposure and each BC subtype defined by ERPR status. Included reproductive factors were: 1) age at menarche, 2) age at menopause, 3) menopause, 4) pregnancy, 5) age at first birth, 6) parity, 7) breastfeeding, 8) years since last birth, 9) oral contraceptive use, and 10) hormone replacement therapy. Random effects models were utilized to account for potential heterogeneity between the studies. Heterogeneity across studies was examined by I^2-statistic[18, 19], publication bias was assessed by Egger and Begg's test [20, 21]. All analyses were conducted using the STATA version 15 (Stata Corp LLC, College Station, TX).

3. RESULTS

Among all deduplicated 6505 studies searched from online database and review of reference lists, 98 studies were included according to the study inclusion and exclusion criteria (**Figure 1**). Among 98 studies, most of the eligible studies (64) were published between 2011 and 2017, 22 studies were published from 2006 to 2010, and 12 studies were published between 2000 to 2005 (**Table 1**). Data sources used in these studies include primary data (72), hospital databases (16), national cancer databases (5), and state registry data (5). However, study regions of five studies were unknown. Of these 98 studies, most studies were conducted in the United States (44), the other studies were conducted in Asia (19), Europe (16), multi-countries (9), Africa (3), Canada

(1), and Australia (1). The 98 included studies investigated pregnancy/parity (64), breastfeeding (55), age at first birth (52), menarche/menstruation (48), OC use (28), hormone (27), menopausal status (22), age at menopause (21), and abortion (7). Among 98 eligible studies, 27 studies evaluated the association between reproductive factors and BC subtypes defined by ERPR status[7-9, 15, 22-44]. Characteristics of included studies are summarized in **Table 1**. Specifically, a total of 22 studies examined ER+PR+ BC subtype[7-9, 22-28, 30-33, 35-41, 43], 14 studies examined ER+PR- BC subtype[7-9, 22, 23, 27, 29, 30, 33, 38, 39, 41-43], 9 studies evaluated ER-PR+ BC subtype[7, 8, 22, 23, 27, 30, 39, 42, 43], and 25 studies evaluated ER-PR- BC subtype[7-9, 15, 22-28, 30-39, 41-44].

3.1 Age at menarche

A total of 16 studies evaluated the association between age at menarche and BC subtypes defined by ERPR status[7-9, 15, 22-28, 30, 31, 36, 37, 39]. Among these, 15 studies researched ER+PR+ subtype[7-9, 22-28, 30, 31, 36, 37, 39], eight studies researched ER+PR- subtype[7-9, 22, 23, 27, 30, 39], seven studies researched ER-PR+ subtype[7, 8, 22, 23, 27, 30, 39], and 16 studies researched ER-PR- subtype[7-9, 15, 22-28, 30, 31, 36, 37, 39]. Of the 15 studies that contain ER+PR+ subtype, 10 studies found a statistically significant decreased likelihood of ER+PR+ subtype in women with late versus early age at menarche[8, 9, 22, 23, 26, 27, 30, 31, 36, 37], while four studies found no statistically significant association[7, 24, 25, 39]. Among these 15 studies, Huang et al and Cotterchio et al evaluated the association by menopausal status, Huang et al found the association was not statistically significant among both pre/peri and post-menopausal women[30]; however, Cotterchio et al found late age at menarche was only associated with ER+PR+ subtype compared with early age at menarche among premenopausal women[28]. A total of 8 studies researched the association between age at menarche and ER+PR- BC subtype[7-9, 22, 23, 27, 30, 39], seven studies were not statistically significant[7-9, 22, 23, 30, 39], while one study found late age at menarche was inversely associated

with ER+PR- subtype[27]. A total of seven studies assessed the association between age at menarche and ER-PR+ BC, while all of them were not statistically significant[7, 8, 22, 23, 27, 30, 39]. Of 16 studies that evaluated the association between age at menarche and ER-PR- BC subtype[7-9, 15, 22-28, 30, 31, 36, 37, 39], 10 studies found no significant association[7, 9, 15, 23, 25, 28, 30, 36, 37, 39], four studies found late versus early age at menarche was associated with a decreased risk of ER-PR- subtype[8, 22, 27, 31]. Chung et al assessed the association by birth groups, although later age at menarche was only significantly associated with a reduced risk of ER-PR- subtype in women born in 1950s but not in 1940s and 1960s[26]. However, Cerne et al found later versus earlier age at menarche was associated with a higher likelihood of ER-PR- subtype[24].

In meta-analysis of 16 studies (**Figure 2**), late versus early age at menarche was associated with a statistically significant reduced risk of ER+PR+ BC subtype (RR:0.79, 95% CI: 0.72, 0.85, I^2=87.9%, p=0.000), ER+PR- BC subtype (RR:0.75, 95% CI:0.58, 0.92, I^2=37.3%, p=0.132), ER-PR+ BC subtype (RR: 0.79, 95% CI:0.63, 0.95, I^2=0.0%, p=0.968), and ER-PR- BC subtype (RR:0.85, 95% CI: 0.79, 0.91, I^2=59.1%, p=0.001). There is some evidence of publication bias (Egger's: -2.09, p-value 0.042; Begg's test: 1.71, p-value 0.087).

3.2 Age at menopause

A total of eight studies examined the association between age at menopause and BC subtypes based on ERPR status[7, 9, 15, 22, 25, 27, 28, 37], seven studies analyzed ER+PR+ subtype[7, 9, 22, 25, 27, 28, 37], four studies analyzed *ER+PR-* subtype[7, 9, 22, 27], three studies analyzed *ER-PR+* subtype[7, 22, 27], and all eight studies analyzed *ER-PR-* subtype[7, 9, 15, 22, 25, 27, 28, 37]. Of seven studies analyzed ER+PR+ subtype[7, 9, 22, 25, 27, 28, 37], three studies were not statistically significant[7, 22, 37], while four studies found that late age at menopause was associated with an increased risk of ER+PR+ subtype[9, 25, 27, 28]. Of four studies evaluated the association between age at menopause and

ER+PR- BC[7, 9, 22, 27], three studies were not significant[7, 9, 22], while one study observed that women with late versus early age at menopause were at a higher risk of getting ER+PR- subtype[27]. Of three studies evaluated the association between age at menopause and ER+PR- BC subtype[7, 22, 27], only one study was significant[27], which observed a higher risk of ER-PR+ subtype in women with later versus earlier age at menopause. Of eight studies assessed the association between age at menopause and ER-PR- BC subtype[7, 9, 15, 22, 25, 27, 28, 37], seven studies were not significant[7, 9, 15, 22, 25, 27, 37], while only one study found later age at menarche was associated with a higher risk of ER-PR- subtype[28].

In the meta-analysis of 8 studies (**Figure 3.**), late versus early age at menopause was associated with an increased risk of ER+PR+ BC (RR:1.30, 95% CI: 1.10, 1.50, I^2=80.8%, p=0.000), ER+PR- BC (RR:1.52, 95% CI: 1.15, 1.90, I^2=0.0%, p=0.937), ER-PR+ BC (RR:1.78, 95% CI:0.98, 2.57, I^2=0.0%, p=0.938), and ER-PR- BC (RR:1.12, 95% CI: 1.00, 1.24, I^2=31.9%, p=0.173). However, the association was only significant for ER+PR+ and ER+PR- subtype. There was evidence of publication bias (Egger's: 6.28, p-value 0.000; Begg's test: 0.34, p-value 0.735).

3.3 Menopausal status

Among eight studies evaluated menopausal status and BC ERPR subtypes[7, 8, 22, 23, 25, 29, 39, 42], six studies analyzed ER+PR+ subtype[7, 8, 22, 23, 25, 39], seven studies analyzed ER+PR- subtype[7, 8, 22, 23, 29, 39, 42], six studies analyzed *ER-PR+* subtype[7, 8, 22, 23, 39, 42], and seven studies analyzed ER-PR- subtype[7, 8, 22, 23, 25, 39, 42]. Of six studies investigated the association between menopausal status and ER+PR+ BC subtype, five studies observed a significantly decreased likelihood of this subtype in women with post- versus pre/peri-menopause [7, 8, 22, 23, 25]; another study observed that post- versus pre-menopause was significantly associated with an increased risk of ER+PR+

subtype[39]. Of seven studies evaluated the association between menopausal status and ER+PR- BC[7, 8, 22, 23, 29, 39, 42], four studies observed no statistically significant associations[7, 8, 22, 23], while two studies found that post- versus pre/peri-menopause was associated with a higher risk of ER+PR- subtype[39, 42]. Moreover, Fujisue et al found that among ER+PR- BC patients, the number of post-menopausal patients is 2.01 times of the number of pre-menopausal women[29]. Of six studies evaluated the association between menopausal status and ER-PR+ subtype[7, 8, 22, 23, 39, 42], five studies were not statistically significant[7, 8, 23, 39, 42], while one study found that post-menopause decreases the risk of ER-PR+ subtype compared to pre/peri-menopause[22]. Of seven studies assessed the association between menopausal status and ER-PR- subtype[7, 8, 22, 23, 25, 39, 42], six studies were not statistically significant[7, 8, 22, 23, 25, 39], only one study observed that post-menopausal women were at a higher risk of this subtype compared to pre/peri-menopausal women[42].

In meta-analysis of eight studies (**Figure 4**), post- versus pre/peri-menopausal was associated with a statistically significant lower risk of ER+PR+ subtype (RR: 0.65, 95% CI: 0.55, 0.75, I^2=45.1%, p=0.091) and ER-PR+ subtype (RR: 0.69, 95% CI: 0.51, 0.88, I^2=24.1%, p=0.253), but a non-significant increased risk of ER+PR- subtype (ES:1.16, 95% CI:0.76, 1.57, I^2=62.6%, p=0.014) and ER-PR- subtype (RR:1.05, 95% CI: 0.88, 1.23, I^2=46.2%, p=0.072) There was some evidence of publication bias (Egger's: 2.21, p-value 0.036; Begg's test: 1.72, p-value 0.086).

3.4 Pregnancy

A total of six studies researched the association between pregnancy and BC ERPR subtypes[8, 22, 23, 26, 37, 43]. Specifically, all six studies analyzed ER+PR+ and ER-PR- subtype[8, 22, 23, 26, 37, 43], four studies analyzed ER+PR- and ER-PR+ subtype[8, 22, 23, 43]. Of six studies analyzed the

association between ER+PR+ subtype and pregnancy, four studies found ever pregnancy was significantly associated with a reduced risk of ER+PR+ BC[22, 26, 37, 43], while other two studies were not statistically significant[8, 23]. Among four studies included ER+PR- BC, three studies were not statistically significant[8, 22, 23], although one study observed a lower likelihood of ER+PR- BC in women with ever versus never pregnant or ever full-term versus never pregnant, but not in women with only non-full term versus never pregnant[43]. Of four studies evaluated ER-PR+ subtype, three studies were not statistically significant[8, 22, 23], while one study only observed a statistically significant lower risk of ER-PR+ BC subtype in women with only non-full-term pregnancy versus never pregnant[43]. Out of six studies examined the association between ER-PR- subtype and pregnancy, none of them was statistically significant[8, 22, 23, 26, 37, 43].

In the meta-analysis of six studies (**Figure 5**), ever versus never pregnancy was associated with a statistically reduced risk of ER+PR+ subtype (RR: 0.62, 95% CI: 0.47, 0.78, I^2=88.0%, p=0.000), ER+PR- subtype (RR: 0.70, 95% CI: 0.57, 0.83, I^2=0.0%, p=0.867), ER-PR+ subtype (RR: 0.68, 95% CI: 0.49, 0.87, I^2=3.5%, p=0.394), but a non-significant reduced risk of ER-PR- subtype (RR:0.97 , 95% CI: 0.86, 1.07, I^2=0.0%, p=0.718) There was no evidence of publication bias (Egger's: 0.54, p-value 0.593; Begg's test: 1.09, p-value 0.277).

