Original Article

Oral contraceptives, hormone replacement therapy and breast cancer risk: A cohort study of 16928 women 48 years and older

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Abstract

Background. Findings on potential interactive effects of oral contraceptives (OCs) and hormone replacement therapy (HRT) on breast cancer risk have been inconsistent. We aimed to use population-based cohort data to determine whether former use of OCs affects breast cancer risk among HRT users, taking into account regimens of HRT, duration and currency of use.

Methods. The cohort consisted of 16 928 Icelandic women who visited the Icelandic Cancer Detection Clinic in 1979–2006 and provided information on use of OCs and HRT when they were 48 years or older. By record linkage to the Icelandic Cancer Registry, all breast cancer diagnosed during follow-up was identified. Using Cox regression, hazard ratios (HRs) for breast cancer according to hormone use were estimated, adjusting for menstrual and reproductive risk factors. Also, interaction analyses were carried out.

Results. Breast cancer risk was significantly increased among ever users of combined estrogen and progesterone (EP-HRT) preparations (HR = 2.61; 95% CI 2.00–3.41) and not among users of estrogen-only regimens (E-only HRT) (HR = 1.13; 95% CI 0.85–1.49). Ever users of both OCs and HRT had higher breast cancer risk than users of only one of the two (HR = 2.19; 95% CI 1.67–2.87). After restricting the analysis to EP-HRT and focusing on long-term and current use, there was an indication of a negative interaction with ever OC use (p = 0.06); HR = 2.87; 95% CI 1.79–4.60 for never OC users and HR = 2.24; 95% CI 1.51–3.34 for former OC users.

Conclusion. After taking HRT regimen, duration and currency of use into account, the results of our population-based cohort study do not support the notion that former OC use increases breast cancer risk among HRT users, on the contrary there was an indication of a slightly lower risk in former OC users, restricted to current, long-term EP-HRT users.
risk. Our principal aim was to explore whether former OC use affects the risk of breast cancer in HRT users and whether this depends on the HRT regimen used, duration and currency of HRT use.

Material and methods

Study design and population

This is a population-based cohort study, the cohort consisting of all women who visited the CDC of the Icelandic Cancer Society (ICS) during a 28-year period (1979–2006) for screening for cervical and/or breast cancer (the CDC cohort). Population-based, centralized programs were initiated by the ICS for cervical cancer in 1964 and breast cancer in 1987. Icelandic women, 20–69 years of age, were invited to visit the CDC every other year for screening for cancer of the cervix (from the age of 20) and breast (from 40 years of age), using mammography, and they were asked to answer a questionnaire about known risk factors for these cancers on a regular basis. Over 92% of all Icelandic women born 1920–1958 participated in the CDC cohort study. Of the subjects in the present study, only 1.5% belonged to the oldest birth cohorts (born 1891–1919) where participation rate was lower (61%).

Our study group consisted of 16 928 women who were 48 years or older when responding to questions on their use of OCs and HRT and were either never-users or ever-users who provided information on regimen type and reported using one of the three most common HRT regimens; that is, estrogen only (E-only HRT) and combined estrogen and progestin regimens (EP-HRT), cyclic or combined. Users of these regimens accounted for 90.5% of the total number of women who could identify the name of the regimen they used for the longest duration.

The CDC cohort was first established in 1964 when population-based cervical cancer screening began in Iceland, and the questionnaires have changed between visits, we supplemented missing information at last visit in the following way for the three variables described hereafter. For “age at menarche” or “age when first giving birth”, we used data from the woman’s first relevant response to those particular questions. For “number of births” for a parous woman who was already aged 50 years or older at last visit, we used the first response given around age 50, if applicable. If a woman gave different answers to this question on different occasions, we used the most consistent data.

Replacing Icelandic national identification numbers with study numbers we linked the cohort data to the Icelandic Cancer Registry, which has registered all cancers diagnosed in Iceland since 1955 [21].

Follow-up and statistical analysis

Only responses given before diagnosis of breast cancer were used. Follow-up began at the women’s last visit to the CDC in 1979 or later, when they were 48 years of age or older and answered questionnaires. It ended at diagnosis of first invasive breast cancer, death or end of study (31 December 2006). Censoring in 2006 was done to reduce misclassification because in many countries women ceased hormonal therapy use after the 2002 publication of the first results from the Women’s Health Initiative trial [24]. We chose the censoring year 2006 instead of 2002 because unpublished information from the CDC cohort indicates that women who had already started using HRT’s continued use for some years after 2002. We used Cox proportional hazard regression models to estimate hazard ratios (HRs) for breast cancer associated with different aspects of OC and HRT use, adjusting for birth year, age when giving information, age at menarche, number of births and age when first giving birth. We estimated potential statistical interaction using a Wald-test by entering a multiplication variable, taking into account exposure status to OC and HRT.

