Systematic Review and Meta-Analysis

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Effect of age at first use of oral contraceptives on breast cancer risk

An updated meta-analysis

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Abstract

Background: We evaluated the relationship between the age at first use of oral contraceptives (OC) and breast cancer (BC) risk.

Methods: We searched PubMed, Embase, and related reviews published through June 28, 2018, and used summary relative risk (RR) and 95% confidence intervals (CIs) to evaluate the cancer risks, and fixed-effects dose–response meta-analysis to assess potential linear and non-linear dose–response relationships.

Results: We included 10 studies, with 8585 BC cases among 686,305 participants. The pooled RR for BC was 1.24 (95% CI: 1.10–1.41), with moderate heterogeneities (I^2 = 66.5%, P < .001). No significant publication bias was found (P = .584 for Begg test, P = .597 for Egger test). A linear dose–response relationship between the age at first OC use and BC risk was detected (P = .518 for non-linearity). Subgroup analyses were restricted to studies done by BC subtypes, region, sample size, follow-up time and study quality. Inconsistent consequences with no statistical significance were explored when limited to studies from Western countries, study quality <7, sample size <10,000, follow-up time <5 years, and BC subtypes defined by estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor-2 (HER-2) expression status in tumor tissue. Sensitivity analyses indicated that our results were stable and reliable after removing each study in turn and omitting studies of adjusted unreported variables.

Conclusion: A significant linear relationship between the age at first OC use and BC risk was confirmed. No further consistent differences are noted in multiple aspects of BC subtypes defined by progesterone or ER status.

Abbreviations: BC = breast cancer, BMI = body mass index, C = cohort study, CC = case-control study, CI = confidence intervals, ER = estrogen receptor, HER-2 = human epidermal growth factor receptor-2, HRT = hormone replacement therapy, NR = not reported, OC = oral contraceptives, PR = progesterone receptor, PY = person-years study, RR = relative risk, TNBC = triple negative breast cancer.

Keywords: age, oral contraceptives and breast cancer risk

1. Introduction

Breast cancer (BC) is the second most common cause of cancer death, in women, accounting for 23% of all women's cancer diagnoses and 14% of their cancer mortality,[1] and these incidences are increasing year by year, apparently because of both women's lifestyle changes and early detection programs.[2] Risk factors include inactivity, obesity, alcohol consumption, and oral contraceptive (OC) use.[3] However, most of these factors are modifiable, which means that the risk of BC can be reduced by taking actions.[4] For example, BC risk can be minimized by reducing OC consumption and starting OC use at an earlier age.

Oral contraceptives (OC) are safe, effective and reversible. Preliminary statistics indicate that over 100 million women currently use them, and approximately 80% of women in western countries are thought to have used them at some time in their reproductive lives[5]; however, the use of OC by women of childbearing age in Africa and Asia has fallen significantly, possible because of experienced or anticipated side effects, such as headache, hypertension, venous thrombosis, and tumors.[6] OC use is associated with a substantial decrease in ovarian cancer, endometrial cancer and colorectal cancer, but its effect on BC risk is unclear.[5,7–10]

Although epidemiological studies and meta-analyses have shown an association between BC incidence and OC use,[7–10] not all studies assessed the effect of the age of first OC use (A1stOC) on BC risk. No previous work has confirmed or clarified the dose–response relationship between A1stOC and BC risk. We therefore investigated the potential relationship between A1stOC and BC risk using a dose–response meta-analysis, which could clarify such an association, as it enables assessment of both potential non-linear and linear relationships and combines eligible studies to offer stronger statistical power.[11,12]

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2. Method

2.1. Search strategy

We planned a systematic review and meta-analysis that followed MOOSE guidelines for meta-analyses of observational studies.[13] Two researchers (J-LW and J-CX) searched the PubMed and EMBASE databases for papers on the association between A1stOC and BC risk, published before 28 June 2018, without language or time limitations. (See the Supplemental Content, http://links.lww.com/MD/D177 for the detailed search strategy and exclusion/inclusion criteria). A manual search through reference lists of included studies and other publications was performed. This meta-analysis was performed in adherence to the PRISMA statement.[14] All analyses were based on previous published studies, thus no ethical approval and patient consent are required.

2.2. Data extraction and quality assessment

Data were independently abstracted from all eligible studies by 2 investigators (Z-SL and P-WC). Information consisted of: the first author's name, publication year, region of the study, study design, follow-up time, categories of A1stOC, endpoints and cases, distributions of cases and/or person-years, values of rate ratios (RRs) and 95% confidence intervals (CIs), and adjustment factors. All studies were quality assessed independently, using the Newcastle–Ottawa scale.[15]

2.3. Statistical analysis

The effective measure of all studies was RR for BC risk. The all eligible studies used "never" status of OC use as a reference except 1 study,[16] and different categorical representations of A1stOC as variables. The lowest age category was set as the reference for Excel software.[17] For each included article, the mean value of the upper and lower bounds was regarded as the A1stOC concentration. For studies with open-ended scales, the upper boundary was defined as the lower boundary plus 1.0 times the width of the neighboring category[18]; and the lower boundary was defined as 12.25 years old—i.e., the overall median age at menarche.[19]