3.5 Age at first birth

A total of 16 studies evaluated the association between age at first birth and BC subtypes defined by ERPR status[7-9, 15, 22-24, 26-28, 30, 31, 33, 37, 39, 43], 15 studies analyzed ER+PR+ BC subtype[7-9, 22-24, 26-28, 30, 31, 33, 37, 39, 43]; 10 studies analyzed ER+PR- BC subtype[7-9, 22-24, 27, 30, 33, 39], eight studies analyzed ER-PR+ BC subtype[7, 8, 22-24, 27, 30, 39], and 16 studies analyzed ER-PR- BC subtype[7-9, 15, 22-24, 26-28, 30, 31, 33, 37, 39, 43].

ER+PR+ BC: A total of 15 studies evaluated the association between nulliparity and age at first birth with ER+PR+ subtype[7-9, 22-24, 26-28, 30, 31, 33, 37, 39, 43]; six studies examined nulliparity versus age at first birth[9, 24, 27, 28, 30, 39], while 13 studies examined late age at first birth versus early age at first birth[7-9, 22, 23, 26, 28, 30, 31, 33, 37, 39, 43]. Among the six studies that evaluated the association between nulliparity versus age at first birth and ER+PR+ subtype[9, 24, 27, 28, 30, 39], four studies evaluated nulliparity versus early age at first birth[9, 28, 30, 39]. Among these four studies, two studies found no statistically significant association[30, 39], while two studies observed that nulliparity versus earlier age at first birth was associated with an increased risk of ER+PR+ subtype[9, 28]. Two studies evaluated this association by menopausal status[28, 30]; Huang et al did not observe any significant associations overall or by subtypes[30], while Cotterchio observed a significantly increased risk in both pre- and post-menopausal women[28]. Two studies evaluated the association between nulliparity versus later age at first birth, while none of them was statistically significant[24, 27]. A total of 13 studies evaluated the association between late versus early age at first birth and ER+PR+ BC subtype[7-9, 22, 23, 26, 28, 30, 31, 33, 37, 39, 43]; four studies observed a significantly increased risk of ER+PR+ subtype[7-9, 37], while seven studies were not significant[22, 23, 30, 31, 33, 39, 43]. Two studies evaluated the association by menopausal status[28, 30]; Huang et al did not observe any significant associations in pre- or post-menopausal women[30], while Cotterchio observed significantly increased risk only in post-menopausal women[28]. Chung et al evaluated the association by birth cohorts and found significant positive associations for the 1950 and 1960 cohort, but not 1940[26].

ER+PR- BC: A total of 10 studies focused on the ER+PR- BC subtype[7-9, 22, 23, 27, 30, 33, 39, 43], three studies examined the association between nulliparity versus early age at first birth, but found no statistically significant results[9, 30, 39]. One study compared nulliparity to late age at first birth, but

still found no statistically significant association[27]. Of the nine studies[7-9, 22, 23, 30, 33, 39, 43] that compared late versus early age at first birth, three studies observed a significantly increased likelihood of ER+PR- BC subtype[7, 9, 39], while the other studies were not statistically significant[8, 22, 23, 30, 33, 43].

ER-PR+ BC: A total of eight studies evaluated the association between age at first birth and ER-PR+ BC subtype[7, 8, 22, 23, 27, 30, 39, 43], three studies evaluated nulliparity versus age at first birth, with two studies[30, 39] compared nulliparity to earlier age at first birth and one studies[27] compared nulliparity to later age at first birth. All these three studies found no statistically significant results. Of the seven studies[7, 8, 22, 23, 30, 39, 43] that assessed late versus early age at first birth, only one study observed that a statistically significant increased risk was associated with late age at first birth[8], while the other studies were not statistically significant[7, 22, 23, 30, 39, 43] .

ER-PR- BC: A total of 16 studies evaluated the ER-PR- BC subtype[7-9, 15, 22-24, 26-28, 30, 31, 33, 37, 39, 43], 4 studies assessed nulliparity versus early age at first birth[9, 28, 30, 39], 2 studies assessed nulliparity versus late age at first birth[24, 27], and none were statistically significant, while 14 studies examined late versus early age at first birth and also found no statistically significant results[7-9, 15, 22, 23, 26, 28, 30, 31, 33, 37, 39, 43].

In meta-analysis of the studies that evaluated age at first birth in relation to BC subtypes (**Figure 6),** nulliparity compared with age at first birth was associated with a statistically significant increased risk of ER+PR+ BC subtype (RR: 1.27, 95% CI: 1.01, 1.54, I^2=50.5%, p=0.059), a statistically significant reduced risk of ER+PR- BC subtype (RR: 0.71, 95% CI: 0.46, 0.96, I^2=0.0%, p=0.44), and a non-significant but reduced risk of ER-PR+ subtype (RR: 0.68, 95% CI: 0.26, 1.11, I^2=0.0%, p=0.663) and ER-PR- subtype (RR: 0.91, 95% CI: 0.71, 1.10 I^2=0.0%, p=0.488) subtypes. Late age at first birth compared with early age at first birth was

associated with statistically increased risk of ER+PR+ subtype (RR: 1.10, 95% CI: 1.04, 1.15, I^2=63.2%, p=0.000) and ER+PR- subtype (RR: 1.45, 95% CI: 1.15, 1.74, I^2=0.0%, p=0.767) , but non-significant for ER-PR+ subtype (RR: 1.03, 95% CI: 0.72, 1.33, I^2=5.7%, p=0.384) and ER-PR- subtype (RR: 0.99, 95% CI: 0.97, 1.01 I^2=0.0%, p=0.476) subtypes. There was some evidence of publication bias (Egger's: 2.27, p-value 0.027; Begg's test: 0.97, p-value 0.333).

3.6 Parity

There are 16 studies in total researched the associations between parity and BC subtypes based on ERPR status[7-9, 15, 22, 24-26, 28, 31-33, 37, 42-44]. Specifically 13 studies assessed ER+PR+[7-9, 22, 24-26, 28, 31, 33, 37, 43, 44], seven studies assessed ER+PR- BC[7-9, 22, 33, 42, 43], five studies assessed ER-PR+ BC[7, 8, 22, 42, 43], and 16 studies assessed ER-PR- BC[7-9, 15, 22, 24-26, 28, 31-33, 37, 42-44]

ER+PR+ BC: A total of 13 studies examined the association between parity and ER+PR+ BC subtype. A total of eight studies evaluated larger parity versus nulliparous[7, 24, 25, 28, 31, 33, 43, 44], and five studies evaluated large parity versus small parity[8, 9, 22, 26, 37]. Among eight studies investigated larger parity versus nulliparity, five studies found that larger parity was significantly associated with a reduced risk of ER+PR+ subtype[7, 28, 31, 43, 44], while one study found no statistically significant association[24]. Moreover, Chen et al and Palmer et al examined by age-group, Chen et al found larger parity reduced the risk of ER+PR+ in women <=22 years and 23-25 years groups but not in >25 years group[25], Palmer et al found that the same association, which was significant overall and in women >=45 years but not in women<45 years[33]. Among five studies evaluated the association between large versus small parity and ER+PR+ subtype[8, 9, 22, 26, 37], three of them were not significant[8, 22, 26], while two studies found a reduced risk for ER+PR+ subtype with large versus small parity[9, 37].

ER+PR- BC: A total of seven studies evaluated the association between parity and ER+PR- BC subtype[7-9, 22, 33, 42, 43], four evaluated larger parity versus nulliparity[7, 33, 42, 43]. Among these, three studies were not statistically significant[7, 33, 42], while one study found that women with larger parity has a reduced risk of ER+PR- subtype compared to nulliparous women[43]. A total of four studies evaluated large versus small parity, three studies found no statistically significant association[8, 9, 22], while one study observed larger parity was in relation to a statistically significant increased risk of ER-PR- subtype[42].

ER-PR+ BC: A total of five studies evaluated the association between parity and ER-PR+ BC subtype[7, 8, 22, 42, 43], three studies examined large parity versus nulliparity, but no study was statistically significant[7, 42, 43]. three studies examined the association between large versus small parity and ER-PR+ subtype but found no statistically results[8, 22, 42].

ER-PR- BC: A total of 16 studies analyzed the association between parity and ER-PR- BC subtype[7-9, 15, 22, 24-26, 28, 31-33, 37, 42-44], with 11 studies examined large parity versus nulliparity[7, 15, 24, 25, 28, 31-33, 42-44] and six studies evaluated larger versus smaller parity[8, 9, 22, 26, 37, 42]. Out of 11 studies that evaluated large parity versus nulliparity, nine studies found no statistically significant results[7, 15, 24, 25, 28, 31, 33, 42, 43]. Palmer et al and Work et al evaluated parity combined with breastfeeding status, Palmer et al found that larger parity without breastfeeding versus nulliparity posts a statistically significant increased risk for ER-PR- subtype[32], but not for large parity with breastfeeding. Differently, Work et al found the opposite result[44]. Out of six studies that evaluated larger versus smaller parity[8, 9, 22, 26, 37, 42], four studies were not statistically significant[8, 9, 26, 37]; however, one study found larger parity was associated with a higher risk of ER-PR- subtype[42], but one study observed that larger parity was associated with a lower risk of ER-PR- subtype[22].

In the meta-analysis that evaluated the association between parity and ERPR BC subtypes (**Figure 7**), large parity versus nulliparity was associated with a statistically reduced risk of ER+PR+ subtype (RR: 0.67, 95% CI: 0.56, 0.78, I^2=75.4%, p=0.000), ER+PR- subtype (RR: 0.54, 95% CI: 0.30, 0.78, I^2=23.5%, p=0.270), a reduced but not statistically significant risk of ER-PR+ subtype (RR: 0.71, 95% CI: 0.33, 1.08, I^2=0.0%, p=0.515) and ER-PR- subtype (RR: 0.96, 95% CI: 0.84, 1.08, I^2=34.2%, p=0.089). Larger versus smaller parity was associated with a statistically significant reduced risk for ER+PR+ subtype (RR: 0.88, 95% CI: 0.77, 0.99, I^2=69.3%, p=0.003), but a statistically increased risk for ER+PR-(RR: 1.08, 95% CI: 0.76, 1.40, I^2=33.9%, p=0.209), and a non-significant reduced risk for ER-PR+ subtype (RR: 096, 95% CI: 0.74, 1.18, I^2=0.0%, p=0.597), and ER-PR- subtype (RR: 0.96, 95% CI: 0.83, 1.10, I^2=61.6%, p=0.011). There is no evidence of publication bias (Egger's: 1.64, p-value 0.107; Begg's test: 0.90, p-value 0.371).

3.7 Breastfeeding

There are 13 studies examined the association between breastfeeding and BC subtypes defined by ERPR status[8, 15, 22-24, 26, 28, 30, 31, 33, 37, 39, 43]. Among all, 12 studies analyzed ER+PR+[8, 22-24, 26, 28, 30, 31, 33, 37, 39, 43], seven studies assessed ER+PR- subtype[8, 22, 23, 30, 33, 39, 43], six studies analyzed ER-PR+ subtype[8, 22, 23, 30, 39, 43], and all 13 studies investigated ER-PR- BC[8, 15, 22-24, 26, 28, 30, 31, 33, 37, 39, 43].

