Oral contraceptives, hormone replacement therapy and breast cancer risk

Íslensk ferilrannsókn

Þuríður Þorbjarnardóttir

Thesis for the degree of Master of Public Health Sciences

University of Iceland

School of Health Science

Faculty of Medicine

HÁSKÓLI ÍSLANDS

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An Icelandic cohort study

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Pillan, tíðahvarfahormón og brjóstakrabbameinsáhætta

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ABSTRACT

BACKGROUND: The use of oral contraceptives (OCs) and hormone replacement therapy (HRT) is common in Iceland. We investigated the influence of these hormonal exposures on breast cancer risk, with emphasis on interaction.

METHODS: This is a population-based cohort study on 31,430 Icelandic women aged 40 years or older when visiting the Cancer Detection Clinic in 1979-2008. Through record linkage of these data to the Icelandic Cancer Registry, we identified women diagnosed with breast cancer during the course of the study. Using Cox regression analyses, we found hazard ratios (HRs) for different aspects of hormone use.

RESULTS: 1,182 women in the cohort developed breast cancer during the study period. Compared to those who never used sex hormones, the increase in breast cancer risk was highest for those who had used both OCs and HRT (HR=1.84; 95% CI 1.51-2.26). The HRs were higher for users of combined regimens than for users of estrogen unopposed HRT (HR=2.19; 95% CI 1.76-2.73 vs. HR=1.25; 95% CI 1.03-1.51, respectively). Higher risk was generally associated with longer duration (HR=1.73; 95% CI 1.41-2.13) and with current rather than past HRT use (HR=1.47; 95% CI 1.17-1.84 vs. HR=1.02; 95% CI 0.66-1.58). Former OC users were at greater risk for breast cancer than non-users of OCs, although we found no interaction between OC and HRT use in a Wald test for interaction (p=0,659; 95% CI 0.82-1.36).

CONCLUSIONS: We did not observe a statistically significant interaction between OC and HRT use, although past OC use tended to increase the risk among HRT users.

ÁGRIP

BAKGRUNNUR: Margar íslenskar konur hafa notað bæði getnaðarvarnarpillur og tíðahvarfahormón, en notkun hvors um sig hefur áhrif á brjóstakrabbameinsáhættu. Við skoðuðum hugsanleg víxlverkunaráhrif þessara hormóna á brjóstakrabbameinsáhættu.

AÐFERÐIR: Þetta er lýðgrunduð ferilrannsókn á 31.430 konum fertugum og eldri sem komu á Leitarstöð Krabbameinsfélags Íslands á tímabilinu 1979-2008 og svöruðu spurningum um kvenhormónanotkun. Gögn úr Heilsusögubanka Leitarstöðvar Krabbameinsfélags Íslands voru tengd við Krabbameinsskrá Íslands og þannig voru fundin brjóstakrabbameinstilfelli sem greindust á rannsóknartímanum. Með Cox aðhvarfsgreiningu var metið hættuhlutfall (hazard ratio=HR) samfara notkun kvenhormóna og víxlverkun könnuð.

NIÐURSTÖÐUR: 1.182 konur greindust með brjóstakrabbamein á rannsóknartímanum. Víxlverkunaráhrif komu ekki fram í Wald víxlverkunarprófi. (p=0,659; 95%; CI 0,82-1,36). Miðað við konur sem notuðu hvorki getnaðarvarnarpillu né tíðahvarfahormón var áhætta brjóstakrabbameins mest hjá þeim sem notuðu bæði (HR=1,84; 95% CI 1,51-2,26). Notendur samsettra tegunda tíðahvarfahormóna voru í meiri brjóstakrabbameinsáhættu en notendur tegunda sem innihéldu eingöngu estrógen (HR=2,19; 95% CI 1,76-2,73 á móti HR=1,25; 95% CI 1,03-1,51). Áhættan var meiri hjá langtíma notendum tíðahvarfahormóna en skammtímanotendum (HR=1,73; 95% CI 1,41-2,13). Núnotkun tíðahvarfahormóna hafði meiri áhættu í för með sér en fyrri notkun (HR=1,47; 95% CI 1,17-1,84 vs. HR=1,02; 95% CI 0,66-1,58) fyrir alla tíðahvarfahormónaflokka. Fyrri notendur getnaðarvarnarpilla meðal notenda tíðahvarfahormóna voru í heldur meiri brjóstakrabbameinsáhættu en þeir sem