We analyzed the effects of ever use of all OCs collectively, E-only HRT and EP-HRT collectively and E-only HRT and EP-HRT separately, on the risk of breast cancer. Furthermore, we investigated effects of the duration of HRT use (less than five years and five or more years) for these two regimen groups and according to former OC use. In addition,
effects of previous and current use of HRT and former OC use on breast cancer risk in HRT users of different regimens was examined in a subgroup of 6444 women for whom this information existed. STATA 10.0 software was used for all statistical analyses.

Ethical issues

The study was approved by the Data Protection Authority and the National Bioethics Committee (VSNa2003090022/03-16/BH—).

Results

The number of women in this study was 16 928 and they were followed for a total of 128 822 person-years with an average follow-up time of 7.6 years per woman. During the 28-year study period, a total of 654 women in the cohort (3.9%) developed invasive breast cancer, with an average follow-up time of 4.7 person-years.

Table I provides an overview of age and reproductive factors in the total cohort and among women who developed breast cancer and in addition, according to exposure to exogenous sex hormones. The women in the study who had neither used OCs nor HRT belonged to the oldest birth cohorts, those who used only HRT were the second oldest and users of both OCs and HRT belonged to the most recent birth cohorts. The women who had used neither OCs nor HRT were likewise the oldest of the exposure groups when giving information (59.2 years old on average), while those who had used both OCs and HRT were the youngest (57.0 years old on average). The time lag between giving information and exiting the study was 8.9 years for the entire cohort and 8.1 years for the subgroup of 4673 women who stated being current users of HRT. Table II summarizes multivariate HRs of breast cancer by ever exposure to OCs and HRT, compared to no hormone use. The results in this table are based on data on ever use of any OCs and the most common regimens of HRT (E-only HRT and EP-HRT). Of all the women in the cohort, 25.9% had used neither OCs nor HRT while 30.9% had used both OCs and HRT. Only 10.8% of the women had used HRT but not OCs and 32.3% had used OCs but not HRT. This corresponds to a total of 63.2% of the women having ever used OCs and a total of 41.7% having ever used HRT. An increase in breast cancer risk was found for ever OC use (HR = 1.32, 95% CI 1.02 – 1.70), ever HRT use (HR = 1.40, 95% CI 1.07 – 1.84), and for ever use of both OCs and HRT (HR = 2.19,
Oral contraceptives, hormone replacement therapy and breast cancer risk

A Wald-test done with these data did not show evidence of interaction. Use of EP-HRT was more prevalent (31.8%) among women ever using OCs than among never-OC users (15.0%).

Table III presents the risk of breast cancer by combined use of OCs and HRT according to HRT regimen, compared to no use of either HRT or OCs. It also shows separately HRs for those women who had used HRT for less than five years on the one hand and for five years or longer on the other hand. Regardless of OC use, ever users of preparations containing both estrogen and progestin (EP-HRT) had statistically significantly increased risk (HR = 2.61; 95% CI 2.00–3.41), but not users of E-only regimens (HR = 1.13; 95% CI 0.85–1.49). Women who had previously used OCs tended to have higher breast cancer risk than never users of OCs, but for E-only preparations the confidence intervals were wide and for EP-HRT this tendency was not seen for long-term use.

Women using HRT for five years or longer were at greater risk for breast cancer than those who used it for shorter duration, whether OCs had formerly been used or not. When examining the two HRT regimen groups, several differences are apparent. First, the women who used E-only HRT belong on average to older birth cohorts than EP-HRT users (average birth year 1939 vs. 1942, respectively). The average duration of HRT use was 7.6 years for E-only regimen users and 6.9 years for users of EP-regimens.

Table IV shows the effects of currency of ever HRT use for the subgroup of 6444 women who answered a question on this aspect of hormone use, and gave information on HRT regimen; 72.5% were current users and 27.5% were previous users. The percentage of current users was approximately equal among users of both types of HRT regimens (71.7% vs. 73.0% for E-only HRT and EP-HRT, respectively). Breast cancer risk was higher among current EP-HRT users than previous EP-HRT users (HR = 2.48; 95% CI 1.88–3.27 vs. 1.91; 95% CI 1.28–2.87, respectively), but the risk difference between current and past E-only HRT users was negligible. E-only HRT users had a higher breast cancer risk if they had ever used OCs than if they had never used OCs (HR = 1.36; 95% CI 0.94–1.96 vs. 0.88; 95% CI 0.59–1.32, respectively). Such a difference was not observed between the OC subgroups among ever EP-HRT users. Table IV also shows adjusted HRs for those women who were current HRT users and had been using HRT for five years or longer.