ER+PR+ BC: Of 12 studies included ER+PR+ BC[8, 22-24, 26, 28, 30, 31, 33, 37, 39, 43], six studies evaluated the association between ever versus never breastfeeding and this subtype[8, 26, 30, 32, 37, 43]; and 11 studies evaluated duration of breastfeeding [8, 22-24, 26, 28, 31, 33, 37, 39, 43]. Of six studies evaluated the association between ever versus never breastfeeding and ER+PR+ subtype, five studies were not statistically significant[8, 26, 30, 33, 37], while one observed that ever breastfeeding is

inversely associated with ER+PR+ subtype[43]. Of 11 studies evaluated the association between breastfeeding duration and ER+PR+ subtype, seven studies found non-significant association[23, 24, 26, 28, 33, 37, 39], whilst 4 studies showed longer duration of breastfeeding is inversely associated with ER+PR+ BC[8, 22, 31, 43].

ER+PR- BC: Of seven studies assessed the association between breastfeeding and ER+PR-BC[8, 22, 23, 30, 33, 39, 43], three studies assessed ever versus never breastfeeding in relation to ER+PR- subtype [8, 30, 43], with only one study observed breastfeeding was associated with a statistically significant reduced risk of ER+PR- subtype[30]. A total of six studies examined the duration of breastfeeding[8, 22, 23, 33, 39, 43], with only one study found breastfeeding longer than one year lowers the risk of ER+PR- BC[23].

ER-PR+ BC: There were six studies evaluated the association between breastfeeding and ER-PR+ subtype[8, 22, 23, 30, 39, 43]. A total of three studies assessed ever versus never breastfeeding[8, 30, 43], although only one study found that ever breastfeeding was associated with a statistically significant reduced risk of ER-PR+ subtype[30]. All six studies assessed breastfeeding duraiton[8, 22, 23, 33, 39, 43], while only one study found, comparing to shorter duration of breastfeeding, longer duration was associated with a lower likelihood of ER-PR+ subtype[8].

ER-PR- BC: Of 13 studies investigated the association between breastfeeding and ER-PR- BC subtype[8, 15, 22-24, 26, 28, 30, 31, 33, 37, 39, 43], seven studies examined ever versus never breastfeeding[8, 15, 26, 30, 33, 37, 43]. Of these, four studies were not significant[8, 30, 33, 35], while two studies observed ever breastfeeding had a lower likelihood of ER-PR- subtype[15, 43]. Additionally, Chung et al evaluated by birth-cohort, and results were not consistent across birth conhorts[26]. Out of 13 total studies, 11 studies assessed duration of breastfeeding[8, 22-24, 26, 28, 31, 33, 37, 39, 43]. Of these, 10 studies were not

statistically significant, while only one study found that longer duration of breastfeeding was associated with a reduced risk of ER-PR- BC[43].

In the meta-analysis that evaluated the association between breastfeeding and BC ERPR subtypes (**Figure 8**), ever versus never breastfeeding was associated with a statistically significant reduced risk of ER+PR+ subtype (RR: 0.87, 95% CI: 0.79, 0.96, I^2=46.0%, p=0.054), ER+PR- subtype (RR: 0.67, 95% CI: 0.52, 0.83, I^2=18.2%, p=0.300), and ER-PR- subtype (RR: 0.81, 95% CI: 0.69, 0.93, I^2= 60.9%, p=0.004), but a non-significant reduced risk for ER-PR+ subtype ((RR:0.67, 95% CI: 0.27, 1.08, I^2=46.0%, p=0.136). Longer versus shorter duration of breastfeeding was in relation to a non-significant reduced risk for ER+PR+ subtype (RR: 0.99, 95% CI: 0.97, 1.01, I^2=72.0%, p=0.000) and ER-PR+ subtype (RR:0.67 , 95% CI: 0.26, 1.08, I^2=48.2%, p=0.102), but a statistically reduced risk of ER+PR- subtype (RR: 0.67, 95% CI: 0.40, 0.94, I^2=52.0%, p=0.064), and no difference for ER-PR- subtype (RR: 1.00, 95% CI: 0.98, 1.01, I^2=60.6%, p=0.002). There is evidence of publication bias (Egger's: -5.96, p-value 0.000; Begg's test: 3.45, p-value 0.001).

3.8 Years since last birth

A total of three studies evaluated the association between years since last birth and ER+PR+ BC[33, 37, 43], two studies found that shorter year since last birth was significantly associated with a higher risk of this subtype[33, 37]. Among these two studies, Palmer et al also evaluated the association by age-group (<45 years, >=45 years), although it was not statistically significant[33]. Another study found shorter year since last birth was inversely associated with ER+PR+BC subtype[43]. A total of 3 studied focused on ER-PR- BC stubtype[33, 37, 43], 2 studies were not significant[37, 43], while Palmer only found a statistically significant increased risk of ER-PR- BC

in women <45 years but not in overall and >=45 years with shorter versus longer since last birth[33].

In the meta-analysis of three studies that assessed the association between years since last birth and BC ERPR subtypes (**Figure 9**), shorter versus longer years since last birth was in relation to a non-significant increased risk of ER+PR+ subtype (RR:1.05, 95% CI:0.53, 1.57, I^2=88.1%, p=0.000) and ER-PR- subtype (RR:1.02, 95% CI:0.81, 1.24, I^2=12.9%, p=0.317). There is no evidence of publication bias (Egger's: -0.11, p-value 0.919; Begg's test: 0.000, p-value 1.000).

3.9 Oral contraceptive (OC) use

Among 10 studies that analyzed OC use, all included ER+PR+ and ER-PR- BC[8, 22-24, 28, 30, 31, 37, 38, 44], five studies included ER+PR-[8, 22, 23, 30, 38], and three studies included ER-PR+BC[22, 23, 30].

ER+PR+ BC: A total of 10 studies evaluated the association between OC use and ER+PR+ BC subtypes[8, 22-24, 28, 30, 31, 37, 38, 44], six studies evaluated ever OC use versus never[8, 22, 23, 30, 38, 44], one evaluated current or past OC use versus never[37], and six studies evaluated OC duration, none of these six studies was statistically significant[22, 24, 28, 31, 37, 38]. Of six studies examined ever OC use versus never[8, 22, 23, 30, 38, 44], five studies were not statistically significant[8, 22, 23, 30, 38], while one study observed ever used OC was significantly associated with a lower likelihood of ER+PR+ subtype[44]. The study that assessed the association between current or past versus never OC use was not significant as well[37].

ER+PR- BC: A total of five studies evaluated the association between OC use and ER+PR- BC[8, 22, 23, 30, 38], all five studies examined the association between ever versus never OC use and ER+PR- subtype and two examined the association between OC use duration and ER+PR- subtype[22, 38], although all of them were not statistically significant.

ER-PR+ BC: A total of three studies evaluated the association between OC use and ER-PR+ BC subtype[22, 23, 30], all three evaluated ever versus never OC use, and one evaluated OC use duraiton[22]; however, none of them was statistically significant.

ER-PR- BC: A total of 10 studies evaluated the association between OC use and ER-PR- BC[8, 22-24, 28, 30, 31, 37, 38, 44], 5 studies evaluated ever OC use versus never[8, 22, 23, 30, 38], one study evaluated OC use prior 1975 versus no[44], one study evaluated current or past OC use versus never[37], and six studies OC duraiton[22, 24, 28, 31, 37, 38]. Of 5 examined ever OC use vs never[8, 22, 23, 30, 38], four studies were not statistically significant[8, 22, 23, 30], while one study found ever OC use versus never had a higher risk of ER-PR- subtype[38]. Among six studies assessed OC duration[22, 24, 28, 31, 37, 38], five of them were not statistically significant[22, 24, 28, 31, 37], while one study found that longer duration of OC use increases the risk of ER-PR- subtype[38].

In the Meta-analysis that evaluated the association between OC use and BC ERPR subtypes (**Figure 10**), ever versus never OC use was associated with a non-significant reduced risk of ER+PR+ subtype (RR: 0.96, 95% CI: 0.81, 1.10, I^2=81.6%, p=0.000), a non-significant increased risk of ER+PR- subtype (RR:1.09 , 95% CI: 0.86, 1.32, I^2=0.0%, p=0.901) and ER-PR+ subtype(RR: 1.09, 95% CI: 0.53, 1.66, I^2=31.5%, p=0.232), a significant increased risk of ER-PR- subtype (RR: 1.17, 95% CI: 1.02, 1.31, I^2=29.3%, p=0.194). Longer versus shorter duration of OC use was associated with a non-significant reduced risk of ER+PR+ subtype (RR: 0.92, 95% CI: 0.81, 1.04, I^2=19.9%, p=0.272) and a non-significant increased risk of ER-PR- subtype (RR: 1.20, 95% CI: 1.00, 1.41, I^2=14.1%, p=0.320). There is evidence of publication bias (Egger's: 3.67, p-value 0.001; Begg's test: 2.13, p-value 0.003).

3.10 Hormone replacement therapy

A total of 13 studies assessed the association between hormone replacement and BC subtypes, 13 studies analyzed ER+PR+ subtype[7-9, 22, 24, 25, 27, 28, 30, 35, 39-41], eight studies analyzed ER+PR- subtype[7-9, 22, 27, 30, 39, 41], six studies analyzed ER-PR+ subtype[7, 8, 22, 27, 30, 39], and 12 studies analyzed ER-PR- subtype[7-9, 22, 24, 25, 27, 28, 30, 35, 39, 41]

ER+PR+ BC: A total of 13 studies focused on the association between hormone replacement therapy and ER+PR+ BC subtypes[7-9, 22, 24, 25, 27, 30, 35, 39-41], 12 studies evaluated hormone replacement therapy (ever, past or current) versus never use[7-9, 22, 24, 25, 27, 30, 37, 39-41], and five studies evaluated hormone replacement therapy duration[7, 24, 25, 28, 41]. Among 12 studies that evaluated the association of hormone replacement with ER+PR+ subtype, seven studies found non-significant associations[7, 8, 22, 25, 30, 39, 41], while two studies observed a statistically significant higher risk associated with hormone replacement therapy[9, 40]. However, Colditz et al only found this association for estrogen and progesterone use but not for estrogen use only[27]. In contrast to Colditz's finding, Cerne et al found a statistically significant reduced risk for estrogen only, and non-significant results for combined hormones[24]. Ritte et al evaluated the association by BMI and found significant associations across all BMI groups among current users, but not among past users[35]. A total of five studies[7, 24, 25, 28, 41] evaluated the association of hormone replacement therapy duration and ER+PR+ BC subtype, two studies found no statistically significant association[7, 28], whilst two studies observed that longer duration of hormone replacement therapy was significantly associated with a higher risk of ER+PR+ subtype[25, 41], and one study found longer duration of hormone replacement therapy was inversely associated with this subtype[24].

ER+PR- BC: A total of eight studies investigated the association between hormone replacement and ER+PR- BC subtype[7-9, 22, 27, 30, 39, 41], all eight studies examined ever versus never hormone

use. Of these, five studies found no statistically significant associations[7, 8, 27, 39, 41], while one study found ever receiving hormone replacement therapy versus never was statistically associated with a reduced risk of ER+PR- subtype[30], and two studies found ever receiving hormone replacement therapy versus never was associated with an increased risk of ER+PR- subtype[9, 22], although Setiawan only observed the significant association for current hormone replacement therapy versus never but not for past hormone replacement therapy versus never[9]. A total of two studies evaluated the association between hormone replacement therapy duration and ER+PR- subtype, none of them was significant[7, 9]

ER-PR+ BC: A total of six studies evaluated the association between hormone replacement therapy and ER-PR+ BC subtype[7, 8, 22, 27, 30, 39]. All these six studies evaluated ever receiving hormone replacement therapy versus never, while none of them was significant. There was only one study examined longer versus shorter duration of hormone replacement, and it was not statistically significant[7].

