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Estradiol therapy and breast cancer risk in perimenopausal and postmenopausal women: a systematic review and meta-analysis

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Abstract

Objective: To investigate the association between estradiol therapy and incidence of breast cancer, taking into consideration of different types of combined progestogen, the duration of exposure and the type of regimen.

Method: A systematic review and meta-analysis.

Result: A total of 14 studies were included in our study. In estradiol-only therapy analysis, meta-analysis resulted a pooled OR = 0.90, 95% CI (0.40, 2.02) from the RCTs and pooled OR = 1.11, 95% CI (0.98, 1.27) from observational studies. However, in the analysis of estradiol-progestogen therapy, the risk of breast cancer varies according to the type of progestogen and the duration with more than five years (OR = 2.43, 95% CI (1.79, 3.29)) presented a higher risk than using less than five years (OR = 1.49, 95% CI (1.03, 2.15)).

Conclusions: Estradiol-only therapy carries no risk for breast cancer, while the breast cancer risk varies according to the type of progestogen. Estradiol therapy combined with medroxyprogesterone, norethisterone and levonorgestrel related to an increased risk of breast cancer, estradiol therapy combined with dydrogesterone and progesterone carries no risk. The breast cancer risk rise progressively by prolonged use, furthermore, comparing to sequential therapy, continuous therapy carries a higher risk.

Introduction

The breast cancer risk of hormone replacement therapy (HRT) has been long debated since the publication of 51 epidemiological studies on hormone therapy conducted by Collaborative Group on Hormonal Factors in Breast Cancer (CGHFBC) in 1997 [1]. To obtain a consensus on this problem, a large number of well-designed studies have been published and applied in clinical practice, many women who bothered by menopausal syndrome are still hesitating to receive hormone therapy, there are many questions have not been figured out yet. Conjugated estrogens with the major composition of estrone are the dominate estrogen used in previous studies, but things changed, CEE is now barely out of market and estradiol is now the most used estrogen in clinical practice, consider of the chemical structure difference between estrone and estradiol, the effect may be different. The number of studies investigate the breast cancer risk of estradiol is limited, and it’s not reviewed before. Besides, current opinions suggest that the progestogen plays a more important role in breast cancer risk, nature progestogen carries less risk comparing to synthetic progestogen. But how about its effect by combining to estradiol is not known. Hence, we conducted a systemic review and meta-analysis to provide a quantitative evaluation on current evidence and draw a conclusion on the precise risk of breast cancer from estradiol-only therapy, taking into consideration of different types of combined progestogen, as well as the duration of exposure and the type of regimen.

Materials and methods

Literature retrieval

Articles were searched from the Embase, Medline and Cochrane Library to October 2015. Search terms included: HRT, estrogen therapy, estrogen progestogen therapy, hormone replacement therapy, estradiol, breast neoplasm, breast cancer, breast carcinoma, breast tumor, mammory neoplasm, mammary cancer, mammary carcinoma, mammary tumor, menopause, postmenopause, perimenopause. First, we scanned the titles and abstracts of the articles identified in the computerized search, and excluded those clearly irrelevant to our topic. Then we read the full texts of remaining articles to determine whether they were included or not. We also reviewed the reference list of our included articles and reviews on the relational topic.

Inclusion and exclusion criteria

Studies met the following requirements were included: (1) published studies conducted in perimenopausal or postmenopausal women who received HRT, including women undergone a hysterectomy without bilateral oophorectomy; (2) publications with abstract in English language; (3) observational or interventional studies with a comparison group including randomized controlled trial (RCT) or cohort study or case control study (CC); (4) with a specific exposure of estradiol (estradiol valerate and
17-beita estradiol) with or without progestogen, regardless of the routes of administration (by oral and by cutaneous); (5) with a control group of “never using of HRT”. Studies designed as case report and cross-sectional studies were excluded. Studies only evaluated estrogen therapy as a mixture of conjugated estrogen, estradiol and estriol without the specific group exposure to estradiol were excluded. Studies on women who developed a breast cancer before inclusion were excluded. Studies without raw data about exposure and control groups were excluded. For series studies conducted by the same research group, only the most up-to-date results, longest follow-up or most pertinent outcomes were included.

Quality assessment

The quality of included studies was assessed by two investigators separately, any disagreement should be discussed and consult an experts to reached the same conclusion. We assessed the risk of bias in RCTs by Cochrane Collaboration’s Risk of bias tool, which containing seven domains: sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting and other sources of bias [21,22]. As for cohort studies and case-control studies, we adopted the Newcastle–Ottawa scale (NOS) to fulfill quality assessment [23]. The NOS uses a star system to assess the quality of cohort study and case-control study with nine items in three dimensions: selection of study groups, comparability of groups and ascertainment of outcomes or exposure. One star for each item except for the item related to comparability that allows the assignment of two stars [23]. The scores range from 0 to 9 stars.

