Hormone Replacement Therapy and Risk of Breast Cancer in Korean Women: A Quantitative Systematic Review

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Running title: HRT and Breast Cancer
Funding sources: This study was supported by a grant funded in 2013 by the Korean Foundation for Cancer Research, Seoul, Republic of Korea (no. 2013-2).

Abstract (195 words) Text (1607 words)
1 table, 3 figures
Abstract

Objectives: The epidemiological characteristics of breast cancer incidence by age group in Korean women are unique. This systematic review aimed to investigate the association between HRT and breast cancer risk in Korean women.

Methods: We searched electronic databases such as KoreaMed, KMBase, KISS, and RISS4U as well as PubMed for publications in Korean breast cancer patients. We conducted manual searching based on references and citations of potential papers. All of the analytically epidemiologic studies that obtained individual data on hormone replacement therapy (HRT) exposure and breast cancer occurrence in Korean women were selected. On the case-control studies, we restricted the inclusion of them to those that included age-matched controls. Estimates of summary odds ratio (SOR) with 95% confidence intervals (CI) were calculated using the random effect models.

Results: One cohort and five case-control studies were finally selected. Based on the heterogeneity that existed among the six studies ($I^2$ = 70.2%), a random effect model was applied. The summary effect size of total 6 articles in HRT history from the six articles indicated no statistical significance in breast cancer risk ($SOR = 0.983, 95\% CI: 0.620 – 1.556$).

Conclusions: These facts support no significant effect of HRT history in the risk of breast cancer in Korean women. It is necessary to conduct a pooled analysis.

Keywords: Breast-breast neoplasms, Risk-factor, Hormone-hormone replacement therapy, Meta-analysis
Introduction

Hormone Replacement Therapy (HRT), improves quality of life in menopausal women, by alleviating symptoms related to menopause and slowing the progression of osteoporosis [1-3]. In spite of these benefits, the greatest reason that menopausal women show a negative attitude towards HRT is because of worries about breast cancer [3, 4].

The publication of results in 2002 from the large-scale randomized clinical trial by the Women’s Health Inititatives (WHI) proved a great turning point in the debate about the occurrence of breast cancer resulting from HRT in post-menopausal women [5-7]. There was a considerable shift in concepts before and after 2002, and the conception that deserves the most attention is that the administration of estrogen alone does not increase the incidence of breast cancer [7, 8]. However, there have been worries that estrogen does not help prevent cardiovascular diseases and that it increases breast cancer [2], and so HRT prescriptions have rapidly decreased since the publication of the WHI study [1, 9].

Meanwhile, the incidence of breast cancer displays different patterns according to ethnicity [10]. In the United States, where breast cancer shows the highest incidence among cancers in women, Asian Americans show a relatively lower incidence and higher survival rate [11, 12]. Furthermore, the incidence trends even show different patterns for different Asian countries [13, 14]. In particular, in terms of incidence curves by age group in nine Asian countries, Korea shows a unique trend of decreasing incidence beyond the age of 50 years old [4, 10, 13, 15-17].

Hence, considering the breast cancer incidence characteristics of Korean women, one might suspect that the risk of breast cancer from HRT is lower than that of other countries, in which incidence increases with age [2]. Therefore, the aim of our study was to assess the risk levels of breast cancer due to HRT in Korean women. To this end, we performed a systematic review of analytical epidemiology...
studies related to breast cancer in Korean women.
Subjects & Methods

a. Search and Selection

The selection criteria for studies were as follows: (1) analytical epidemiology studies on breast cancer in Korean post-menopausal women; (2) individuals providing data about their status of HRT medication; (3) if it is a case-control study, studies needed to include an age-matched control group; needs to be age-matched to the cases.

For the search terms, on the basis that these were studies to investigate breast cancer in Korean women, and the hypothesis that the hormone formulation would be for oral administration, we used the following search formula: [(Korean) AND (Breast) AND (cancer OR neoplasms) AND [(hormone replacement therapy) OR (oral contraceptives)]]. Also, taking into account publications in not only overseas journals, but also domestic journals, we applied our search formula to the five information portals: such as PubMed (http://www.ncbi.nlm.nih.gov/pubmed), KoreaMed (http://www.koreamed.org/SearchBasic.php), KMBase (http://kmbase.medric.or.kr/Default.htm), KISS (http://kiss.kstudy.com/), and RISS4U (http://www.riss.kr/index.do). We performed hand-manual searching for of the reference literatures of papers obtained from our search, and we used a snowballing search for papers that cited papers that met our search criteria [18-21].

b. Statistical analysis

From the final selection of papers, we calculated relative risk (RR) or odds ratio (OR), as well as 95% confidence intervals (CI), based on the frequency distribution of status of HRT medication and breast cancer occurrence. We calculated the standard error of log relative risk (SElogRR) by applying the equation {\ln (OR_upper) – \ln (OR_lower)}/3.92, using the upper 95% confidence interval (OR_upper)
and the lower 95% confidence interval (OR_lower) [22].