ER-PR- BC: A total of 12 studies assessed the association between hormone use and ER-PR- BC subtype[7-9, 22, 24, 25, 27, 28, 30, 35, 39, 41], with 11 studies assessed ever receiving hormone replacement therapy versus never[7-9, 22, 24, 25, 27, 30, 35, 39, 41], and five studies assessed duration of hormone replacement therapy[7, 24, 25, 28, 41]. Of 11 studies evaluated ever receiving hormone replacement therapy versus never, eight studies were not statistically significant[7-9, 22, 24, 27, 39, 41], while one study found past hormone replacement therapy was associated with a lower risk of ER-PR- subtype[25]. Huang et al evaluated the association by menopausal status[30], and Ritte et al evaluated by BMI-group[35]. However, Huang et al only detected ever versus never hormone replacement therapy was inversely associated with ER-PR- subtype in peri- and post-menopausal women[30]; Ritter et al only observed that current hormone replacement therapy versus never use

was associated with a higher risk of ER-PR- subtype among women with BMI <=22.5[35]. A total of five studies evaluated the association between duration of hormone replacement therapy and ER-PR- subtype, although all of them were not significant[7, 24, 25, 28, 41].

In the meta-analysis of the association between hormone replacement therapy and BC ERPR subtypes (**Figure 11**), ever versus never receiving hormone replacement therapy was associated with a statistically significant increased risk of ER+PR+ subtype (RR:1.25 , 95% CI: 1.08, 1.42, I^2=83.4%, p=0.000) a non-significant increased risk of ER+PR- subtype (RR: 1.10, 95% CI: 0.78, 1.42, I^2=75.3%, p=0.000), a non-significant reduced risk for ER-PR- subtype (RR: 0.98, 95% CI: 0.86, 1.10, I^2=35.8%, p=0.053), but no difference for ER-PR+ subtype (RR:1.00 , 95% CI: 0.71, 1.30, I^2=0.0%, p=0.746). Longer versus shorter duration of hormone replacement therapy was in relation to a statistically increase likelihood of ER+PR+ subtype (RR: 1.39, 95% CI: 1.02, 1.76, I^2=86.2%, p=0.000), but a non-significant increased likelihood of ER-PR- subtype (RR: 1.01, 95% CI: 0.82, 1.20, I^2=0.0%, p=0.429). There is some evidence of publication bias (Egger's: 1.63, p-value 0.107; Begg's test: 1.99, p-value 0.047).

3.11 Summary of the meta-analysis

Out of ten reproductive factors included in the meta-analysis, the effect of age at menarche was consistent across subtypes, and the strongest association was observed in ER+PR- subtype. Moreover, the impact of pregnancy and ever breastfeeding was relatively less consistent (**Table 2**), and the strongest association for these two factors were respectively for ER-PR+ and ER+PR- subtypes. In addition, nulliparity versus early at first birth has conflicting results across ER+PR+ and ER+PR- subtypes. What is more, larger versus smaller parity only showed a statistically significant reduced risk for ER+PR+, and HRT only associated with a higher risk for ER+PR+. Larger versus smaller duration of breastfeeding was only associated with a reduced risk for

ER+PR- subtype. Years since last birth and OC use were not statistically significant. Age at menopause, menopausal status, late versus early age at first birth, and larger parity versus nulliparity was associated with differently two subtypes. Considering the magnitude of these association overall, six out of 13 comparison groups has the strongest associations with ER+PR-, and two strongest association were observed for ER+PR+ subtype.

4. DISCUSSION

This study reviewed 98 eligible studies for all subtypes and the meta-analysis included 27 studies about the association between reproductive factors and BC subtypes defined by ERPR status. It has been reported that BC is a heterogeneous cancer with different distributions of reproductive factors; however, no meta-analysis is available for ER+PR+ and ER-PR+ subtypes. Additionally, currently available systematic reviews and meta-analyses solely evaluated a few reproductive factors[3, 5, 14-16, 45]. However, this study summarized and assessed the association between ERPR subtypes and ten reproductive factors (age at menarche, age at menopause, menopausal status, pregnancy, age at first birth, parity, breastfeeding, years since last birth, OC use, and HRT). To our knowledge, this meta-analysis is the first study that investigated the association between joint ERPR subtypes (ER+PR- and ER-PR+) and reproductive factors. For ER+PR+ and ER-PR- subtypes, this meta-analysis also firstly evaluated menopausal status, years since last birth, OC use, and HRT.

Similar to other findings[3, 4, 14, 15], BC is heterogeneous and reproductive factors patterns vary by subtypes. Moreover, this meta-analysis found that consistency of associations across subtypes differs by risk factors (**Table 2**). Specifically, late age at menarche was protective for all four

ERPR subtypes. Ever pregnancy was observed to be protective for ER+PR+, ER+PR-, and ER-PR+ subtypes. Breastfeeding reduces the risk of ER+PR+, ER+PR-, and ER-PR- subtypes. Additionally, the effects of age at menopause, menopausal status, age at first birth, parity, breastfeeding duration, and HRT are believed to be relatively less consistent across ERPR subtypes. No significant results were found for OC use and years since last birth. Generally, most significant associations were found for ER+PR+ and/or ER+PR- subtype (Age at menopause, age at first birth, parity, and HRT). Differently, late versus early age at menarche was associated with a reduced risk for all subtypes. Post- versus pre-menopause were associated with PR+ BC (ER+PR+ and ER-PR+ subtypes). Most of our strongest association was observed for ER+PR- subtype, which broadens studies which only investigated ER+PR+ and ER-PR- subtypes[16]. It also expands the result from another finding that hormone receptor positive BC had the strongest strength[3].

Factors that have been evaluated in meta-analyses include age at menarche, age at menopause, parity, age at first birth, and breastfeeding. However, in this meta-analysis, more recent studies were included and additional reproductive factors (menopausal status, years since last birth, OC, use, and HRT) were examined through a meta-analysis. A few systematic reviews found most studies observed an inverse association between age at menarche and ER+PR+ subtype[3, 5, 16]. The systematic review from Ma et al found ER+PR+ subtype has a stronger association compared to ER-PR-[16]. However, our meta-analysis found late age at menarche reduced the risk of all four ERPR subtypes. The association was strongest for ER+PR- subtype and was weakest for ER-PR- subtype in this analysis. However, among eight studies included in the meta-analysis for ER+PR- subtype, only one study conducted by Colditz observed a statistically significant lower risk with a narrow confidence interval[27]. For age at menopause, a meta-analysis conducted by Li et al

found an increased risk in luminal subtype (defined as ER+ or PR+, HER2+ or HER2-) and ER-PR- subtypes[15], while our meta-analysis found late age at menopause increases the risk of ER+PR+ and ER+PR- subtypes. Different results might be due to more recent studies included in our study. For age at first birth, the meta-analysis conducted by Ma et al found late versus early age at first birth was only associated with ER+PR+ subtype but not ER-PR- subtype[16]. However, another meta-analysis found it was associated with an insignificant increased risk for luminal BC but a reduced risk for ER-PR-[15] and our meta-analysis found a statistically significant increased risk for ER+PR+ and a reduced risk for ER-PR- subtype. Additionally, our study also observed that nulliparity versus age at first birth was associated with a higher risk for ER+PR+ but a lower risk for ER+PR- subtype. Regarding pregnancy, a meta-analysis found ever pregnant was associated with a reduced risk only for luminal BC[4], while ever pregnant was associated with a reduced risk for all subtypes except for ER-PR- subtype, and the strongest association is observed for ER+PR+ subtype in our study. For parity, which is defined as the number of children a women gave birth to, Li et al observed that nulliparity was associated with a higher risk for luminal subtype compared to larger parity[15], and Ma et al only found highest versus lowest parity reduces the risk for ER+PR+ subtype[16]. Similarly, our study found large parity versus nulliparity was associated with a reduced risk for both ER+PR+ and ER+PR- subtype. We also observed that larger versus smaller parity was only associated with a 12% reduced risk of ER+PR+ subtype. In addition. As the finding by Isiami et al[14] for ever breastfeeding, a reduced risk was observed for ER+PR+ and ER-PR-; however, our meta-analysis also found a statistically significant lower risk for ER-PR+ subtypes. Moreover, the association was stronger for ER-PR- compared to ER+PR+ subtype, and it was strongest for ER+PR- subtype. No meta-analysis evaluated the association between BC ERPR subtypes and breastfeeding duration, while

our study found large versus small duration of breastfeeding was also protective for all four subtypes except for ER-PR- subtype, although it was only statistically significant for ER+PR- subtype. No significant association was observed for years since last birth and OC use. Additionally, the impact of OC varies by subtypes with only Work et al[44] found a statistically significant reduced likelihood for ER+PR+ subtype. For ER-PR- subtype, only Rosernberg et al[38] and Work et al[44] found a statistically significant increased risk. Further studies are required for a deeper assessment for the impact of OC use by subtypes. A 35% reduced risk and a 31% reduced risk were separately observed for ER+PR+ and ER-PR+ subtype with post- versus pre-/perimenopause, which reflects previous findings[7, 8, 22, 23, 25] and differs from Rusiecki's finding[39]. For HRT, ever received HRT and long versus short duration of HRT were only associated with a higher risk of ER+PR+ subtype, which confirms previous findings[9, 25, 43], although it contrasts with some other findings[24, 30, 39].

Age at menopause, age at first birth, and parity were significantly associated with ER+ (ER+PR+ and ER+PR- subtypes) in our meta-analysis. HRT was only associated with ER+PR+ subtypes. These factors might work through the effect of estrogen and/or progesterone[8]. For instance, later age at menarche leads to a shorter duration of hormone exposure, which is probably associated with a lower risk of all ER+BC[37]. For factors that were significantly associated with ER+ BC, estrogen circulating level might be impacted by those factors and thus changes the risk of ER+ BC[45]. Evidence has shown that pregnancy probably reduces risk through hormone circulating level change and breast structure change from undifferentiated to differentiated breast epithelial cells[46, 47]. Breastfeeding is also believed to be associated with breast structure changes.[47] For menopausal status, pre-menopausal women were believed to have a higher level of steroid and

thus are more likely to develop PR+ subtype in pre-menopausal status and to develop PR- in post-menopausal status[42].

There are a few gaps, for studies focusing on the association between reproductive factors and ERPR subtypes, should be addressed. To begin with, abortion was not included in the meta-analysis due to insufficient studies of this factor. Moreover, no significant association was observed for years since last birth and OC use. These suggest that more studies should focus on abortion, years since last birth, and OC use. What is more, definitions of these reproductive factors vary by studies, which might cause misclassification of these factors. For instance, most studies refer parity as number of children[7, 28, 44]; however, some studies refer it as ever pregnant[4, 23]. Clear definitions would help reduce the confusions and misclassification of these reproductive factors. Moreover, risk patterns of BC were believed to be different by menopausal status[48]. However, a meta-analysis, stratifying by menopausal status for any association between reproductive factors and BC ERPR subtypes, was not conducted due to insufficient primary studies. Primary studies researching the association stratified by menopausal status could help better understand these associations in pre/peri- and postmenopausal women.