notuðu aldrei getnaðarvarnarpillu, einkum meðal langtíma notenda estrógen tegunda (HR=1,15; 95% CI 0,79-1,66 á móti HR=1,70; 95% CI 1,19-2,42).

ÁLYKTANIR: Tölfræðilega marktæk víxlverkunaráhrif milli notkunar getnaðarvarnarpilla og tíðahvarfahormóna fundust ekki, en tilhneiging var fyrir aukinni brjóstakrabbameinsáhættu hjá fyrri pillunotendum meðal þeirra sem tóku tíðahvarfahormón með eingöngu estrógeni.

ÞAKKIR

Ég vil byrja á að þakka Krabbameinsfélagi Íslands (KÍ) fyrir að gera mér kleift að gera þessa rannsókn. Án aðgangs að gögnum Heilsusögubanka Leitarstöðvar KÍ og Krabbameinsskrár Íslands og aðstoðar starfsfólks Krabbameinsskrár Íslands hefði hún aldrei orðið að veruleika.

Ég vil þakka sérstaklega Laufeyju Tryggvadóttur, framkvæmdastjóra Krabbameinsskrár Íslands, fyrir að samþykkja umsókn mína um rannsóknarverkefni og að hvetja mig og leiðbeina í gegnum þetta ferli, allt frá ákvörðun um rannsóknarverkefni, framkvæmd þess og smíði þessarar ritgerðar, og ekki síst að leiða mig um hinn spennandi og flókna heim faraldsfræðinnar. Elínborgu J. Ólafsdóttur, sérfræðingi hjá Krabbameinsskrá Íslands, vil ég þakka fyrir aðstoð og óþrjótandi þolinmæði við undirbúning og úrvinnslu gagna. Enn fremur vil ég þakka Unni A. Valdimarsdóttur, forstöðumanni Miðstöðvar í lýðheilsuvísindum við Háskóla Íslands, fyrir hvatningu og óbilandi trú á verkefninu.

Síðast, en ekki síst, vil ég þakka eiginmanni mínum, Hálfdani Ómari Hálfdanarsyni, fyrir stuðning og hvatningu til að leggja út í þetta ævintýri og fylgja því til enda.

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TÖFLUSKRÁR

SKAMMSTAFANIR

C	combined (containing estrogen and progestagen)
C-HRT	Combined hormone replacement therapy
CDC	Cancer Detection Clinic
CI	Confidence Interval
E	Estrogen
E-HRT	Estrogen unopposed Hormone Replacement Therapy
HR	Hazard Ratio
HRT	Hormone ,Replacement Therapy
ICR	Icelandic Cancer Registry
ICS	Icelandic Cancer Society
KÍ	Krabbameinsfélag Íslands
OC	Oral Contraceptive
RR	Relative Risk
WHO	World Health Organization
-/+	never/ever (pertaining to hormone use)

BACKGROUND

Breast cancer is the leading cancer in women worldwide. The incidence of breast cancer varies in different parts of the world and is considerably higher in Western societies than in Asia and Africa (1). Breast cancer incidence has been on the rise over the past fifty years or so. In Iceland, it has been the leading cancer among women ever since the nationwide Icelandic Cancer Registry (ICR) was established in 1955. Since then, age-adjusted breast cancer incidence has doubled, with breast cancers accounting for 29% of all cancers in Icelandic women for the five-year period 2004-2008. The mortality rate of breast cancer has not risen in spite of this increase, which may be due to both earlier diagnosis and more effective treatment (2, 3).