We tested heterogeneity using I-square values (%) [23], and according to the result, we performed meta-analysis to obtain the effect size (ES) and its 95% CI using a random effect model. In order to evaluate the effect of small-scale studies, we performed Egger’s test for small-study effects, and in order to test for publishing errors, we confirmed symmetry of the funnel plot. The statistical significance level was defined as 5%, and we used the StataSE 14 statistical program (STATA Co., Texas, US) to perform the meta-analysis and to draw the two plots.
Results

The selected articles

When we applied our search function to the five information portals—such as PubMed, KoreaMed, KMBase, KISS, and RISS4U—we produced a list of 20, 6, 15, 9, and 2 articles respectively, constituting a total of 52 (Fig 1). Excluding six duplicate articles, we reviewed the content of the remaining total of 46 articles that we had acquired, and found a total of 4 that fitted our search criteria [24-27]. Among the papers cited in these 46 articles, we acquired additional 106 papers about Korean females, and after reviewing the contents, we selected one more paper for our investigation [28]. Among the articles citing the original 46, we found another 66 articles about Korean females, and after reviewing the contents, we added an additional four articles for our investigation [29-32].

Of the above nine final articles, there was one cohort study [25], and the other eight were case-control studies. Of these, the controls were age-matched to the patients in five articles [27,28,30-32]. Accordingly, there were six articles that were ultimately applied to the meta-analysis.

Meta-analysis

Three articles [28, 31, 32] among the final selected showed the mixed results within pre- and post-menopausal women. Information regarding the post-menopausal women in these articles were obtained by contacting the authors directly. In addition, some subjects of two articles written by the same authors [27, 28] might be suspected to overlap because the inclusion periods were between December 1997 and August 1999 versus and between March 1999 and August 2003, respectively. Thus the case numbers of reference [28] were adjusted based on the author’s reply.

Fig 2 displays a forest plot for the six selected articles. Because the I-squared value of 70.2% indicated heterogeneity, we applied a random effect model. In the results, the pooled ES was 0.983 (95%
CI, 0.620–1.556), which was not statistically significant. When we performed Egger’s test, the p-value was 0.996, showing that the results were not influenced by small-scale studies, and the relevant funnel plot showed symmetry (Fig 3).

When we performed a meta-analysis on the five case-control studies, excluding the single cohort study, the I-squared value increased by 75.9%, but when we applied the random effect model, there was no change in the statistical significance of the pooled ES, at 0.957 (95% CI, 0.551–1.662).
Discussion

The results of our meta-analysis of six articles suggest that HRT treatment does not have a statistically significant effect on the incidence of breast cancer in Korean women. This finding supports our hypothesis that, considering the epidemiological characteristic of breast cancer incidence decreasing beyond 50 years old in Korean women, the risk of breast cancer caused by HRT is low compared to females in other countries [2]. In particular, according to the administration guidelines that less than five years of HRT medication does not affect risk [1], it is expected that the benefits of HRT prescription for peri-menopausal women in Korean will be higher than for Western women. Additionally, there is a report that the majority of breast cancers diagnosed in Korean women during HRT are diagnosed at an early stage and show low malignancy, and suggesting that the prognoses are good [33]. Therefore, there is a need to actively consider HRT prescription for menopausal women [4].

Because of the requirement to limit our study to research on Korean females, in accordance with our objectives, we had to search for articles published in domestic as well as international journals. Therefore, this was a good opportunity to determine whether KoreaMed, KMBase, KISS, and RISS4U provide systems that enable systematic review studies on Koreans. Given that the authors employed a hand-manual searching method for cited and citing papers, in addition to applying a logical search formula, we expect that this will provide a research methodology for systematic reviews on Korean subjects in the future.

A limitation on performing systematic review studies for Korean subjects is that the research quality is relatively low, as a result of the domestic epidemiological research environment. Of the six articles selected in our study, the only paper to directly investigate the causal relationship between HRT and breast cancer was the one cohort study [25], and the other five case-control studies [27,28,30-32], which aimed to investigate the hypotheses of other studies, only provided HRT medication status among the general characteristics for the patient and control groups. This is the reason why we limited our analysis to articles where the control group was age-matched to the case group. Even in the cohort study [25], the exposure
group and the non-exposure group showed average ages of 57.0 and 53.3, respectively, and this was a statistically significant difference (p=.000). In spite of this, we had no choice but to calculate an uncorrected RR for that paper. Hence, there is a need for further studies that directly investigate the effect of HRT on breast cancer in Korean women.