We performed fixed-effects meta-analyses to summarize the RRs for the highest vs lowest A1st OC categories in the included studies, as proposed by DerSimonian and Laird (high vs low meta-analysis).[20] We used $I^2$and Cochran Q to evaluate heterogeneity, by the following criteria—high heterogeneity: $I^2 \geq 75\%$; moderate heterogeneity: $I^2 = 50\%$ to 75%; low heterogeneity: $I^2 < 50\%$.[21] $P < .10$ was considered significant for the Q test. According to whether significant heterogeneity was found, data was assessed with a random-effects model or a fixed-effects model. Potential publication bias was assessed by Funnel plots,[22] Begg rank correlation test,[23] and Egger linear regression test.[24]

To identify potential sources of heterogeneity, we conducted stratified analyses by exposure categories: region, study quality, sample size, follow-up time, and BC subtypes. Sensitivity analysis was used to evaluate the stability of associations by removing each study in turn and omitting studies of adjusted unreported variables.

Next, the generalized least-squares trend model proposed by Longnecker and Greenland was used to estimate the effect of the trend for dose–response meta-analysis; a corrected linear relation could be obtained by this approach.[25,26] The potential non-linear dose–response relationship between the A1stOC and BC risk was probed by using three knots to restrict cubic splines; P values were explored by hypothesis testing for non-linearity.[27] Lastly, individual studies of the linear trend of RR per 1.0 year for A1stOC was summarized with fixed-effects or random-effects analyses in our study.

All P values were two-sided, and $P < .05$ was considered significant. The statistical analyses were performed with Stata version 14.0 (StataCorp, TX).

3. Results

3.1. Study selection

Details of the screening and search process are presented in Figure 1. After removing 752 duplicates, we reviewed the titles and abstracts of 831 articles. Our supporting information shows the search strategy and inclusion/exclusion standards. We included 10 eligible studies in the meta-analysis, with a total of 686,305 participants (of whom 8585 developed BC).[28–37] These studies included 9 articles in the dose–response meta-analysis, which reported results for 619,644 participants (of whom 8530 developed BC).[28,29,31–37] All eligible studies were read as full manuscripts and were regarded as high quality according to the Newcastle–Ottawa Quality Assessment Scale (Table 1).

3.2. Study characteristics

All of the articles used A1stOC as the exposure. OC formulations were not defined in all eligible studies. Table 1 summarizes the characteristics of included studies. These studies were published from 1995[28] to 2014.[35–37] Two studies were conducted in Europe,[28,29] four in America,[31–33,37] and four in Asia.[30,34–36] One study was stratified by age[35]; three were stratified by BC subtypes.[31–33] The risk estimates were not adjusted in 2 studies.[34,35] All 10 studies were found to be of high quality.

We removed one study from our dose–response analysis, as it divided the A1stOC data into only 2 categories.[30] Detailed RRs and numbers of BC cases for different A1stOC levels are shown in Table 2. Subgroup study was carried out by removing each study in turn and omitting studies of adjusted unreported variables.

3.3. Overall analysis

For the meta-analysis of highest vs lowest RR, we included 10 studies, the combined RR of BC was 1.24 (95% CI: 1.10–1.41), with moderate heterogeneity ($I^2 = 66.4\%$, $P < .001$; Figure 2). No significant publication bias was found (Begg test $P = .584$; Egger test $P = .597$ see Supplemental Figure 1, http://links.lww.com/MD/D177).

3.4. Subgroup analyses and sensitivity analyses

Twelve subgroup analyses were conducted to examine the stability of the meta-analysis's results (Table 3). Four provided results consistent with the overall analysis. Inconsistent outcomes with no statistical significance were found when analyses were restricted to those studies from Western countries, study quality <7, sample size <10,000, follow-up time <5 years, and BC subtypes. According to their I^2 values, significant heterogeneities were explored when subgroup analyses were restricted to studies