This study has its own limitations. To begin with, our eligible studies were restricted to papers published in English, which reduces the comprehensiveness of this study. However, we included 98 studies that investigated these associations and were published in the most commonly used language. Moreover, not enough studies were available to conduct a meta-analysis for abortion, and only three studies examined years since last birth. Thus, more studies are needed to be done to address gaps in these factors. However, except for these two factors, we still assessed the association between other eight factors and BC ERPR subtypes. Moreover, different etiologies of pre-menopausal and post-menopausal BC have been reported[42]. However, not enough studies

were available for a meta-analysis stratified by menopausal status. Nevertheless, menopausal status was investigated as a risk factor, which enables us to summarize whether ERPR subtypes have a different distribution of menopausal status. Additionally, sample sizes were not considered during the review process, and the proportion of ER+PR- and ER-PR+ are relatively small. However, this studies still serve as a comprehensive meta-analysis for the associations. In light of comprehensive reproductive factors included and its potential applications, strengths outweigh limitations. Specifically, regarding preventive guideline, not having children, not breastfeeding, birth control, and hormone therapy after menopause increase the risk of BC overall according to the American Cancer Society[49]. However, most of them lack recommendations by BC subtypes. Through this study, summarization for the effects of most reproductive factors by ERPR subtypes will be available, and the current risk factor pattern could possibly be revised. Moreover, the reproductive factors patterns could be combined with family history and other risk factors to predict risks of developing specific BC subtypes. Modifiable reproductive factors such as breastfeeding could be promoted, especially among populations with high incidences of ER+PR+, ER+PR-, and ER-PR- BC subtypes, which have a significant association with breastfeeding. Regarding BC screening, the risk assessment tool (the Gail model) provided by the National Health Institute only considers age at first birth and age at menarche among all reproductive factors. Through this study, other consistent reproductive factors such as breastfeeding could possibly be included in this risk calculation model and thus help with screening recommendation.

5. CONCLUSIONS

This study offers better understanding of the associations between reproductive factors and BC ERPR subtypes. Throughout all reproductive factors, age at menarche, pregnancy, and breastfeeding showed a relatively consistent finding. Out of four ERPR subtypes, strongest associations were observed for ER+PR- subtypes, although more studies with bigger sample sizes for ER+PR- and ER-PR+ subtypes should be conducted. With this finding, possible preventive guidance and the risk calculation model could be possibly revised. More studies stratifying menopausal status are also needed to be conducted to deeply investigated the difference for the association between reproductive factors and ERPR subtypes by menopausal status.

Figure 1. PRISMA Flowchart of Selected Articles

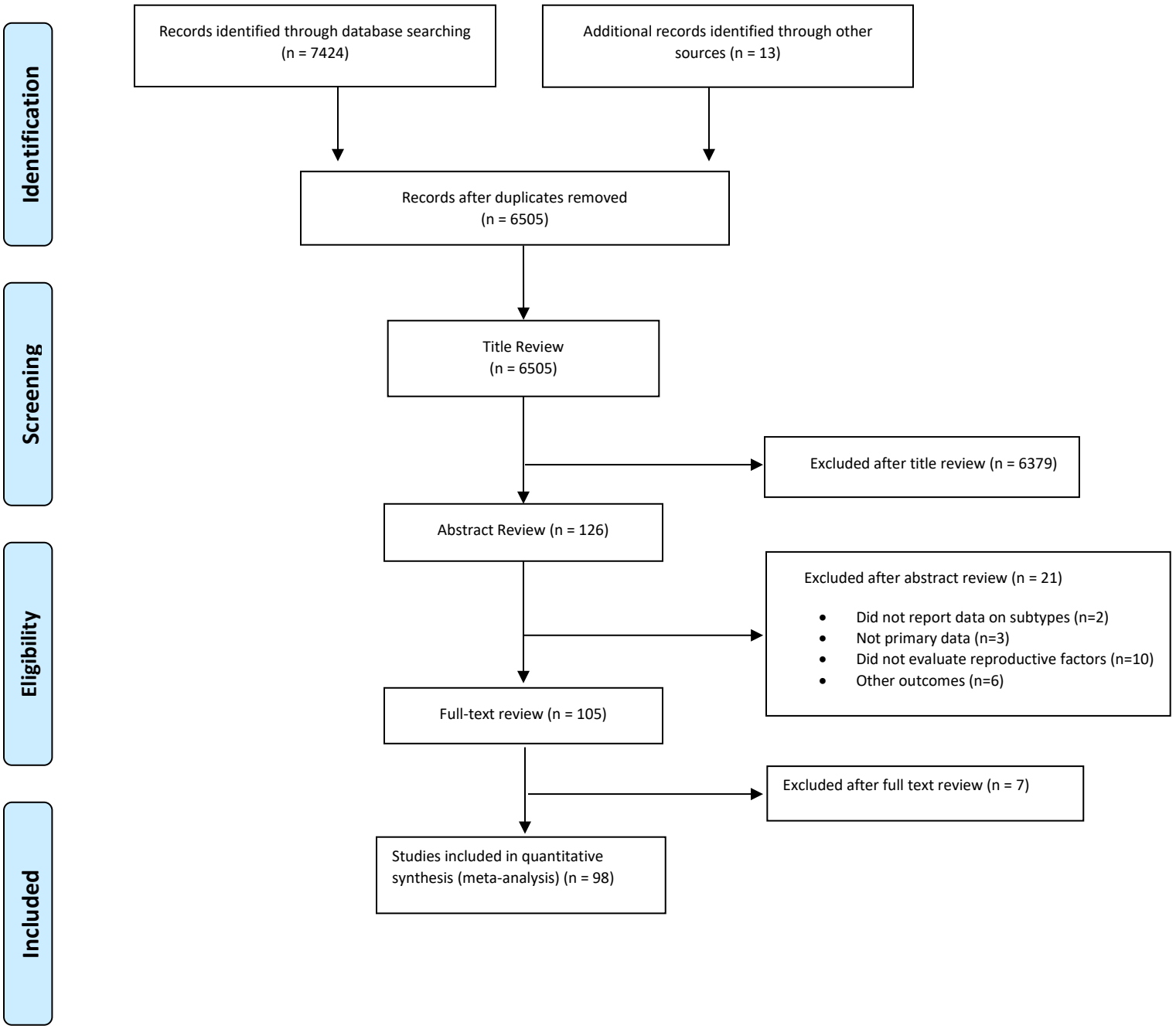


Table 1. Summary statistics for studies included after full-text review (N=98)

	Total Number of Studies (n=98)	ER+PR+ (n=22)	ER+PR- (n=14)	ER-PR+ (n=9)	ER-PR- (n=25)
Publication Years					
2011-2017	64	10	6	5	13
2006-2010	22	5	3	0	5
2000-2005	12	7	5	4	7
Data Source					
Primary Data	72	20	12	7	21
Hospital database	16	1	2	2	3
National Cancer Database* (E.g. SEER, CRN)	5	0	0	0	0
State Registry data	5	1	0	0	1
Region of study					
USA	44	11	9	5	13
Asia	19	4	3	3	5
Europe	16	2	1	1	2
Multi-countries	9	3	0	0	4
Unknown	5	0	1	0	0
Africa	3	0	0	0	0
Australia	1	1	0	0	0
Canada	1	1	0	0	1
Exposure of Interest					
Pregnancy/parity	64	13	8	6	15
Breastfeeding	55	15	8	7	16
Age at first birth	52	15	10	8	16
Menarche/menstruation	48	15	8	7	16
OC** use	28	11	5	4	11
HRT[§]	27	14	6	6	14
Menopausal status	22	6	7	6	8
Age at menopause	21	7	4	3	8
Abortion	7	2	1	1	2

*SEER: Surveillance, Epidemiology and End Results; CRN: Cancer Registry of Norway

**OC: Oral Contraceptive

[§] HRT: Hormone replacement therapy

Table 2. Summary of the meta-analysis

Reproductive factors	Contrast	ER+PR+	ER+PR-	ER-PR+	ER-PR-
Age at menarche	Late vs. early	S-	S-	S-	S-
Age at menopause	Late vs. early	S+	S+	NS+	NS+
Menopausal status	Post vs. pre/peri	S-	NS+	S-	NS+
Pregnancy	Ever vs. never	S-	S-	S-	NS-
Age at first birth	Nulliparous vs. early age at FB	S+	S-	NS-	NS-
	Late vs. early	S+	S+	NS+	NS-
Parity	Large parity vs. nulliparity	S-	S-	NS-	NS-
	Larger vs. smaller	S-	NS+	NS-	NS-
Breastfeeding	Ever vs. never	S-	S-	NS-	S-
	Larger vs. smaller	NS-	S-	NS-	NO
Years since last birth	Short vs. long	NS+	-	-	NS+
OC use	Ever vs. never	NS-	NS+	NS+	NS+
HRT	Ever vs. never	S+	NS+	NO	NS+