Data extraction

From all the 14 included studies, two investigators extracted data independently using an agreed data extraction excel form, details of data including the title, authors, year of publication, study design, inclusions and exclusions, menopause state, patient age, patient population, exposure details (type and dose of hormone, means of administration, exposure duration), follow-up and results (number of breast cancer case, odds ratio, incidence rate ratio and hazard ratio). All data must be confirmed by a second investigator. If any elements were confused or missing, we contacted the authors to get the precise information.

Statistical analysis

We conducted a meta-analysis of studies on the estradiol therapy and its effect to incidence of breast cancer. The subgroup analysis was conducted in our study sorted by study design, types of progestogen, duration of exposure and the type of regimen. The random effects model by DerSimonian and Laird method [24] was used to calculate the pooled odds ratio (OR) and 95% confidence intervals (CI) by Stata version 12.0 software using the “metan” command (StataCorp LP, College Station, TX). The statistical heterogeneity among studies was evaluated to assess the consistency by Cochrane Q test; \( I^2 \) was also presented [25]. As recommended by Cochrane Collaboration, \( p \) values < 0.10 indicated heterogeneity. Publication bias was evaluated by Egger’s test and Begg’s test. \( p \) values less than 0.05 indicated publication bias [26].

Results

Search results

We did a comprehensive search of literature in the Embase, Medline and Cochrane Library published to October 2015, a total of 2482 articles were viewed (1393 from Medline, 863 from Embase and 249 from Cochrane Library). From which, we included 14 studies at final, including five RCTs, six cohort studies, two nested case control studies and one case-control studies [27–40]. Those including studies ranged subject size from 152 to 39 824, with a total of 14 475 breast cancer cases. There were 12 studies evaluated the breast cancer risk of estradiol-only therapy and nine studies evaluated the risk of estradiol-progestogen therapy. Most of our including studies were conducted in Europe, because the dominant estrogen in Europe was estradiol.

Estradiol-only therapy and risk of breast cancer

Five RCTs, seven observational studies addressed the association between estradiol therapy and risk of breast cancer [27–37,39]. Meta-analysis of these 12 studies results in an overall OR = 1.11, 95% CI (0.98, 1.27), with Q test \( p = 0.309 \) and \( I^2 = 13.9% \), suggesting no heterogeneity among those studies.

By stratified into two subgroups by study design, the RCTs (pooled OR = 0.90, 95% CI (0.40, 2.02), with the Q test \( p = 0.871 \) and \( I^2 = 0.0% \)) result a no statistically change of breast cancer risk, the observational studies results in a pooled OR = 1.18, 95% CI (0.99, 1.42), with the Q test \( p = 0.076 \) and \( I^2 = 47.5\% \) (Figure 1).

Five RCTs provide the exact exposure duration of estradiol-only therapy by less than 3 years with a pooled OR = 0.90, 95% CI (0.40, 2.02).

Publication bias is assessed. The Begg’s funnel plot presents the expected funnel shape. (Figure not displayed) The \( p \) values for the Begg’s test and Egger’s test are \( p = 0.592 \) and \( p = 0.216 \), respectively, suggesting no publication bias in involving studies.

Estradiol-progestogen therapy and risk of breast cancer

Nine observational studies evaluated the association between estradiol-progestogen therapy and risk of breast cancer were included in our meta-analysis [32–40]. We stratified our data into subgroups by types of progestogen, including medroxyprogesterone acetate (MPA), norethisterone acetate (NETA), levonorgestrel (LNG), dydrogesterone, progesterone and mixed progestogen (containing studies without specific classification of progestogen and subjects exposed to more than one kind of progestogen). After stratified into six subgroups, the meta-analysis based on a random effects model results in an overall OR = 1.48, 95% CI (1.30, 1.68), with the Q test \( p < 0.001 \) and \( I^2 = 85.3\% \), indicating heterogeneity.