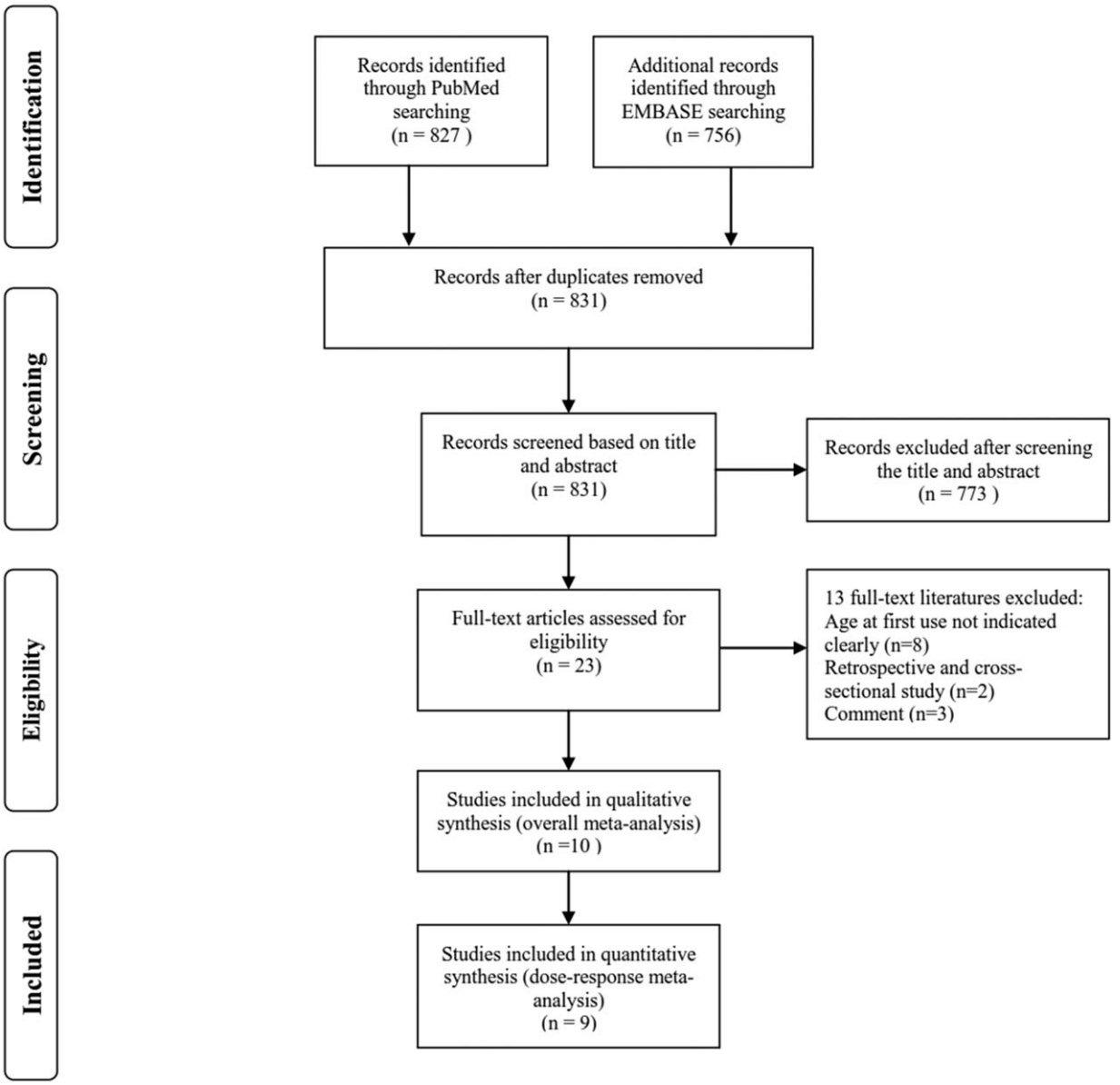

Figure 1. Flow diagram of literature screening for studies of relationship between age of first OC use and BC risk. BC = breast cancer, OC = oral contraceptives.

for which study quality <7, sample size <10,000, and follow-up time >5 years. Removing each individual study in turn did not alter the summary RR for BC risk (Supplementary Table 1, http://links.lww.com/MD/D177). Removing studies of adjusted unreported variables and repeating meta-analyses did not change our trends.

3.5. Dose–response analysis

Nine eligible studies were included in our dose–response analysis. In the overall meta-analysis of highest vs lowest, the combined RR of BC was 1.16 (95% CI:1.01–1.34), with no evidence of heterogeneity (I^2 = 25.4%, P = .187; Figure 3) or publication bias (Begg test P = .583, Egger test P = .678; Supplemental Figure 2, http://links.lww.com/MD/D177). No significant non-linear association was found among the included studies (P = .518 for non-linear trend). Therefore, the dose–response analysis was carried out with a linear model. The combined RR for BC with no statistical significance for each one-year-old increase in the A1stOC was 1.007 (95% CI: 1.002–1.013, P = .003), without significant heterogeneity (I^2 = 2.26%, P = .133; Figure 4).

4. Discussion

4.1. Result summary

Oral contraceptive use is known to correlate with BC risk in some populations. However, evidence for an effect from A1stOC is controversial. The study by Jee et al found that earlier A1stOC could increase BC risk.[38] In contrast, the study by Palmer et al.

Table 1

Summary of basic characteristics of prospective studies included in this systematic review and meta-analysis of age of first OC use and BC risk.