Figure 2. Age at menarche and BC subtypes defined by ERPR status

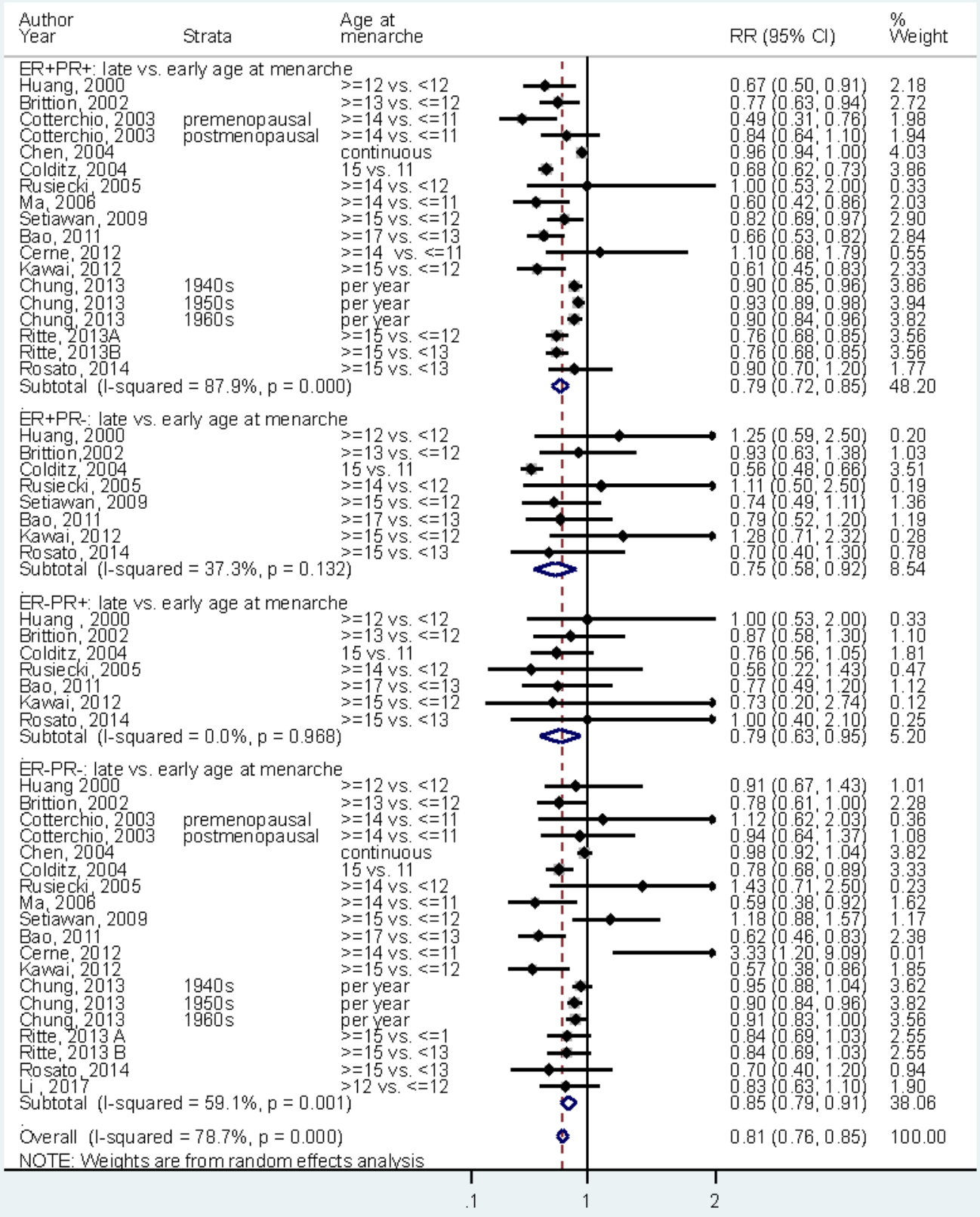


Figure 3. Age at menopause and BC subtypes defined by ERPR status

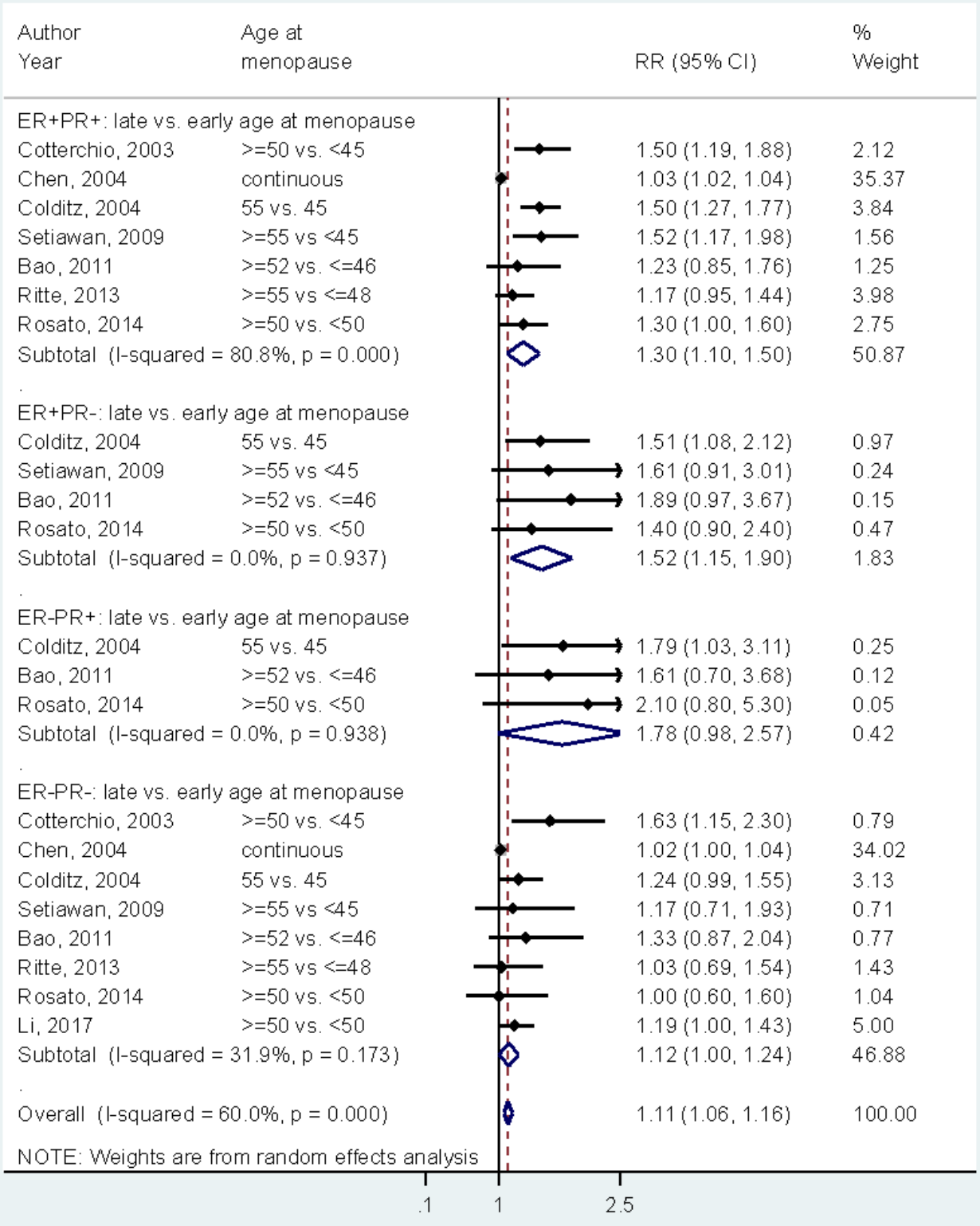


Figure 4. Menopause and BC subtypes defined by ERPR status

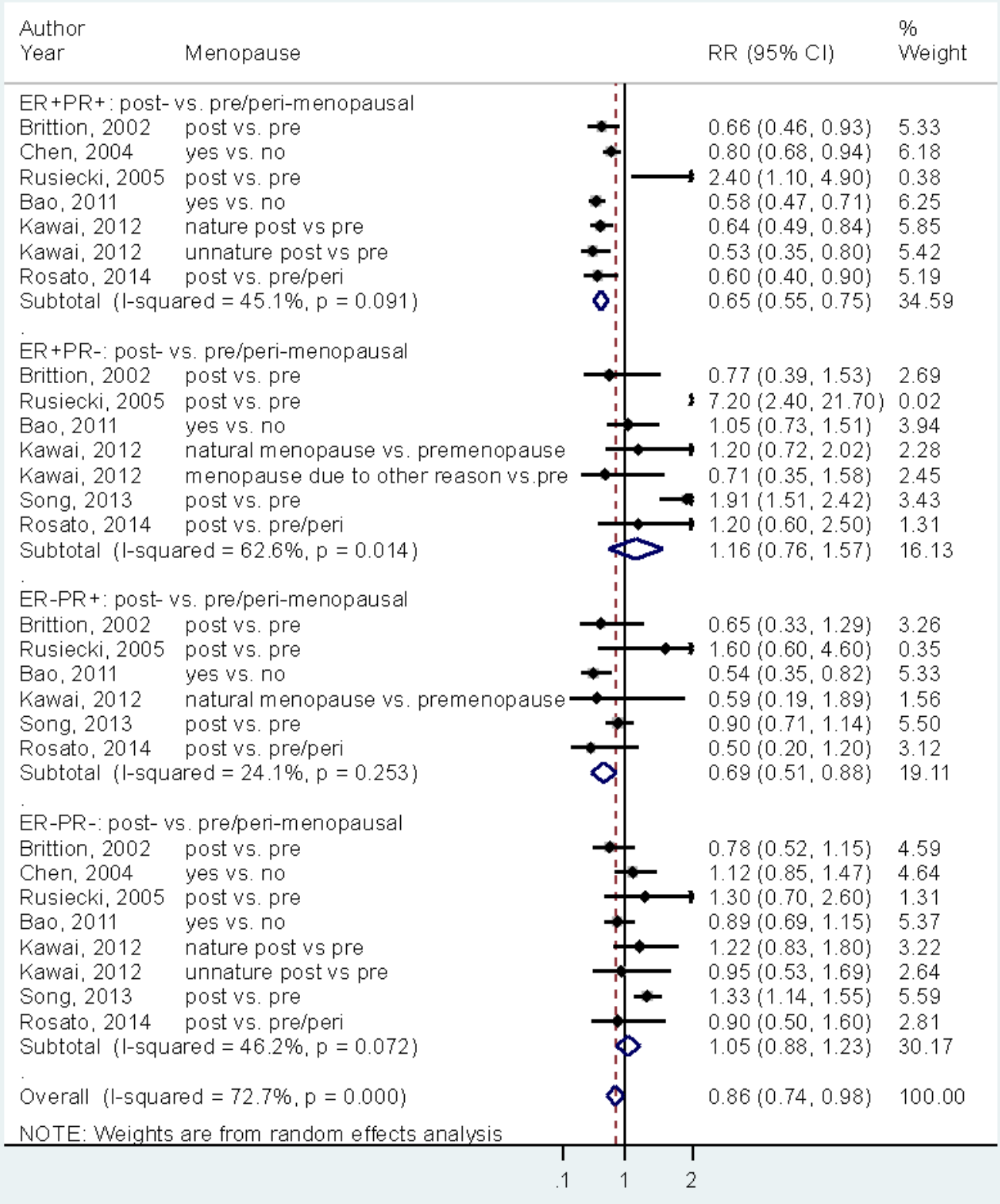


Figure 5. Pregnancy and BC subtypes defined by ERPR status