When considering risk factors for breast cancer, researchers have studied both genetic and environmental factors (4). A family history of breast cancer is an important factor, and it is believed that inherited factors are connected to at least 10% of breast cancers (5). Several known mutations in the BRCA1 and BRCA2 genes are strongly related to an increased risk of breast cancer and other cancer types. For example, there are two mutations known in the Icelandic population, one in each gene, of which the one in the BRCA2 gene, a founder mutation, is much more prevalent in the population (0.6%) and is present in 5-6% of breast cancer patients (6-9).

Other factors that are important in the etiology of breast cancer are reproductive history, height and weight, and lifestyle factors such as alcohol consumption, physical activity, ionizing radiation, and exogenous sex hormone use (4). The effects of environmental factors appear when observing changes in incidence among immigrants coming from a country with a different breast

cancer incidence than the host country. The incidence among immigrants may be quite different from that of native inhabitants of the host country to begin with, but in only a few generations it changes to that of the inhabitants in the host country (10-13). Geographical and/or lifestyle factors in the host country, in addition to diagnostic activity, obviously have substantial weight.

It is widely acknowledged that several aspects of reproduction affect breast cancer risk, thus indicating the importance of female sex hormones in the etiology of the disease. The risk of breast cancer is affected by the age at menarche, parity, number of births, age at first birth, age at menopause, and total breastfeeding time (4, 14-16).

Use of exogenous sex hormones has been increasing since 1960, when oral contraceptives (OCs) first became available. In 2005, it was estimated that 10% of women of reproductive age worldwide, or a total of 100 million women, were current users of combined OCs; that is, OCs containing both estrogen and progestagen. When “ever use” was considered, the number increased to 300 million, with use varying notably between countries and more common in developed countries (17). In Iceland, use of OCs has increased ever since 1965, when they first became available in the country. Some 90% of women born after 1944 used OCs in the period 1965-1989 (18, 19).

OCs contain either estrogen and progestagen (combined preparations) or progestagen only (so-called mini-pills). The first combined OCs contained considerably larger amounts of estrogen than those currently available, and many different types have been developed in order to meet the needs of individual women.

Hormone replacement therapy (HRT) was first used to treat climacteric symptoms characteristic of menopause in the 1930s (20). Use of HRT increased tremendously after 1980 and was very common in the 1990s among middle-aged women. HRT has been shown to help prevent osteoporosis, which can be a serious health problem after menopause (21). In the latter half of the twentieth century, it was also believed that HRT lowered the risk of cardiovascular diseases; consequently, many women used HRT as a preventive measure against these diseases. In 1995, approximately 38% of post-menopausal women in the United States used HRT (22). According to two Icelandic studies on HRT use, the proportion of women who had used HRT rose steadily in Iceland from 1979 to 2001, reaching approximately 55% among women aged 50-70 years in the period 1996-2001. The duration of use grew steadily longer with time (23, 24).

The original types of HRT contained only estrogen. It became apparent that such therapy increased the risk of developing endometrial cancer. Consequently, hormone preparations were developed that contained progestagen in addition to estrogen (25). These combined types of hormone therapies seemed not to increase the risk of endometrial cancer in the earliest studies, but they did prove to increase the risk of breast cancer, although recent studies show that all HRT regimens affect the risk of developing endometrial cancer to some extent (26).

New types of combined hormone replacement therapy are being developed, and it is hoped that, before long, hormone therapies will be available that will relieve climacteric symptoms without an associated increased risk of breast cancer (27).

According to the IARC monograph on carcinogenicity of combined estrogen-progestagen contraceptives and hormone replacement therapies, both combined

OCs and HRT are considered carcinogenic to humans (17). The role of the female sex hormones in carcinogenicity mechanisms varies depending on tissue type, but both hormones enhance cell proliferation in human breast epithelial tissue (28-32).

A large number of studies have addressed the question of whether there is an increased risk of breast cancer among users of OCs (33-40). The collaborative group on hormonal factors in breast cancer re-analyzed individual data from 54 epidemiological studies on breast cancer and concluded that, while women are using OCs and ten years after discontinuation, there is an increase in risk of breast cancer compared to never use of OCs (41). In contrast, OC use lowers the risk of ovarian cancer according to the IARC monograph (17).