Study	Design	Menstrual status	Region	case/total	Duration of follow-up (years)	Sample size*	Adjusted variables
Schuurman 1995[28]	C	Postmenopause	Netherlands	471/62,573	3.3	7	Age, benign breast disease, mother with breast cancer, sister (s) with breast cancer, parity, age at first birth, age at menarche, age at menopause, induced menopause, education, current cigarette smoking, BMI, alcohol use, energy consumption, HRT use
Kumle 2002[29]	C	Premenopause	Sweden	1008/103,027	7	7	Age, parity, age at first birth, age at menarche, use of HRT, menopausal status, history of breast cancer in first-degree relatives, duration of breastfeeding, BMI, region, and interaction between BMI and menopausal status
Dorjgochoo 2009[30]	C	NR	China	558/66,661	7.5	8	Education, age at menarche, number of live births, cumulative duration of breast feeding, BMI, physical exercise in past five years, smoking, menopausal status, first-degree family history of cancer, and other contraceptive method
Dolle 2009[31]	CC	Premenopause	USA	898/1,569	9	6	Age, family history of breast cancer, and breastfeeding history
Ma 2010[32]	CC	NR	USA	1197/264,344	4	7	Race, education, age, family history of breast cancer, age at menarche, menopausal status, BMI.
Phipps 2011[33]	PY	Postmenopause	USA	2917/155,723	7.9	8	Age, study arm, race, education level, family history of breast cancer, BMI, hormone therapy use, smoking history, history of mammography (at baseline), mammography during follow-up, age at menarche, age at menopause, nulliparity
Ehsanpour 2013[34]	CC	NR	Iran	175/525	5	5	NR
Veisy 2014[35]	CC	NR	Iran	235/470	NR	5	NR
Poosari 2014[36]	C	NR	Thailand	70/11,414	21	8	Age at recruitment, marital status, family history of cancer, and breastfeeding history
Beaber 2014[37]	C	Premenopause	USA	1056/19,999	6	8	Age, race/ethnicity, and education distributions

BC = breast cancer, BMI = body mass index, C = cohort study, CC = case-control study, HRT = hormone replacement therapy, NR = not reported, OC = oral contraceptives, PY = person-years study.
* Evaluated by the 9-star Newcastle-Ottawa Scale.

demonstrated that older age was associated with BC risk,[39] whereas other studies had uncertain results.[28,32–35,37] Furthermore, the association between A1stOC and BC risk is inconsistent among different categorical representations,[29–31,36] and BC subtypes.[31–33] However, no studies have examined the exact dose–response relationship between A1stOC and BC risk before. Our meta-analysis aimed to explore the potential relationship between A1stOC and BC risk.

This meta-analysis, with a total of 686,305 participants, showed a significant association between A1stOC and the risk of BC without significant heterogeneity and publication bias. By pooling nine articles that included 619,644 participants, we showed a linear relationship between A1stOC and BC risk (P=.21for a non-linear trend), and a borderline significant association of 0.7% increase in the BC rate for every 1.0-year increase in A1stOC (i.e., RR: 1.007 [CI: 95%: 1.002–1.013] for each 1.0-year increment). Subgroup analyses showed inconsistent and statistically insignificant consequences when limited to studies of Western countries, low study quality (<7), small sample size (<10,000), short follow-up (<5 years), and all BC subtypes. Sensitivity analyses indicated that our results were stable and reliable after removing each study in turn and omitting studies of adjusted unreported variables.

4.2. A1stOC and BC risk

Four previous meta-analyses indicated that, BC risk was higher for OC users than for non-users.[7–10]

However, our result shows, for the first time, a steeply linear curve for the association of A1stOC and BC risk. Some plausible mechanisms could account for this association. Many studies support a role for OC in BC carcinogenesis, through estrogen and progesterone themselves,[40–42] disrupting endocrine systems,[43] or even stimulating breast tumor stem cells,[44,45] Moreover, OC can increase the metastatic ability of existing BC cells,[9,46–49] and interact with BC through various signaling pathways.[50–52]

Although little or no heterogeneity was seen in most studies of the association between A1stOC and BC risk, we also conducted stratified analyses to explore potential effect modifiers. Among studies with Western countries, low study quality (<7), small sample size (<10,000), short follow-up (<5 years), and all BC subtypes, we found no significant association between A1stOC and BC risk. Considering their limited participants and relatively wide CIs for risk estimates, the failure to detect significant associations was possibly caused by lack of statistical power. Use of OC was not associated with BC risk in women aged 50 to 79 years,[33] however, Dolle et al reported an increased risk of BC in women who were younger than 40 years, with different effects in premenopausal and postmenopausal women.[31] Thus, menstruation status is another potential modifier. Previous meta-analyses indicated that women who use OC are more likely to develop triple-negative BC (TNBC) than non-users,[10] but no similar results were seen in this study. The most likely explanation is that differences in risk factor distributions do not explain differences in incidence rates.

Table 2

Diagram of rate ratios for BC in studies on age of first OC use and BC risk.