The subgroups analysis shows a statistically increased breast cancer risk in LNG subgroup (pooled OR = 1.47, 95% CI (1.17, 1.85), with the Q test \( p = 0.341 \) and \( I^2 = 0.0% \)), MPA subgroup (OR = 1.19, 95% CI (1.07, 1.33), with the Q test \( p = 0.637 \) and \( I^2 = 0.0% \)), NETA subgroup (pooled OR = 1.44, 95% CI (1.26, 1.65), with the Q test \( p = 0.231 \) and \( I^2 = 30.2\% \)) and mixed progestogen subgroup (pooled OR = 1.99, 95% CI (1.57, 2.52), with the Q test \( p < 0.001 \) and \( I^2 = 86.1\% \), but no statistically difference is found in dydrogesterone subgroup (OR = 1.10, 95% CI (0.89, 1.36), with the Q test \( p = 0.060 \) and \( I^2 = 64.6\% \) and
progesterone group (OR = 1.00, 95% CI (0.83, 1.20), with the Q test $p = 0.318$ and $I^2 = 0.0\%$) (Figure 2).

**Duration of estradiol-progestogen therapy and risk of breast cancer**

Five cohort studies and two case control studies provided estimates on the duration of estradiol-progestogen therapy [32,34,35,37–40]. We divided the therapeutic duration into “less than 5 years” and “at least 5 years” groups. Because of the insufficient data of including studies, we fail to estimate the exposure duration of different progestogen.

Using estradiol-progestogen therapy less than 5 years results a higher pooled OR $= 1.39, 95\%\ CI (1.09, 1.78)$, estradiol-progestogen therapy for more than 5 years results a higher pooled OR $= 2.25, 95\%\ CI (1.82, 2.80)$, both analyses are heterogeneous ($p < 0.00$).

**Type of regimen and risk of breast cancer**

Four cohort studies and one case-control study provided data of estradiol-progestogen therapy by sequential or continuous therapy groups, and their associations with breast cancer risk were evaluated separately [32–35,40]. The heterogeneity is found in both analyses. The meta-analysis based on a random effects model shows statistically increase of breast cancer risk in both treatment groups.

Sequential estradiol-progestogen therapy results in the overall OR $= 1.76, 95\%\ CI (1.28, 2.42)$. Continuous estradiol-progestogen therapy results in an overall OR $= 2.90, 95\%\ CI (1.82, 4.61)$, which present a dramatically increase of breast cancer risk comparing with sequential therapy.

**Discussion**

As the progressing of ovary failure, menopause comes to all women at an average age of 51 [2], and brings a series menopausal symptoms, including hot flushes, night sweating, sleeplessness, arthralgia, lethargy, depression, urogenital atrophy and vaginal dryness [2,3]. Symptoms frequently start years before the last menstruation and last for few years. HRT has long been known to perimenopausal and postmenopausal women as the most effective means to release the menopausal symptoms [2], as well as to prevent the bone loss [3,4], lower the incidence of fragility fractures in postmenopausal women. In addition, in the cumulative follow-up of the WHI, combined EPT was reported to reduce the risk of colorectal cancer and endometrial cancer [5,6]. HRT has been used more than six decades [2], but the overall long-term health consequence is still not fully understood yet, especially breast cancer risk.

In our study, we included five RCTs and nine observational studies. Among all the 14 included studies, the incidence of breast cancer was the primary outcome in the observational studies [32–40], but not in all the RCTs. Four RCTs evaluated estradiol therapy for the prevention of cardiovascular diseases; the incidence of breast cancer was the second outcome [27–29,31]. Due to no association was found between cardiovascular diseases and breast cancer incidence [13], we combined the data from healthy women and those from women with cardiovascular disease, and figure out the association between estradiol therapy and risk of breast cancer.

In the meta-analysis of five RCTs and seven observational studies of using estradiol-only therapy, no association is found between estradiol-only therapy and the risk of breast. The combined effect is strongly affected by the observational studies,
perimenopausal and postmenopausal women (R R similar breast cancer risk by using estrogen for less than 5 years in mixture of estradiol and conjugated equine estrogen reported the collaborative re-analysis, which classified estrogen therapy as estradiol-only therapy carries no risk for breast cancer. A previous and observational studies are in good consistence, suggesting investigating estrogen-only therapy, our results from both RCTs However, unlike the conflicting results from previous study 
cancer cases is too small to provide a precise statistic power. RCTs should have stronger validity, but the number of breast 
cases account for 97.47% in overall weight. The evidence from