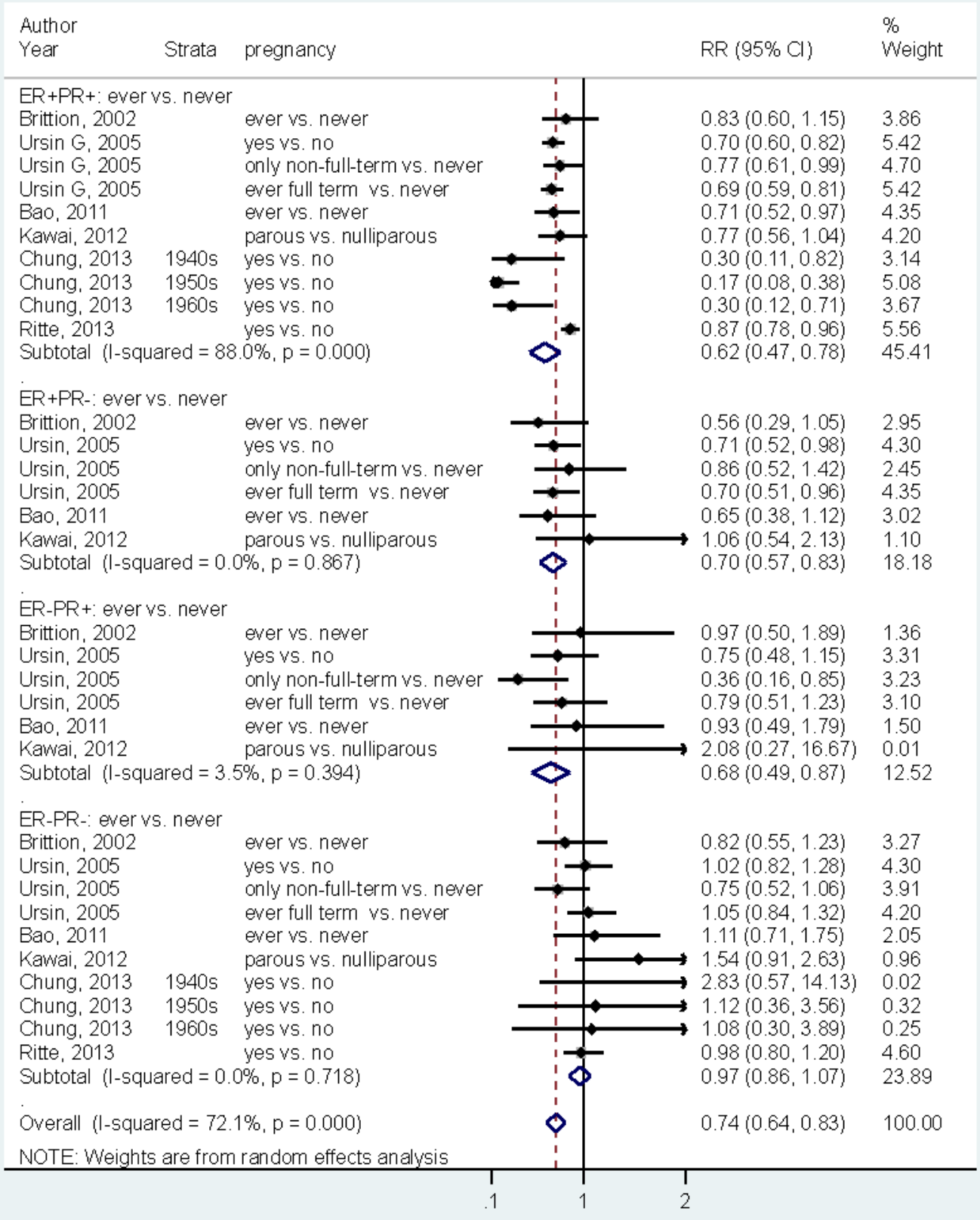


Figure 6. Age at first birth and BC subtypes defined by ERPR status

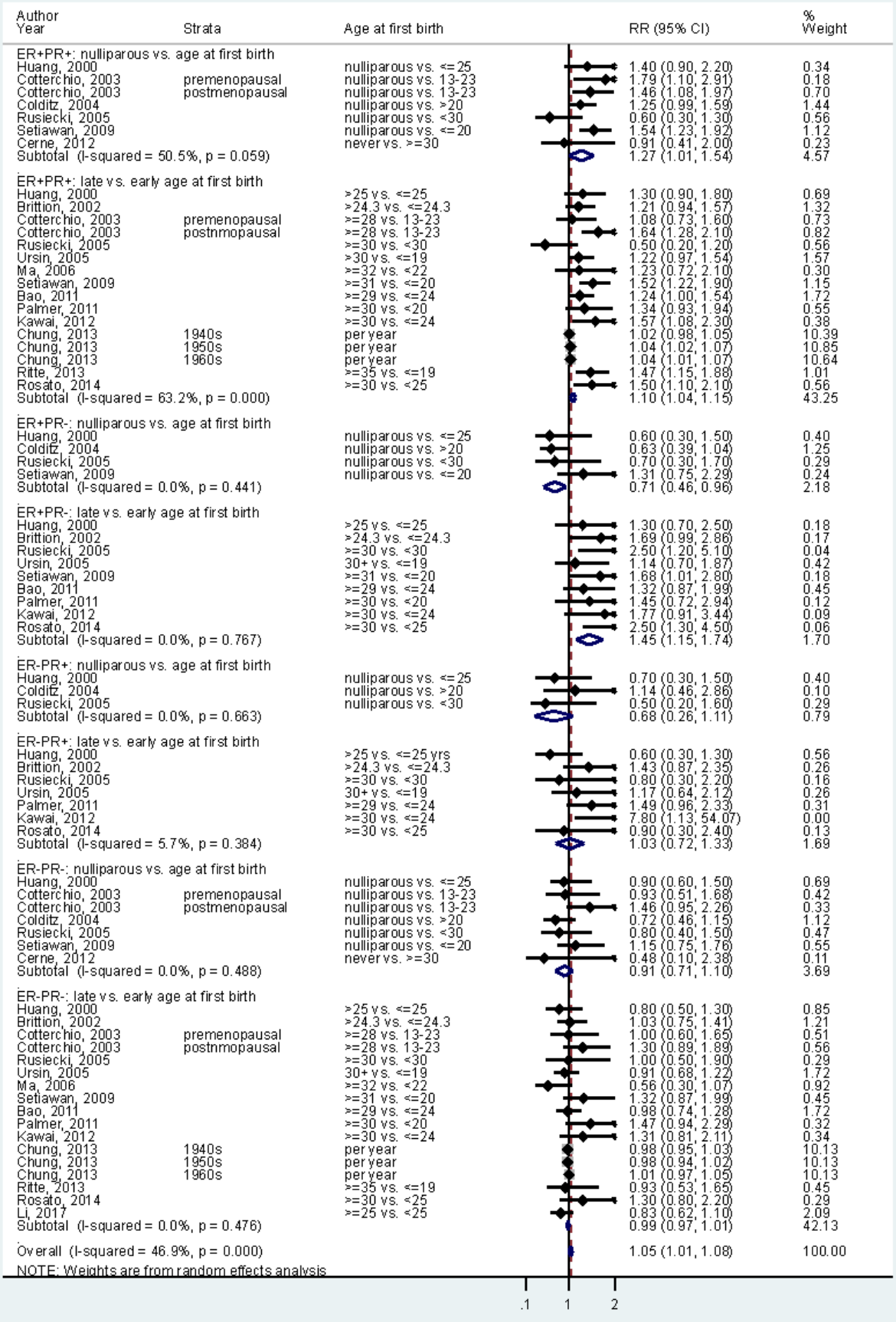


Figure 7. Parity and BC subtypes defined by ERPR status

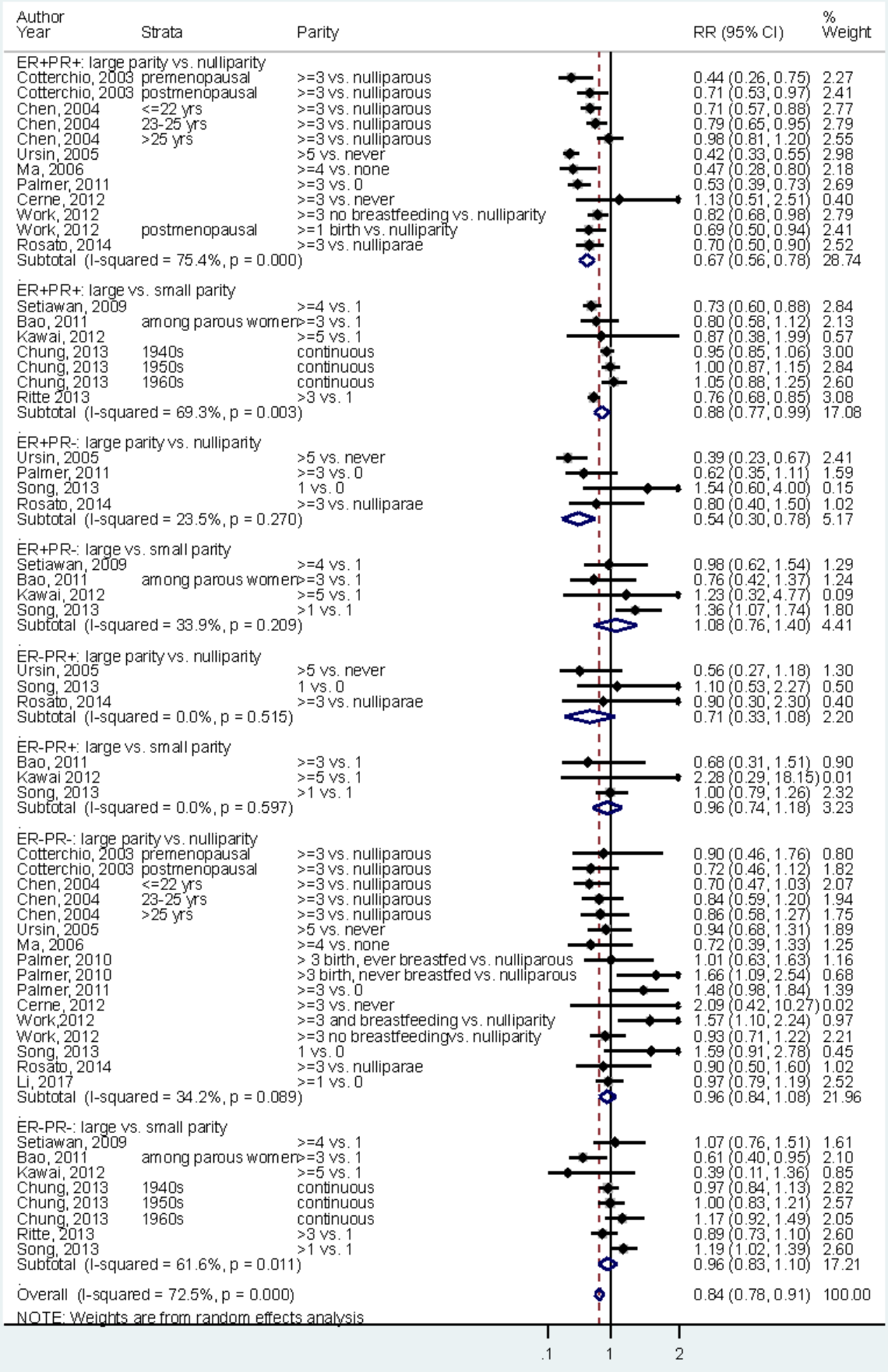


Figure 8. Breastfeeding and BC subtypes defined by ERPR status

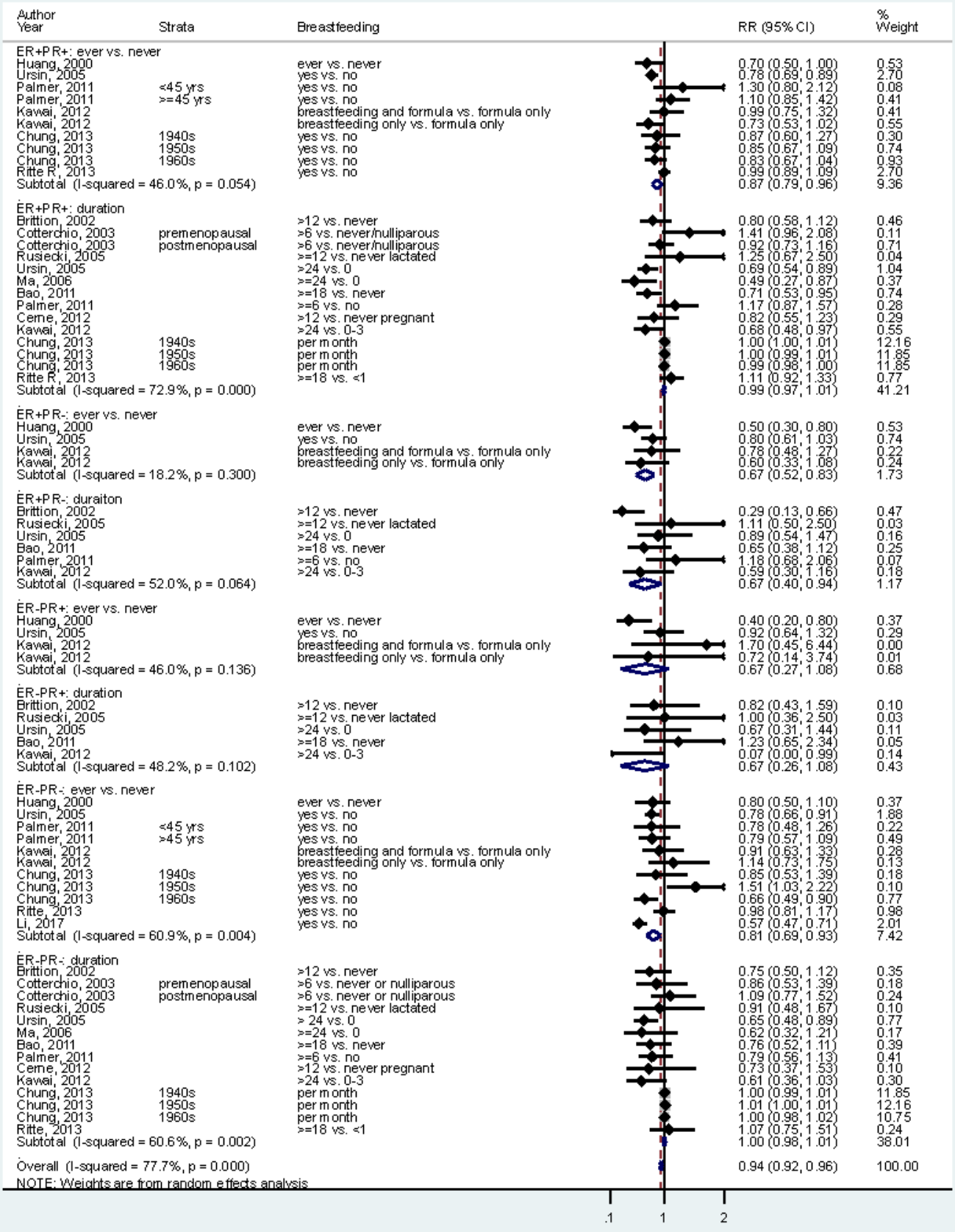