Similarly, many studies have been carried out in the last three decades on the effects of HRT on breast cancer risk, but their results are not all concordant (27, 42-51). They discuss numerous different aspects of the effects of HRT on breast cancer risk; for example, according to different regimens of HRT (52), various duration of use, age at initiation, and characteristics of breast cancer tumors (38, 53-55). The overall message of these studies is that the risk of being diagnosed with breast cancer is elevated in women using HRT, especially in current users, and increases with longer duration of use, as was reported in a meta-analysis by the collaborative group on hormonal factors in breast cancer (57). The effect levels off when use has ceased and has disappeared for the most part five years after discontinuation (22, 57). The attributable risk of breast cancer due to HRT use is considerably higher than that for OC use because women are exposed to HRT at ages when the background risk of breast cancer is already elevated. It has become evident that HRT regimens containing both estrogen and

progestagen (combined regimens) increase the risk of breast cancer substantially, while estrogen unopposed regimens have little effect on breast cancer risk (58).

HRT use is believed to have reached its peak around the year 2000, with an estimated 20 million women in developed countries using it at that time (59). As is mentioned above, HRT use is very common in Iceland, with about 55% of Icelandic women 50-70 years old currently using HRT and two thirds of ever-users using it for seven years or longer in 1996-2001 (24). The use of HRT has declined worldwide since 2002, when the Women's Health Initiative Estrogen Plus Progestagen Trial was stopped because the risks of HRT use outweighed the benefits (60). The same results were observed in an even larger cohort study in the UK, the Million Women Study (61). Consequently, breast cancer incidence seems to be declining (55, 62-65).

Since the 1990s, the number of women who have been exposed to both OCs and HRT has been on the rise. This raises a question about whether these women are at greater risk of developing breast cancer than those who have used only OCs or only HRT. Only a few studies have been conducted on this subject, and their results are not all in agreement (66-72).

In 1998, Brinton *et al.* conducted a case-control study on breast cancer risk in women under 55 years of age (1,031 cases and 919 controls). Women in this study who had taken OCs for over ten years and HRT for three or more years had an increased risk of breast cancer, with a relative risk of 3.2 compared to non-users of both (66). There was no mention of HRT regimens in the research article. Olsson *et al.* found no interaction between HRT use and former OC use in a cohort study on 29,508 women 25-65 years of age in southern Sweden.

They did not study different regimens of HRT (67). In a population-based study on 1,897 postmenopausal cases and 1,637 controls in 2002, Ursin *et al.* found that OC use did not modify the effect of HRT on breast cancer risk, independent of HRT regimen (68). In a case-control study on postmenopausal women (4,575 cases and 4,682 controls) by Norman *et al.* in 2003, the results were not in agreement with Brinton *et al.*, in that breast cancer risk in long-term users of HRT was not higher among former long-term OC users than non-users of both hormones. In fact, Norman *et al.* found a negative interaction, with the risk of breast cancer higher in never-users of OCs than ever-users. This study considered different HRT regimens and duration (69). Dumeaux *et al.* conducted a large-scale cohort study on 68,670 postmenopausal French women in 2005 and found no significant interaction between OC and HRT use on postmenopausal breast cancer risk. They did not study different HRT regimens (70). In a population-based cohort study on 30,118 postmenopausal Norwegian women conducted by Lund *et al.* in 2007, HRT users who were also former users of OCs were found to be at greater risk of developing postmenopausal breast cancer than those who had never used OCs, with a relative risk (RR) of 2.55 compared to an RR of 1.67 in HRT users who were not former OC users. They found no difference in risk depending on HRT regimen (71). In the same year, Shantakumar *et al.* found, in a study on pre- and postmenopausal women (1,478 cases and 1,493 controls), that using both hormonal birth control and HRT elevated risk more than using only one or the other, especially in premenopausal women. They did not investigate whether this depended on type of hormone regimen. (72).