<table>
<thead>
<tr>
<th>Study ID</th>
<th>OR (95% CI)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>MPA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jernstrom H. 2003</td>
<td>1.69 (0.39, 7.27)</td>
<td>0.73</td>
</tr>
<tr>
<td>Lytynen H. 2010</td>
<td>1.19 (1.07, 1.33)</td>
<td>7.51</td>
</tr>
<tr>
<td>Subtotal (I-squared = 0.0%, p = 0.637)</td>
<td>1.19 (1.07, 1.33)</td>
<td>8.23</td>
</tr>
<tr>
<td>LNG</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jernstrom H. 2003</td>
<td>2.45 (0.84, 7.15)</td>
<td>1.25</td>
</tr>
<tr>
<td>Lytynen H. 2010</td>
<td>1.43 (1.13, 1.82)</td>
<td>6.30</td>
</tr>
<tr>
<td>Subtotal (I-squared = 0.0%, p = 0.341)</td>
<td>1.47 (1.17, 1.85)</td>
<td>7.54</td>
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<tr>
<td>NETA</td>
<td></td>
<td></td>
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<tr>
<td>Jernstrom H. 2003</td>
<td>2.17 (1.31, 3.59)</td>
<td>3.63</td>
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<tr>
<td>Lytynen H. 2010</td>
<td>1.46 (1.34, 1.59)</td>
<td>7.68</td>
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<tr>
<td>Persson I. 1997</td>
<td>1.50 (0.96, 2.33)</td>
<td>4.14</td>
</tr>
<tr>
<td>Schneider C. 2009</td>
<td>1.26 (1.02, 1.55)</td>
<td>6.62</td>
</tr>
<tr>
<td>Subtotal (I-squared = 30.2%, p = 0.231)</td>
<td>1.44 (1.26, 1.65)</td>
<td>22.08</td>
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<tr>
<td>Dydrogesterone</td>
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<tr>
<td>Lytynen H. 2010</td>
<td>1.25 (1.05, 1.48)</td>
<td>6.97</td>
</tr>
<tr>
<td>Schneider C. 2009</td>
<td>0.83 (0.62, 1.11)</td>
<td>5.62</td>
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<tr>
<td>Fournier A. 2008</td>
<td>1.18 (0.97, 1.45)</td>
<td>6.66</td>
</tr>
<tr>
<td>Subtotal (I-squared = 64.6%, p = 0.060)</td>
<td>1.10 (0.89, 1.36)</td>
<td>19.26</td>
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<tr>
<td>Progesterone</td>
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<td></td>
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<td>Espie M. 2007</td>
<td>0.57 (0.19, 1.74)</td>
<td>1.17</td>
</tr>
<tr>
<td>Fournier A. 2008</td>
<td>1.02 (0.84, 1.23)</td>
<td>6.82</td>
</tr>
<tr>
<td>Subtotal (I-squared = 0.0%, p = 0.318)</td>
<td>1.00 (0.83, 1.20)</td>
<td>7.99</td>
</tr>
<tr>
<td>Mixed progestin</td>
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<td></td>
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<tr>
<td>Olsson H. 2003</td>
<td>3.34 (2.57, 4.33)</td>
<td>6.02</td>
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<tr>
<td>Stahilberg C. 2004</td>
<td>2.52 (1.87, 3.39)</td>
<td>5.61</td>
</tr>
<tr>
<td>Espie M. 2007</td>
<td>1.01 (0.49, 2.07)</td>
<td>2.32</td>
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<tr>
<td>Bakken K. 2004</td>
<td>2.07 (1.51, 2.66)</td>
<td>6.12</td>
</tr>
<tr>
<td>Fournier A. 2008</td>
<td>1.62 (1.45, 1.81)</td>
<td>7.50</td>
</tr>
<tr>
<td>Lytynen H. 2010</td>
<td>1.62 (1.42, 1.85)</td>
<td>7.33</td>
</tr>
<tr>
<td>Subtotal (I-squared = 86.1%, p = 0.000)</td>
<td>1.99 (1.57, 2.52)</td>
<td>34.90</td>
</tr>
<tr>
<td>Overall (I-squared = 85.3%, p = 0.000)</td>
<td>1.48 (1.30, 1.68)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

NOTE: Weights are from random effects analysis

which account for 97.47% in overall weight. The evidence from RCTs should have stronger validity, but the number of breast cancer cases is too small to provide a precise statistic power. However, unlike the conflicting results from previous study investigating estrogen-only therapy, our results from both RCTs and observational studies are in good consistence, suggesting estradiol-only therapy carries no risk for breast cancer. A previous collaborative re-analysis, which classified estrogen therapy as mixture of estradiol and conjugated equine estrogen reported the similar breast cancer risk by using estrogen for less than 5 years in perimenopausal and postmenopausal women (RR = 0.99, 95% CI (0.83, 1.15)) [3]. The consistency of breast cancer risk between estradiol-only therapy and mixed estrogen-only therapy may be explained by the conclusion from a recent study, which claimed the risk of breast cancer was not significantly different between women who currently used CEE-only compared with estradiol-only formulations (CEE versus estradiol: RR = 1.15, 95% CI (0.78, 1.69)) [41].