However, Nevertheless, it can be deduced that the reasons for the difficulty into conducting epidemiological studies on HRT are that because of the decreasing incidence in breast cancer after 50 years old for in Korean women, and because of the low level of HRT medication. Even among case-control studies, the highest number of subjects in the patient group was 152, for Do et al. [28], and exposure was approximately 9%. Cho & Park [34] reported that 4.5% of women over 50 years of age had taken the HRT in the year 2010. Awareness of HRT might have been changed by the results of the Women’s Health Initiative Study [35]. In order to investigate causality, more patient groups need to be secured. To this end, we propose a pooled-analysis of original data that contains this information [36].

Acknowledgement

This study was supported by a grant funded in 2013 by the Korean Foundation for Cancer Research, Seoul, Republic of Korea (no. 2013-2).
References


<table>
<thead>
<tr>
<th>Study Design</th>
<th>First Author</th>
<th>Reference Number</th>
<th>Year of Publication</th>
<th>Inclusion Periods</th>
<th>Cases (medication/Total)</th>
<th>Controls (medication/Total)</th>
<th>Effect size (95% confidence intervals)</th>
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</thead>
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<tr>
<td>Case-control</td>
<td>Do MH</td>
<td>[27]</td>
<td>2001</td>
<td>Dec 1997 – Aug 1999</td>
<td>9/48</td>
<td>8/54</td>
<td>1.327 (0.467, 3.768)</td>
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<tr>
<td></td>
<td>Do MH(^{1})</td>
<td>[28]</td>
<td>2007</td>
<td>Sep 1999 – Aug 2003</td>
<td>14/152</td>
<td>30/304</td>
<td>0.927 (0.476, 1.805)</td>
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<tr>
<td></td>
<td>Kim MK(^{1})</td>
<td>[31]</td>
<td>2008</td>
<td>Oct 2004 - Jun 2006</td>
<td>42/127</td>
<td>41/127</td>
<td>1.036 (0.613, 1.751)</td>
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<tr>
<td></td>
<td>Cho YA(^{1})</td>
<td>[32]</td>
<td>2010</td>
<td>Jul 2007 - Sep 2008</td>
<td>28/142</td>
<td>54/142</td>
<td>0.400 (0.235, 0.683)</td>
</tr>
</tbody>
</table>

\(^{1}\) modified based on correspondence with Author’s author reply

\(^{2}\) number of incident cases per-in medication group vs non-medication group
Papers retrieved from databases (n = 52): Pubmed (20), KoreaMed(6), KMBase(15), KISS(9), RISS4U(2)

6 papers excluded due to duplication

Full text retrieved for more detailed evaluation (n = 46)

42 papers excluded by selection criteria

4 papers selected

1 paper added using 106 related references
4 papers added by the 66 cited articles

3 case-control studies excluded due to no age-matched design

6 papers selected finally

Figure 1. Flow chart of article selection
Fig 2. Forest plot of using mix-effects summary estimates in 6 articles. REF: reference number; ES: effect size; CI: confidence intervals

NOTE: Weights are from random effects analysis
Overall (I-squared = 70.2%, p = 0.005)

<table>
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<tr>
<th>Study</th>
<th>ID</th>
<th>ES (95% CI)</th>
<th>Weight</th>
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<tr>
<td>Do(2001)[27]</td>
<td></td>
<td>1.32 (0.47, 3.76)</td>
<td>10.86</td>
</tr>
<tr>
<td>Do(2007)[28]</td>
<td></td>
<td>0.93 (0.48, 1.80)</td>
<td>16.22</td>
</tr>
<tr>
<td>Kim(2008)[31]</td>
<td></td>
<td>1.04 (0.61, 1.75)</td>
<td>18.64</td>
</tr>
<tr>
<td>Cho(2010)[32]</td>
<td></td>
<td>0.40 (0.23, 0.68)</td>
<td>18.47</td>
</tr>
<tr>
<td>Park(2012)[25]</td>
<td></td>
<td>1.14 (0.58, 2.21)</td>
<td>16.26</td>
</tr>
<tr>
<td>Kim(2014)[30]</td>
<td></td>
<td>1.72 (1.07, 2.76)</td>
<td>19.55</td>
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<tr>
<td>Overall</td>
<td></td>
<td>0.98 (0.62, 1.56)</td>
<td>100.00</td>
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NOTE: Weights are from random effects analysis
Fig 3. Funnel plot of using mixed-effects summary estimates in 6 articles. LogOR: log odds ratio; SElogOR: standard error of log odds ratio.