Age at first OC use (years)	No of cases	Person-years (PY)/total	RR (95% CI)	RR (95% CI)*
Schuurman 1995[28]				
Never users	348	4,103	1	
<35	21	207	1.3 (0.7–2.4)	1
35–39	25	459	0.8 (0.5–1.4)	0.68 (0.31–1.5)
40–44	37	417	1.1 (0.7–1.7)	0.85 (0.4–1.79)
≥45	16	220	1.2 (0.6–2.2)	0.92 (0.38–2.23)
Kumle 2002[29]				
Never users	261	28,171	1	
<20	229	30,959	1.1 (0.8–1.4)	1
20–24	332	28,881	1.2 (1.0–1.5)	1.1 (0.8–1.49)
25–29	128	10,477	1.2 (0.9–1.5)	1.1 (0.77–1.55)
≥30	50	3,849	1.3 (0.9–1.7)	1.18 (0.79–1.76)
Dorjgochoo 2009[30]				
Never users	481	750	1	
<29	28	750	0.68 (0.46–1.00)	1
≥29	82	750	1.29 (1.01–1.65)	1.9 (1.21–1.98)
Dolle 2009[31]				
Never users	197	407	1	
≤18	150	228	1.9 (1.3–2.7)	1
18–22	390	674	1.2 (0.9–1.6)	0.63 (0.42–0.94)
≥22	159	260	1.2 (0.9–1.7)	0.63 (0.42–0.96)
TNBC				
Never users	22	407	1	
≤18	42	228	3.7 (1.9–7.2)	1
18–22	92	674	2.3 (1.3–4.1)	0.62 (0.27–1.45)
≥22	31	260	2.0 (1.0–4.1)	0.54 (0.21–1.38)
Non-TNBC				
Never users	175	407	1	
≤18	108	228	1.6 (1.1–2.3)	1
18–22	298	674	1.1 (0.8–1.4)	0.69 (0.44–1.07)
≥22	128	260	1.1 (0.8–1.6)	0.69 (0.42–1.12)
ER-				
Never users	59	407	1	
<18	64	228	2.8 (1.7–4.6)	1
18–22	170	674	1.8 (1.2–2.8)	0.64 (0.34–1.22)
≥22	71	260	1.7 (1.1–2.9)	0.61 (0.31–1.2)
ER+				
Never users	138	407	1	
<18	95	228	1.4 (0.9–2.2)	1
18–22	220	674	1.0 (0.7–1.3)	0.71 (0.42–1.21)
≥22	79	260	1.0 (0.7–1.5)	0.71 (0.4–1.26)
HER2+				
Never users	73	407	1	
<18	47	228	1.8 (1.1–2.9)	1
18–22	120	674	1.1 (0.7–1.6)	0.61 (0.33–1.14)
≥22	49	260	1.0 (0.6–1.6)	0.56 (0.28–1.09)
Ma 2010[32]				
TNBC				
Never users	59	410	1	
<18	71	305	1.12 (0.72–1.74)	1
18–19	62	332	1.00 (0.65–1.55)	0.89 (0.5–1.58)
20–24	89	569	0.96 (0.65–1.42)	0.86 (0.5–1.47)
≥ 25	54	399	0.99 (0.66–1.48)	0.88 (0.51–1.53)
HER-2+				
Never users	19	410	1	
<18	12	305	0.85 (0.36–2.00)	1
18–19	17	332	1.13 (0.53–2.42)	1.33 (0.43–4.07)
20–24	28	569	1.31 (0.68–2.55)	1.54 (0.54–4.43)
≥ 25	21	399	1.26 (0.66–2.42)	1.48 (0.52–4.23)
Luminal A				
Never users	155	410	1	
<18	80	305	0.89 (0.62–1.28)	1
18–19	80	332	0.78 (0.55–1.11)	0.88 (0.56–1.37)
20–24	194	569	1.03 (0.78–1.36)	1.15 (0.78–1.71)
≥ 25	136	399	0.91 (0.69–1.20)	1.02 (0.69–1.51)
Luminal B				
Never users	21	410	1	
<18	17	305	1.23 (0.57–2.64)	1
18–19	26	332	1.66 (0.84–3.27)	1.35 (0.5–3.65)
20–24	34	569	1.26 (0.68–2.34)	1.02 (0.39–2.66)
≥ 25	22	399	1.07 (0.57–2.00)	0.87 (0.33–2.27)
Phipps 2011[33]				
ER+				
Never users	1,562	87,861 (PY)	1	
<20	21	1,623 (PY)	1.08 (0.67 to 1.72)	1
20–24	223	15148 (PY)	0.97 (0.81 to 1.15)	0.9 (0.55–1.46)
≥25	800	45783 (PY)	0.94 (0.85 to 1.03)	0.87 (0.55–1.38)
TNBC				
Never users	171	87,861 (PY)	1	
<20	2	1,623 (PY)	0.62 (0.15 to 2.60)	1
20–24	46	15148 (PY)	1.12 (0.72 to 1.76)	1.81 (0.41–8)
≥25	88	45783 (PY)	0.98 (0.73 to 1.32)	1.58 (0.37–6.73)
Ehsanpour 2013[34]				
≤20	14	23	3.28 (0.90–9.13)	
21–25	26	34	2/61 (0.92–7/40)	
26–30	22	25	2/27 (0/77–6/64)	
≥31	7	14	1	
Beaber 2014[37]				
All women (age 20–44)				
Never users	119	103	1	
<18	323	284	1.0 (0.7–1.4)	1
18–20	288	279	0.9 (0.7–1.3)	0.9 (0.58–1.4)
≥21	255	216	1.0 (0.7–1.4)	1 (0.63–1.6)
Age 20–39				
Never users	45	44	1	
<18	138	131	1.0 (0.6–1.7)	1
18–20	115	106	1.1 (0.7–1.9)	1.1 (0.54–2.23)
≥21	76	74	1.0 (0.6–1.7)	1 (0.49–2.06)
Age 40–44				
Never users	74	59	1	
<18	185	153	0.9 (0.6–1.5)	1
18–20	173	173	0.8 (0.5–1.2)	0.89 (0.48–1.65)
≥21	179	142	1.0 (0.7–1.5)	1.11 (0.62–1.98)
Veisy 2014[35]				
No use	63	92	1	
13–18	20	22	0.88 (0.44–1.61)	1
19–24	64	69	0.9 (0.61–1.34)	1.02 (0.5–2.1)
25–30	50	28	1.99 (1.20–3.30)	2.26 (1.03–4.9)
>30	29	5	6.47 (2.46–17.4)	7.35 (2.33–23.19)
Poosari 2014[36]				
Never	11	2153	1	
<30	9	1252	1.17 (0.36–3.73)	1
30–39	18	2813	1.07 (0.42–2.76)	0.91 (0.21–4.08)
40–49	22	3252	1.10 (0.49–2.50)	0.94 (0.23–3.88)
>50	10	1944	1.23 (0.45–4.26)	1.05 (0.21–5.29)