Aims

In this study, we used large cohort data to examine sex hormone use in Icelandic women over a thirty-year period. Our main aim was to investigate whether former use of OCs affects the risk of breast cancer in HRT users. We studied whether this potential interaction depends on regimen of HRT used, duration of use, and whether HRT use was past or current. This is an important public health issue for Icelandic women, as breast cancer has been on the rise in the last half-century and the use of exogenous sex hormones has been increasing at the same time.

ARTICLE

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Oral contraceptives, hormone replacement therapy and breast cancer risk

An Icelandic cohort study

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Keywords: breast cancer risk interaction oral contraceptives hormone replacement therapy

INTRODUCTION

Use of exogenous sex hormones, both for birth control purposes and for the relief of climacteric symptoms associated with menopause, is very common in Iceland, as it is in other Western societies (19-23). Exogenous estrogen and progesterone are classified as group I carcinogens (18). Many studies have been carried out on the effects of oral contraceptives (OCs) and hormone replacement therapy (HRT) individually on breast cancer risk and generally found that both increase the risk of developing breast cancer (4, 21, 26, 32-49, 54). Meanwhile, few studies have explored possible interactive effects of both OC and HRT use on breast cancer risk, and their results are not all in agreement (66-72). In this study, we use the remarkable resources of the nationwide database of the Cancer Detection Clinic (CDC) to follow sex hormone use in Icelandic women over a thirty-year period and study their potential combined effects on breast cancer risk. Our principal aim was to explore whether former use of OCs affects the risk of breast cancer in HRT users and whether this potential interaction depends on the HRT regimen used, duration of use, and whether HRT use was past or current.

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) in 1979-2008 for screening for cervical and/or breast cancer (the CDC cohort). Population-based, centralized programs were initiated by the ICS for cervical cancer and breast cancer in 1964 and 1987, respectively. Icelandic women 20-69 years of age are encouraged 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 every tenth year they are asked to answer a questionnaire about known risk factors for these cancers.

A total of approximately 96,000 women visited the CDC during the study period and responded to a questionnaire, but the study group consisted of the 38,642 women who were at least forty years of age when responding to questions on their never/ever use of OCs and HRT. We further restricted the group by including all never-users but only those ever-users who used the three most common HRT regimens; that is, estrogen unopposed (E-HRT), cyclic combined and continuous combined regimens. Users of these three 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. We classified all women using cyclic and continuous combined regimens in one group, the combined HRT (C-HRT) group. If women had provided information on more than one occasion, we used information from the last occasion before censoring or end of follow-up. Women who had developed breast cancer prior to responding to the questions were excluded from the study, as were women who had been

diagnosed with ovarian cancer and undergone an oophorectomy. The final study group consisted of 31,430 women forty years and older.

Databases

The CDC cohort was first established in 1964 when population-based cervical cancer screening began in Iceland, and the questionnaires have changed several times since then. Every tenth year, women visiting the CDC respond to questions about known risk factors of breast cancer. These are age at menarche, parity, number of births, age at first birth, total breastfeeding time, use of OCs and HRT, smoking, height and weight. Questions about type of OC and HRT use were added in 1979 and have been included in the questionnaire ever since; hence our study commences with data from 1979.

We used data given by the women in their most recent visit to the CDC, but for the women who developed breast cancer, we used the most recent visit before diagnosis, even if they were diagnosed in that visit. For information that would not 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 at first birth", we used data from the woman's first 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 after age 50, if applicable. If a woman gave different answers to this question on different occasions, we used the most consistent data.

We focused only on hormones taken orally. We classified the women into never- and ever-users of OCs and HRT. Based on the answers to questions on the brand names of OCs and HRT used for the longest duration, we grouped the brands into two groups depending on regimen; i.e., E-HRT and combined (C-

HRT) regimens. Other types of HRT preparations were named, but they were far less common than the regimens previously mentioned and were not investigated. No visual aids were applied to help in recalling brand names. We did not exclude women who did not respond to all questions on hormone use but used all data available for each aspect of use. Of the 31,430 women in our study group, all women replied to the question on never/ever use of OCs and HRT and gave information about HRT regimen. 7,432 women, or 81.5% of users, responded to the question on duration of HRT usage. In 1995, questions on never, past or current use replaced older questions on never/ever use of both OCs and HRT. Approximately 42% of the 3,790 HRT users who answered this question for HRT were past or current users.