With respect to progestogen administration, there is no universal agreement on the effect of different types of progestogen and the breast cancer risk. Prior meta-analysis found that the type of progestogen did contribute to the heterogeneity in their analysis [13], but no investigation was made to figure out this problem. In addition, there are laboratory studies suggesting that progestogen may be related to the growth of breast epithelial cells [42,43], mitogenic effect may be varied by the type of progestogen [44]. Our study deeply estimates the breast cancer risk of estradiol-progestogen therapy. Subgroup analysis according to types of progestogen is performed, different progestogen plays unequal role in breast cancer risk. Using of NETA, MPA and LNG carries an increased risk for breast cancer, while dydrogesterone and natural progesterone users present no risk for breast cancer compared with no users. In a previous review, an estimate was conducted in 1900 users between MPA, norethisterone and levonorgestrel, the breast cancer all increased by the administration of progestogen, but no statistical difference was found between different types of progestogen [13]. Our study conforms their results and also evaluates the effect of dydrogesterone and natural progesterone, which are never reviewed in previous meta-analysis. As for the duration of estrogen-progestogen therapy, general speaking, the previous studies have already drew a consistent conclusion that using estrogen-progestogen therapy is associated with a significant increase of breast cancer risk within 5 years and the risk continues to rise after

Figure 2. Analysis of the association between estradiol-progestin therapy and breast cancer risk, stratified by the type of progestin. The odds ratio and 95% CI for each study are displayed. Pooled estimated by random-effect model.
before clinical application. Our study reaches the agreement with the previous conclusion. Due to the proliferated effect of progestogen [42,43], the continuous combined estradiol-progestogen therapy should have a higher risk of breast cancer than sequential therapy. Our study results match a previous meta-analysis, which also claimed that sequential therapy was associated with a lower OR than continuous combined therapy [17].

Meta-analysis are vulnerable to biases and be affected by confounding factors in primary studies, especially for HRT, as previous systematic reviews and meta-analyses were misclassified of CEE and estradiol or even estrogen therapy and estrogen progestogen therapy. Therefore, we conducted a study on estradiol therapy and designed multi-subgroup meta-analyses by type of progestogen; the effect of dydrogesterone and natural progesterone was first assessed in our study. Besides, our analyses included both RCTs and observational studies, comparing to RCTs, the observational studies were prone to recruitment and interviewer bias, which may be the explanation of why previous observational studies reported a higher breast cancer risk than randomized trial. To detect the source of bias, we estimated the risk of bias of primary studies and all of our including studies supposed to be good quality. Taking account the possible publication bias in included studies, we did additional analyses to test the bias to strength the credibility of evidence for our results, and no publication bias was found in including studies.

Our study has several other superiorities. First, most of our including studies have large number of samples, by extracting raw data from included studies to pool number of cases and controls, the statistical power increase greatly in our study. Furthermore, our systematic review was assessed according to preferred reporting items for systematic reviews and meta-analyses (PRISMA) checklist and meeting all the criteria [45].

However, some important limitations must be fully considerate in our study. First, the vulnerability of our results to biases and confounding in primary trials which could not be detected or adjusted, such as the inadequately reported of random sequence generation and allocation concealment in one RCT [28], which may lead to potential selection bias in primary study. Second, as estradiol is the dominate estrogen used in Europe, most of our including studies were undertook in Europe, the ethnic differences may put restriction on the popularization of our conclusion, new studies are still needed to evaluate the breast safety in different population, but the conclusion may not be varied because of the large sample size of present studies. In addition, we find that the estradiol combined with dydrogesterone and natural progesterone therapy carries no risk for breast cancer in our study, but data including the duration of exposure or the type of regimen was insufficient in including studies to conduct further analysis, without those information, the results should be interpreted with caution, further studies are needed to reassess this problem.

Conclusions
In summary, our meta-analysis concludes that estradiol-only therapy carries no risk for breast cancer, while the breast cancer risk varies according to the administration of different types of progestogen. Estradiol progestogen therapy combined with medroxyprogesterone, norethisterone and levonorgestrel related to an increased risk of breast cancer, while combined with dydrogesterone and progesterone carries no risk. The breast cancer risk rise progressively by prolonged use, furthermore, comparing to sequential therapy, continuous therapy carries a higher risk. Although the overall effect of estradiol therapy on breast cancer risk is approximately determined, caution is also advised for women with certain additional medical conditions before clinical application.

Disclosure of interest
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References