Table II. Adjusted* hazard ratios for breast cancer according to exogenous sex hormone never/ever use.

<table>
<thead>
<tr>
<th>Hormone use</th>
<th>n cohort (%)</th>
<th>n BC (%)</th>
<th>HR [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>OC use/HRT use</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never OC/never HRT</td>
<td>4390 (25.9)</td>
<td>168 (25.7)</td>
<td>1.0 [ref.]</td>
</tr>
<tr>
<td>Ever OC/never HRT</td>
<td>5472 (32.3)</td>
<td>171 (26.1)</td>
<td>1.32 [1.02–1.70]</td>
</tr>
<tr>
<td>Never OC/ever HRT</td>
<td>1834 (10.8)</td>
<td>90 (13.8)</td>
<td>1.40 [1.07–1.84]</td>
</tr>
<tr>
<td>Ever OC/ever HRT</td>
<td>5232 (30.9)</td>
<td>225 (34.4)</td>
<td>2.19 [1.77–2.87]</td>
</tr>
</tbody>
</table>

*Adjusted for birth year, age when giving information, age at menarche, number of births, age at first birth.

Table III. Adjusted* hazard ratios for breast cancer according to HRT regimens and duration of use, exclusively and by OC use.

<table>
<thead>
<tr>
<th>Hormone use by regimen/duration</th>
<th>Overall N cohort (BC)</th>
<th>HR [95% CI]</th>
<th>Never OC n cohort (BC)</th>
<th>HR [95% CI]</th>
<th>Ever OC n cohort (BC)</th>
<th>HR [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never HRT/never OC</td>
<td>4390 (168)</td>
<td>1.00 [ref.]</td>
<td>890 (32)</td>
<td>0.89 [0.60–1.31]</td>
<td>1832 (57)</td>
<td>1.43 [1.00–2.05]</td>
</tr>
<tr>
<td>Ever E-only HRT</td>
<td>2722 (89)</td>
<td>1.13 [0.85–1.49]</td>
<td>305 (12)</td>
<td>0.73 [0.44–1.45]</td>
<td>547 (22)</td>
<td>1.29 [0.79–2.12]</td>
</tr>
<tr>
<td>Duration &lt; 5 years</td>
<td>852 (34)</td>
<td>1.04 [0.70–1.54]</td>
<td>426 (17)</td>
<td>1.08 [0.64–1.80]</td>
<td>890 (25)</td>
<td>1.43 [0.88–2.32]</td>
</tr>
<tr>
<td>Duration 5+ years</td>
<td>1316 (42)</td>
<td>1.24 [0.86–1.78]</td>
<td>159 (3)</td>
<td></td>
<td>395 (10)</td>
<td></td>
</tr>
<tr>
<td>Duration missing</td>
<td>554 (13)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration &lt; 5 years</td>
<td>1449 (88)</td>
<td>1.87 [1.32–2.64]</td>
<td>282 (21)</td>
<td>1.75 [1.08–2.83]</td>
<td>1167 (67)</td>
<td>1.87 [1.26–2.77]</td>
</tr>
<tr>
<td>Duration 5+ years</td>
<td>2049 (103)</td>
<td>2.58 [1.88–3.56]</td>
<td>485 (29)</td>
<td>2.58 [1.66–4.01]</td>
<td>1564 (74)</td>
<td>2.48 [1.73–3.55]</td>
</tr>
<tr>
<td>Duration missing</td>
<td>846 (35)</td>
<td>177 (8)</td>
<td></td>
<td></td>
<td>669 (27)</td>
<td></td>
</tr>
</tbody>
</table>

*Adjusted for birth year, age when giving information, age at menarche, number of births and age at first birth; †This category consists of both cyclic and continuous combined HRT regimens.
**Table IV. Adjusted hazard ratios for breast cancer according to HRT regimens and currency, exclusively and by OC use.**