Using Icelandic national identification numbers, we linked the cohort data to the Icelandic Cancer Registry, which has registered all cancers in Iceland since 1955.

Follow-up and statistical analysis

Follow-up began at the women's first visit to the CDC in 1979 or later when they had turned forty or older at which they responded to the questionnaire (date of entry to the study), and ended when their first breast cancer was diagnosed or when they were censored from the study because of death or end of study (December 31, 2008).

We analyzed the effects of all OCs collectively, E- and C-HRTs collectively, and E-HRT and C-HRT separately, on the risk of breast cancer. Furthermore, we investigated effects of the duration of HRT use, past and current HRT use and whether OCs had been used previously on breast cancer risk.

Excel and Access software from Microsoft Office XP was used to prepare the data for statistical analyses. Controlling for potential confounding factors, we

used Cox proportional hazard regression models to estimate hazard ratios of breast cancer associated with different aspects of OC and HRT use. We estimated their potential interaction with a Wald test by entering a multiplication variable, taking into account exposure status to OCs and HRT. 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 total number of women in this study was 31,430, and the average follow-up time was 14.8 person-years. During the study period, a total of 1,182 women in the cohort (3.8%) developed breast cancer, with an average follow-up time of 12.0 person-years. The mean age at diagnosis was 61.6 years.

Table 1 provides an overview of age and reproductive factors in the cohort as a whole and among women developing breast cancer. Women who developed breast cancer were, on average, born nine years earlier than the entire cohort. On average, they were two and a half years older than the entire cohort when giving data and approximately the same age (0.1 year older) as the cohort when exiting the study. The time lag between giving data and exiting the study was eight years for the entire cohort and 5.6 years for those developing breast cancer. When considering factors related to reproductive history, the women who developed breast cancer tended to be older at menarche, have fewer births, and be older when giving birth to their first child. The percentage of nulliparous women was higher among the women developing breast cancer than in the cohort (9.1% vs. 5.9%, respectively). The mean number of visits to the CDC was higher for those developing breast cancer than for the entire cohort (1.92 vs. 1.88).

Table 2 summarizes hazard ratios of breast cancer by exposure status to exogenous sex hormones, both OCs and HRTs, independently and combined, compared to no use of either. The results in this table are based on data on use of any OC and the most common regimens of HRT (E-HRT and C-HRT). Of all women, 69.3% ever used OCs, and they were at increased risk of breast cancer (HR=1.36; 95% CI 1.17-1.58). Ever-users of HRT constituted 29% of the

cohort, and they also demonstrated an increased risk for breast cancer (HR=1.45; 95% CI 1.28-1.64). Approximately 22% of the women in our study were ever-users of both OCs and HRT, and when compared to never-users of either, they were at increased risk of breast cancer (HR=1.84; 95% CI 1.51-2.26). There was not a statistically significant interaction between ever OC and HRT use on breast cancer risk, according to the Wald test of interaction (p=0.659; 95% CI 0.82-1.36). Of the women in the cohort, approximately 48% had only used OCs (HR 1.28; 95% CI 1.06-1.55) and 7.5% had only used HRT (HR=1.36; 95% CI 1.11-1.66). Of the women in the cohort, 23.2% had used neither OCs nor HRT. HRT users who had formerly used OCs were almost three times as many as those who had not.

Table 3 presents the risk of breast cancer by the combined use of OCs and HRT according to regimen and duration of use, compared to no HRT or OC use. The overall result for HRT ever-users, regardless of OC use, was that they were at increased risk compared to those who never used any exogenous sex hormones (HR=1.56; 95% CI 1.33-1.83). