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,[11] 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]
2. Method

2.1. Search strategy

We planned a systematic review and meta-analysis that followed MOOSE guidelines for meta-analyses of observational studies.[11,12] 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 A1stOC categories in the included studies, as proposed by DerSimonian and Laird (high vs low meta-analysis).[20] We used I² and Cochran Q to evaluate heterogeneity, by the following criteria—high heterogeneity: I² ≥ 75%; moderate heterogeneity: I² = 50% to 75%; low heterogeneity: I² < 50%. I² < .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,[36] 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 (I² = 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 I² values, significant heterogeneities were explored when subgroup analyses were restricted to studies
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 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.
demonstrated that older age was associated with BC risk, whereas other studies had unexplained results. Furthermore, the association between A1stOC and BC risk is inconsistent among different categorical representations and BC subtypes. 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. Sensitivity analyses indicated that our results were stable and reliable after removing each study in turn and omitting subtypes.

### 4.2. A1stOC and BC risk

Four previous meta-analyses indicated that, BC risk was higher for OC users than for non-users. 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, disrupting endocrine systems, or even stimulating breast tumor stem cells. Moreover, OC can increase the metastatic ability of existing BC cells and interact with BC through various signaling pathways.

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, however, Dolle et al reported an increased risk of BC in women who were younger than 50 years, with different effects in premenopausal and postmenopausal women. 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, 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) |
|----------------------------|-------------|-------------------------|-------------|-------------|
| Never users                | 348         | 4,103                   | 1           |             |
| <18                       | 21          | 297                     | 1.3 (0.7–2.4) | 1          |
| 20–24                      | 332         | 26,881                  | 1.2 (1.0–1.5) | 1.1 (0.8–1.49) |
| ≥25                       | 128         | 10,477                  | 1.2 (0.9–1.5) | 1.1 (0.77–1.55) |
| Never users                | 481         | 750                     | 1           |             |
| <20                       | 29          | 750                     | 1.29 (1.01–1.65) | 1.3 (1.21–1.98) |

### Table 2 (continued)

| Age at first OC use (years) | No of cases | Person-years (PY)/total | RR (95% CI) | RR (95% CI) |
|----------------------------|-------------|-------------------------|-------------|-------------|
| Never users                | 197         | 407                     |             |             |
| <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) |

### Table 2 (continued)

| Age at first OC use (years) | No of cases | Person-years (PY)/total | RR (95% CI) | RR (95% CI) |
|----------------------------|-------------|-------------------------|-------------|-------------|
| Never users                | 175         | 407                     |             |             |
| <20                       | 108         | 228                     | 1.6 (1.1–2.3) | 0.69 (0.44–1.07) |
| 20–24                      | 298         | 674                     | 1.1 (0.8–1.4) | 0.69 (0.42–1.12) |
| ≥22                       | 128         | 260                     | 1.1 (0.8–1.6) | 0.69 (0.42–1.12) |

### Table 2 (continued)

| Age at first OC use (years) | No of cases | Person-years (PY)/total | RR (95% CI) | RR (95% CI) |
|----------------------------|-------------|-------------------------|-------------|-------------|
| Never users                | 138         | 407                     |             |             |
| <20                       | 95          | 228                     | 1.4 (0.9–2.2) | 1           |
| 20–24                      | 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 (0.41–1.28) |

### Table 2 (continued)

| Age at first OC use (years) | No of cases | Person-years (PY)/total | RR (95% CI) | RR (95% CI) |
|----------------------------|-------------|-------------------------|-------------|-------------|
| Never users                | 73          | 407                     |             |             |
| <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) |

### Table 2 (continued)

| Age at first OC use (years) | No of cases | Person-years (PY)/total | RR (95% CI) | RR (95% CI) |
|----------------------------|-------------|-------------------------|-------------|-------------|
| Never users                | 59          | 410                     |             |             |
| <18                       | 71          | 305                     | 1.12 (0.72–1.74) | 1           |
| 18–19                      | 62          | 332                     | 1.00 (0.65–1.53) | 0.89 (0.51–1.58) |
| 20–24                      | 89          | 569                     | 0.96 (0.65–1.52) | 0.86 (0.54–1.39) |
| ≥25                       | 54          | 399                     | 0.99 (0.66–1.50) | 0.88 (0.51–1.53) |

### Table 2 (continued)

| Age at first OC use (years) | No of cases | Person-years (PY)/total | RR (95% CI) | RR (95% CI) |
|----------------------------|-------------|-------------------------|-------------|-------------|
| Never users                | 19          | 410                     |             |             |
| <18                       | 12          | 305                     | 0.85 (0.56–1.36) | 1           |
| 18–19                      | 17          | 332                     | 1.13 (0.53–2.42) | 1.33 (0.43–4.07) |
| 20–24                      | 28          | 569                     | 1.31 (0.66–2.65) | 1.54 (0.54–4.43) |
| ≥25                       | 21          | 399                     | 1.26 (0.67–2.42) | 1.48 (0.52–4.23) |

### Table 2 (continued)

| Age at first OC use (years) | No of cases | Person-years (PY)/total | RR (95% CI) | RR (95% CI) |
|----------------------------|-------------|-------------------------|-------------|-------------|
| Never users                | 155         | 410                     |             |             |
| <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) |

### Table 2 (continued)

| Age at first OC use (years) | No of cases | Person-years (PY)/total | RR (95% CI) | RR (95% CI) |
|----------------------------|-------------|-------------------------|-------------|-------------|
| Never users                | 21          | 410                     |             |             |
| <18                       | 17          | 305                     | 1.23 (0.57–2.64) | 1           |
| 18–19                      | 26          | 332                     | 1.66 (0.84–3.27) | 1.35 (0.55–3.65) |
| 20–24                      | 34          | 569                     | 1.26 (0.68–2.34) | 1.02 (0.39–2.68) |
| ≥25                       | 22          | 399                     | 1.07 (0.57–2.00) | 0.87 (0.33–2.27) |

To our knowledge, this is the first meta-analysis of published prospective studies on A14OC and BC risk to find a positive linear relationship between them. The sample size was sufficiently large (686,305 participants, of whom 8855 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/HER2+/HER2−. 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,[14,15] which prevented us from an in-depth analysis of potential confounders and effect modifiers. What’s more, a

### 4.3. Strengths and limitations

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

Table 3
Subgroup analyses.

| Criteria                     | No. of studies | Model   | Pooled RR (95% CI) | P value | I² (%) | 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.
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.

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.

Acknowledgments

The authors gratefully acknowledge Juan Ye for her assistance in study design and statistical analyses. We also thank Marla Brunker, from Liwen Bianji, Edanz Group China (www.liwenbianji.cn/ac), for editing the English text of a draft of this manuscript.
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