<table>
<thead>
<tr>
<th>Hormone use by regimen/currency</th>
<th>Overall</th>
<th>Never OC</th>
<th>Ever OC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never HRT/never OC</td>
<td>4361 (167)</td>
<td>1.00 [ref.]</td>
<td>832 (31)</td>
</tr>
<tr>
<td>Ever E-only HRT</td>
<td>2503 (83)</td>
<td>1.09 [0.82–1.45]</td>
<td>479 (16)</td>
</tr>
<tr>
<td>past E-only HRT</td>
<td>708 (28)</td>
<td>1.04 [0.69–1.55]</td>
<td>353 (15)</td>
</tr>
<tr>
<td>Current E-only HRT</td>
<td>1795 (55)</td>
<td>1.20 [0.84–1.71]</td>
<td>479 (16)</td>
</tr>
<tr>
<td>≥ 5 years of use</td>
<td>936 (25)</td>
<td>1.03 [0.64–1.65]</td>
<td>668 (18)</td>
</tr>
<tr>
<td>past EP-HRT</td>
<td>1063 (40)</td>
<td>1.91 [1.28–2.87]</td>
<td>221 (9)</td>
</tr>
<tr>
<td>≥ 5 years of use</td>
<td>1373 (75)</td>
<td>2.52 [1.79–3.55]</td>
<td>321 (24)</td>
</tr>
</tbody>
</table>

*Adjusted for birth year, age when giving information, age at menarche, number of births and age at first birth.

When the risk of breast cancer for these women is examined the data indicate a risk difference according to previous ever OC use among E-only HRT users, but the confidence intervals are very wide. For EP-HRT users, however, we found evidence of a negative interaction with a higher HR among those EP-HRT users who never used OCs compared to ever users of OCs (HR = 2.87; 95% CI 1.79–4.60 vs. HR = 2.24 95% CI 1.51–3.34, respectively). The proportion of current users of E-only HRT regimens was higher among women who were former OC users than among those who never used OCs (78.8% vs. 57.6%, respectively). This difference was not observed among current EP-HRT users (72.9% vs. 73.7%, respectively).

Table V shows an overview of adjusted HRs for long-term current users of E-only HRT and EP-HRT and the p-value for interaction between OC and HRT use for these groups using a Wald-test. No interaction was found between OC and E-only HRT use while an almost statistically significant negative interaction was indicated between OC and EP-HRT use (p = 0.062). When restricting to current EP-HRT users irrespective of duration we found a statistically significant negative interaction (p = 0.043). Of the women who were current HRT users with duration of five years or longer, 39% used E-HRT and 61% EP-HRT.

**Table V. Overview of adjusted hazard ratios according to regimen, only considering current HRT use for 5 years or longer and p-values for Wald-tests of interaction.**

<table>
<thead>
<tr>
<th>Hormone group</th>
<th>E-HRT</th>
<th>EP-HRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never OC/never HRT</td>
<td>1.0 [ref.]</td>
<td>1.0 [ref.]</td>
</tr>
<tr>
<td>Ever OC/never HRT</td>
<td>1.32 [1.02–1.70]</td>
<td>1.32 [1.02–1.70]</td>
</tr>
<tr>
<td>Never OC/ever HRT</td>
<td>0.72 [0.52–1.04]</td>
<td>2.37 [1.79–4.60]</td>
</tr>
<tr>
<td>EverOC/ever HRT</td>
<td>1.27 [0.73–2.23]</td>
<td>2.24 [1.91–3.34]</td>
</tr>
<tr>
<td>p for interaction</td>
<td>0.523</td>
<td>0.062</td>
</tr>
</tbody>
</table>

*Adjusted for birth year, age when giving information, age at menarche, number of births and age at first birth.

**Discussion**

**Main findings**

In this cohort study in which 16 928 women were followed for up to over 20 years women who had ever used both OCs and HRT tended to be at greater risk of breast cancer than women who had ever used only OCs or only HRT, irrespective of HRT regimen and duration. In spite of this, we found no statistically significant interaction between ever OC and HRT use according to Wald-tests. After taking into account regimen, duration and currency of use, no interaction was found between use of OCs and E-only HRT, but among current users of EP-HRT there was a statistically significant negative interaction (p = 0.043).

The initially observed higher HR for ever users of OCs and HRT compared to HRT users who had never used OCs may be related to the higher level of use of EP-HRT regimens (31.8%) among former OC users, than among never users of OCs (15.0%), as breast cancer risk is substantially greater among users of preparations that contain both estrogen and progesterone, than those that contain only estrogen.