BC = breast cancer, ER = estrogen receptor, HER-2 = human epidermal growth factor receptor-2, OC = oral contraceptives, PR = progesterone receptor, TNBC = Triple negative breast cancer.
* Transforming the reference group using EXCEL and software.

4.3. Strengths and limitations

To our knowledge, this is the first meta-analysis of published prospective studies on A1stOC and BC risk to find a positive linear relationship between them. The sample size was sufficiently large (686,305 participants, of whom 8585 had BC), and came from different regions (Europe, North America and Asia). The measure of exposure was consistent in all of the studies. The subgroup analyses show disparate outcomes when they were restricted to studies of Western countries, low study quality (<7), small sample size (<10,000), short follow-up (<5 years), and all BC subtypes by exposure categories: Western/Eastern country, low/high study quality, small/large sample size, short/long follow-up time and TNBC/non-TNBC/HER-2+/ER+. Our sensitivity analysis was stable and reliable when we removed individual studies in turn and omitted studies of adjusted unreported variables.

This study had several limitations. First, 1 study was excluded for the dose–response meta-analysis for having only two exposure categories. Second, as only 3 studies reported BC subtypes,[31–35] no definite result was presented due to lack of available datasets. Third, 2 studies did not report adjusted variables,[34,35] which prevented us from an in-depth analysis of potential confounders and effect modifiers. What's more, a