Figure 9. Years since last birth and BC subtypes defined by ERPR status

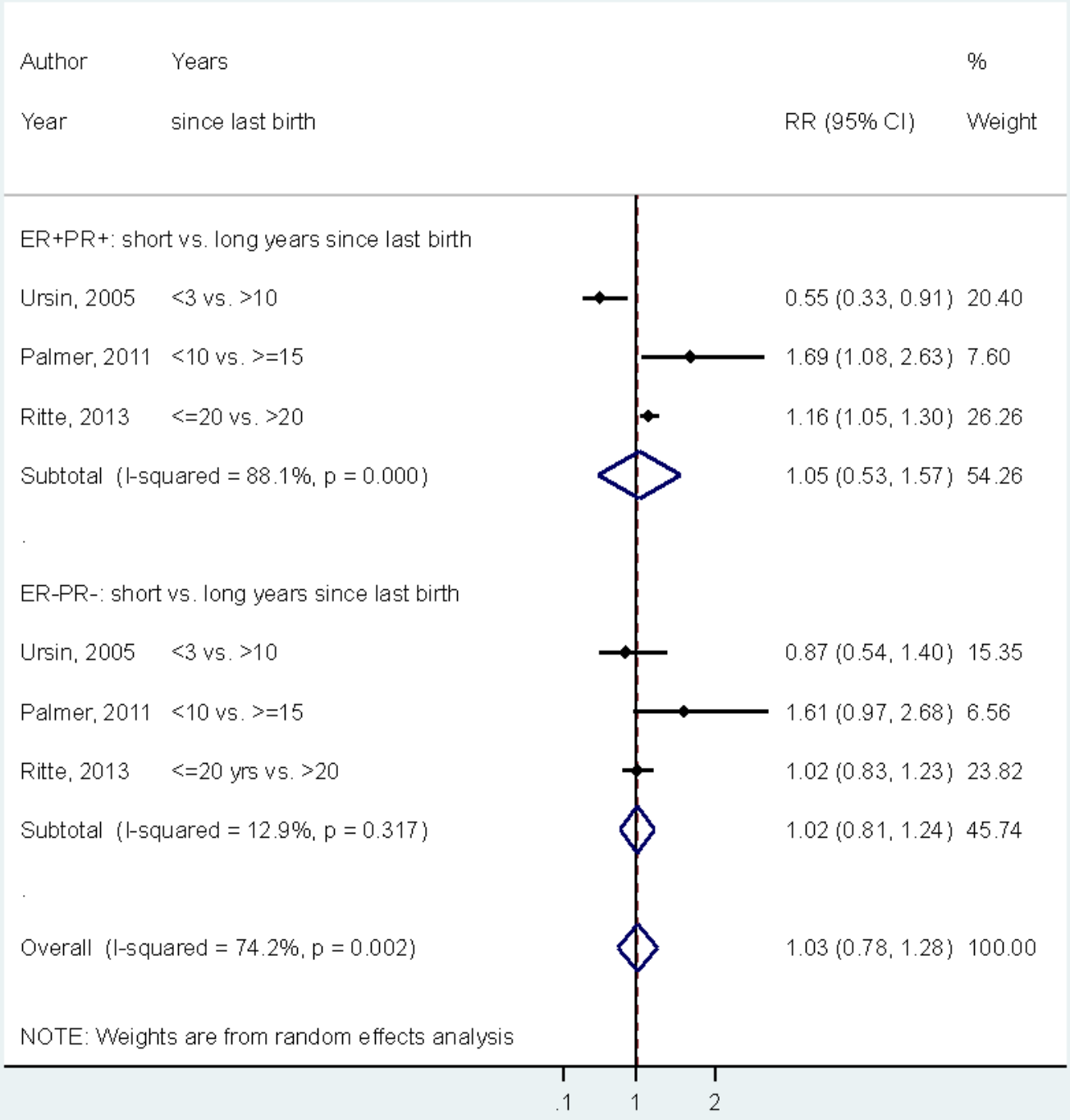


Figure 10. OC use and BC subtypes defined by ERPR status

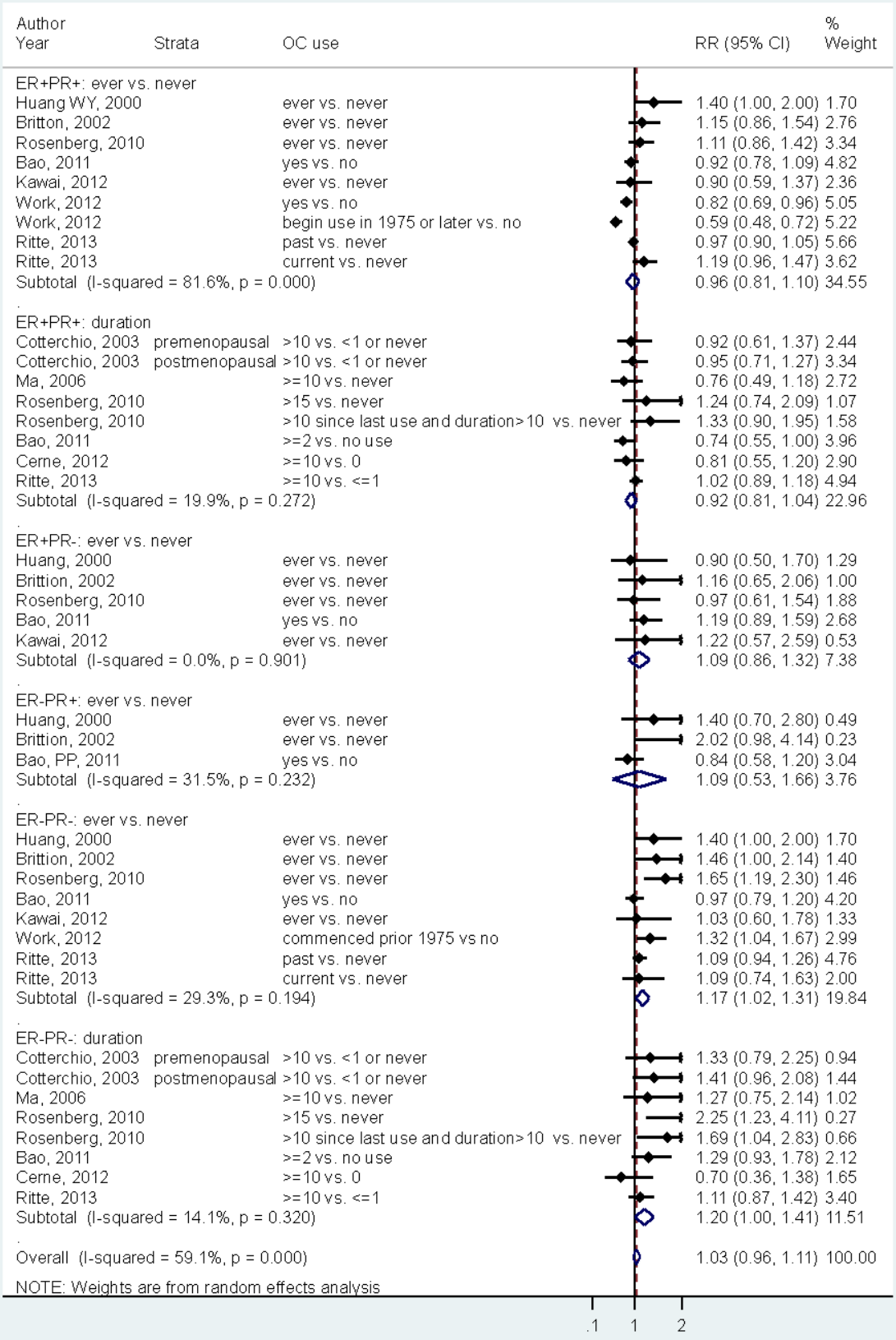
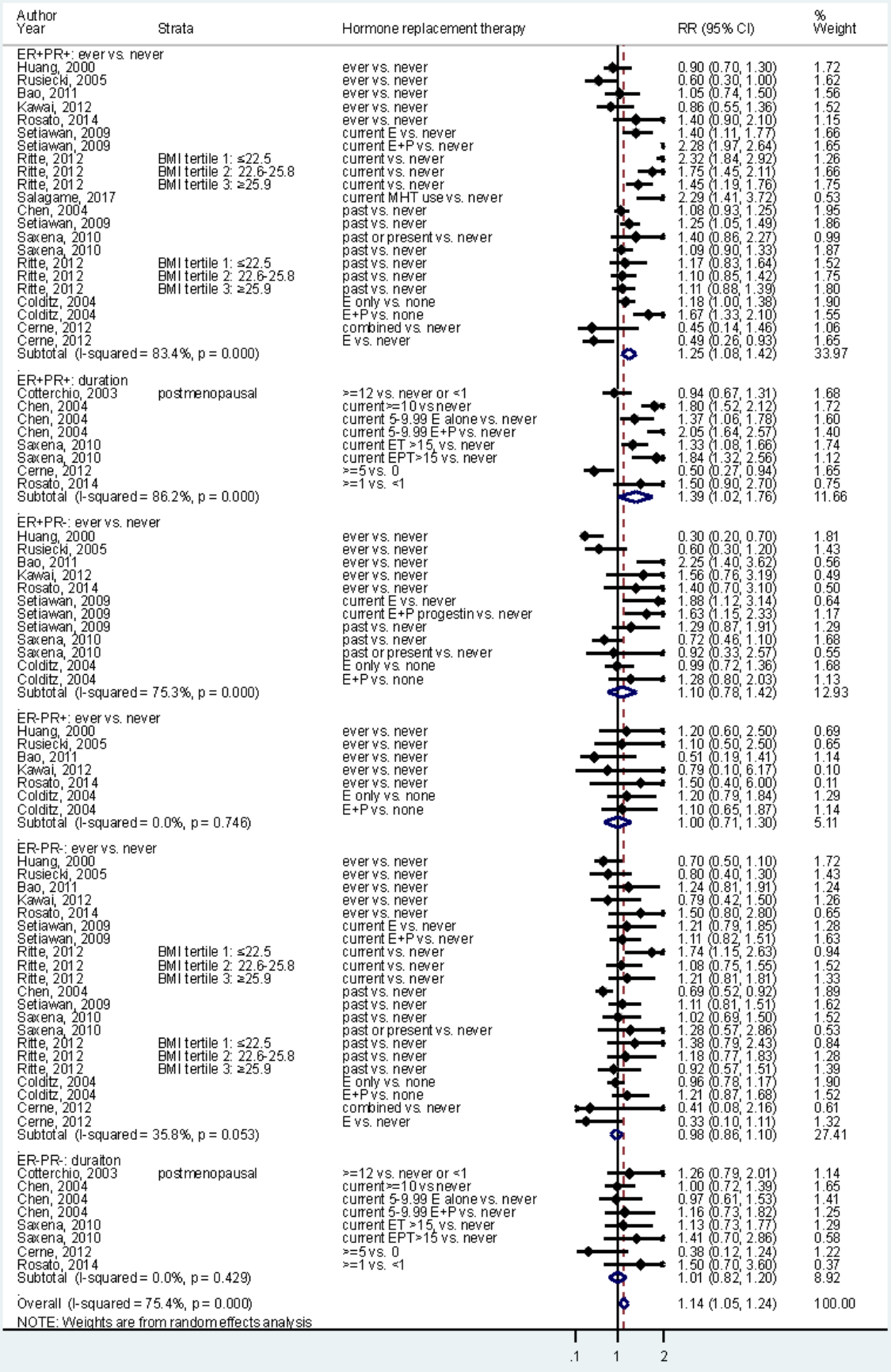


Figure 11. Hormone replacement therapy and BC subtypes defined by ERPR status



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