Previous study results have been conflicting, which may partly be explained by differences between them in taking into account regimen, duration or currency of use. In summary, Shantakumar et al. [14], Brinton et al. [15] and Lund et al. [20] found an increased risk of breast cancer in HRT users who had previously used OCs compared to women who had never used OCs, while Olsson et al. [16], Ursin et al. [17] and Dumeaux et al. [19] found no such increase and Norman et al. [18] found a negative interaction between OC and combined HRT use. The results of the present study indicate that there may be a lower risk in former OC users who are currently using combined HRT, in accordance with Norman et al. [18].
The risk varied between HRT regimens, with a considerably lower risk associated with E-only HRT than with EP-HRT and a greater risk associated with continuous combined regimens than cyclic combined regimens (data not shown) and longer duration of use. These findings are in agreement with other studies [3–5,13–20]. We also found that currency of use affected breast cancer risk more in EP-HRT users than in E-only HRT users.

Exposure to exogenous sex hormones has changed much over the past 50 years. OCs were first introduced in the 1960s, they were initially administered only to parous women [22] and their chemical composition has changed with time. The use of HRT increased dramatically during the period 1980–2002 [23] and the first preparations on the market contained only estrogen, while the combined preparations became increasingly popular with time. This is reflected by our data as women who used E-only HRT belonged to older birth cohorts than EP-HRT users, they were older when entering the study and, their average duration of HRT use was higher. The proportion of current users of E-only regimens was higher among former OC users than among women who never used OCs. This difference was not observed among current users of EP-regimens. These differences between HRT groups by regimen may contribute to the differences we found in interaction analyses.

It has been proposed that OC use can enhance tumors already present in the breast when use is commenced. Estrogen is known to enhance tumor growth, and use of HRT later in life may promote tumor growth even further [25]. It is also known that progestin enhances cell proliferation in breast epithelium [26,27].

Strengths and limitations

The main strength of this study is the population-based study design. Over 90% of all Icelandic women of screening ages since the establishment of the CDC cohort in 1964 participated in the cohort. The data were collected over a nearly 30-year period when HRT use was on the rise. We used information from the most recent visit to the CDC so as to have the most recent information possible on sex hormone use. In addition, we were able to distinguish between HRT regimens which is important as E-only HRT regimens and EP-HRT regimens are chemically different and have been shown to have quite different effects with respect to breast cancer risk [9,12]. Furthermore, it was possible to describe the effects of duration of use for 80.2% of HRT users, and importantly also, the effects of current use for approximately 91.2% of the women who used HRT.

Finally, it is a strength of this study that the Icelandic personal identification number is invariably used for all contact with the healthcare system, making follow-up of subjects easy and loss to follow-up negligible.

Limitations of this study include a relatively small size of the study group, although it was taken from a cohort comprising the majority of the female population of Iceland, resulting in less power for detecting potential interactions.

Also, the menopausal status was not known, but we used only data from women who were 48 years or older when giving information. The mean age at menopause among participants in the CDC cohort in the period 1964–1995 (before HRT use became widespread) was 48–49 years (unpublished data). Another potential weakness is that data on regimens may not have been accurate and were obtained only for the regimen with the longest duration of use. We restricted the cohort to women who used the three most common HRT regimens (90% of those answering the question on this subject). However, when asked about total duration time it is possible that all HRT use was included, not only the type used for the longest duration.

In addition, the time lag between the age when information was given and age at exit from the study (a median of eight years) limits this study, since it is likely that HRT use changed during this time. Thus, there is a risk of non-differential misclassification, both for never/ever hormone use and duration of HRT use. It is reasonable to conclude that, because of this time lag, duration was, on average, longer than indicated by our data and ever users more numerous. This may result in an underestimate of breast cancer risk in association with exogenous sex hormone use but does not necessarily influence our conclusion regarding interaction between use of OCs and HRT on breast cancer risk.

Conclusions

After taking into account HRT regimen, duration and currency of use, the results of our population-based cohort study do not support the notion that former OC use increases breast cancer risk among users of exogenous hormones containing both estrogen and progestin. On the contrary, we found evidence of a statistically significant negative interaction between current use of combined HRT and ever use of OCs.

A possible explanation is that there may exist subgroups of women who are unusually sensitive to exogenous sex hormones with respect to breast cancer risk, and if they have been exposed to OCs they may already have developed breast cancer. Those
women would not have entered our cohort, resulting in a slight “lack” of women developing breast cancer among former OC users. A somewhat similar explanation was suggested by Norman et al. [18].

Implications
The results of this study demonstrate the importance of accounting for different regimens, duration and currency of HRT use when studying effects of potential interaction of OCs and HRT. They are in accordance with previous results suggesting a lower risk in current users of combined HRT who had used OCs earlier [18].

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

References
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