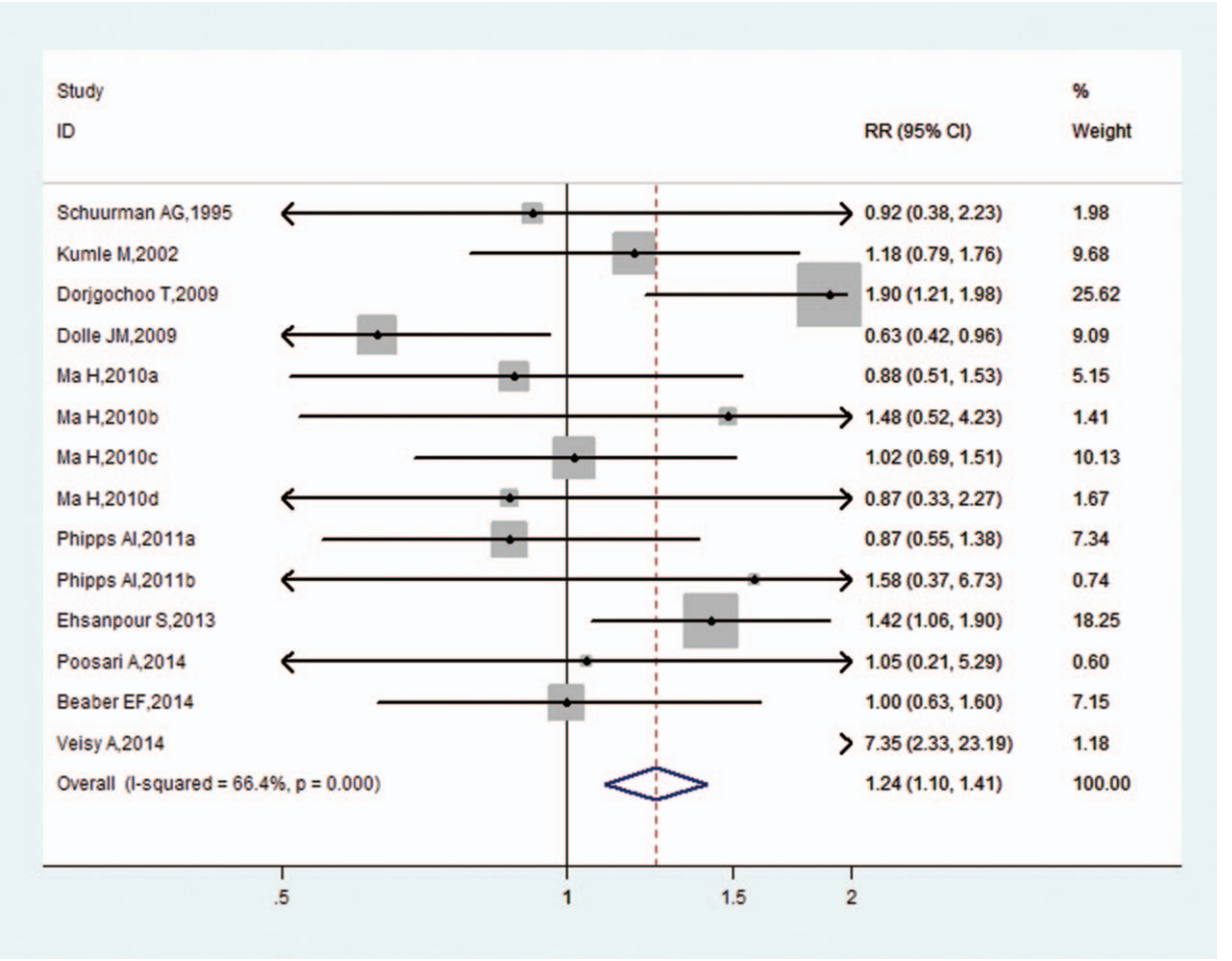

Figure 2. Forest plot of overall meta-analysis. Weights from fixed-effects analysis.

Table 3

Subgroup analyses.

Criteria	No. of studies	Model	Pooled RR		Heterogeneity	
			RR (95%CI)	*P* value	I^2 (%)	*P* value
Main effect	10	Fixed	1.24 (1.10–1.41)	0.001	66.4	<0.001
Study design						
CC	4	Random	1.10 (0.92–1.31)	0.311	72.4	0.001
CH+PY	6	Fixed	1.38 (1.17–1.64)	<0.001	56	0.034
Region						
Eastern country	4	Random	1.73 (1.44–2.08)	<0.001	67.5	0.033
Western country	6	Random	0.94 (0.79–1.11)	0.445	0	0.692
Study quality						
<7	3	Random	1.57 (0.64–3.87)	0.329	90.1	0.528
>7	7	Fixed	1.27 (1.10–1.47)	0.01	45.1	0.052
Sample size						
<10,000	3	Random	1.17 (0.93–1.48)	0.18	90.1	<0.001
>10,000	7	Fixed	1.27 (1.10–1.47)	0.001	45.1	0.052
Follow-up time						
<5	2	Fixed	0.99 (0.75–1.30)	0.916	0	0.93
>5	8	Random	1.32 (1.15–1.51)	<0.001	76.8	<0.001
BC subtypes						
TNBC	3	Random	0.83 (0.53–1.31)	0.426	0	0.449
Non-TNBC	3	Random	0.90 (0.71–1.14)	0.381	0	0.661
HER-2+	2	Random	0.75 (0.42–1.32)	0.35	57	0.127
ER+	3	Random	0.89 (0.69–1.15)	0.39	0	0.78
Menstrual status						
Premenopause	3	Fixed	0.91 (0.71–1.16)	0.422	0.09	58.4
Postmenopause	2	Random	0.92 (0.62–1.36)	0.673	0.744	0

ER = estrogen receptor, HER-2 = human epidermal growth factor receptor-2, TNBC = Triple negative breast cancer.

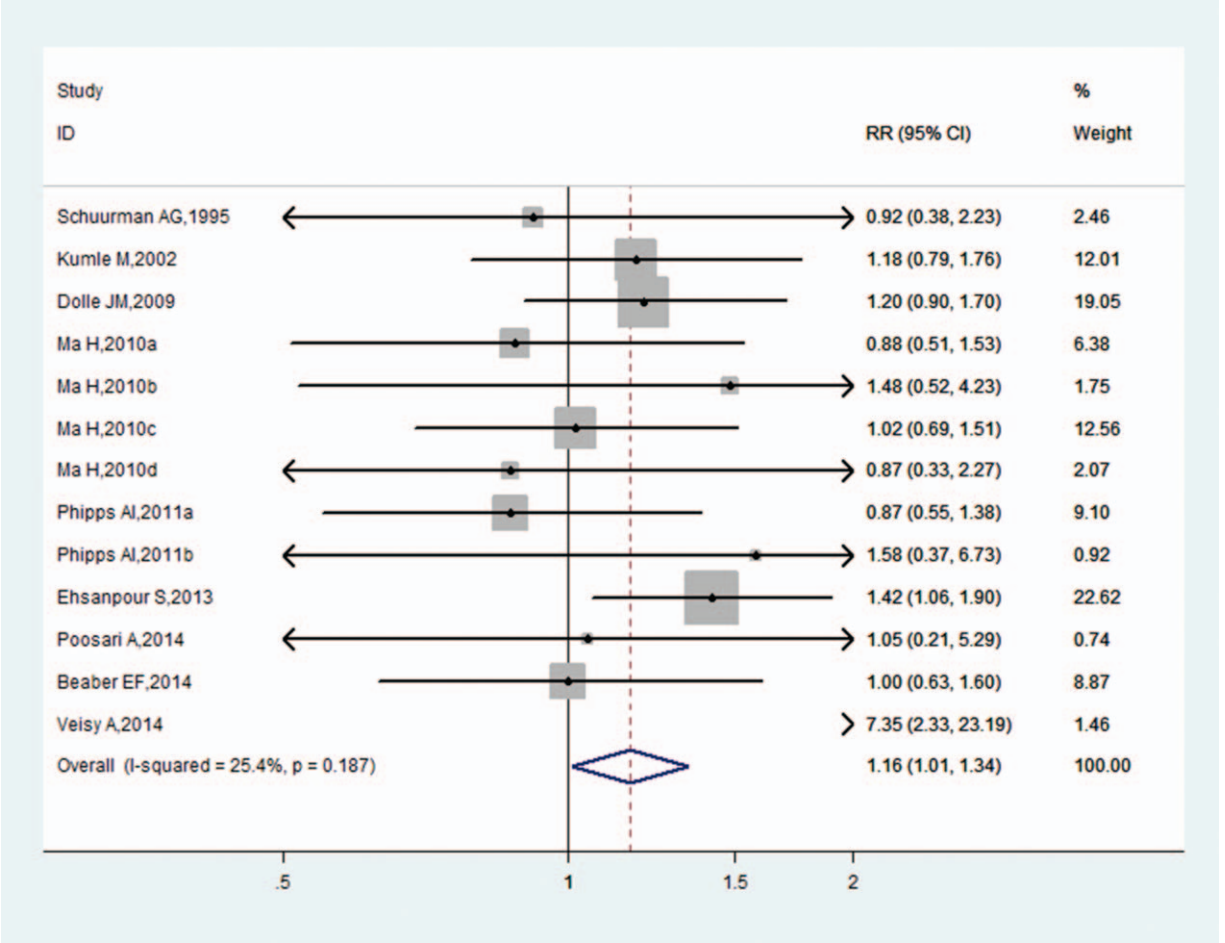

Figure 3. Forest plot of dose-response meta-analysis. Weights from fixed effects analysis.

chance of unmeasured or residual confounding remains (e.g., pathological information, that has not been considered in our analysis). Fourth, no study reported OC formulation, frequency of administration or menstrual status at onset, so no associated subgroup analyses were performed. Fifth, the threshold of A1stOC that increases BC risk was not assessed in our study. Finally, our study used summary statistics rather than individual data which could have allowed more precise delineation and controlled potential residual confounding, leading to more accurate and reliable results, which is an important limitation related to the original design of the studies.

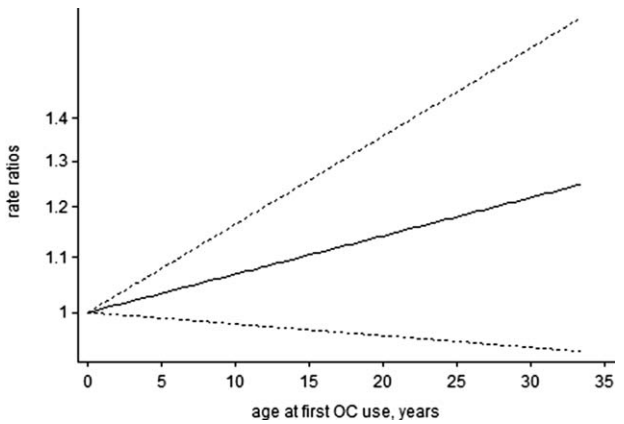

Figure 4. Dose-response relationship between age of first OC use and BC risk. Solid line: linear relationship; dashed line: 95% CI of the estimated relationship. BC = breast cancer, OC = oral contraceptives.

5. Conclusions

Our study discovered a significant linear dose–response relationship between A1stOC and BC risk that every 1.0-year increase in age is associated with a 0.7% increase in BC incidence; the association was not confirmed by BC progesterone or estrogen receptor status. Long-term effect of various OC on cancer risk need to be determined by future and ongoing studies.

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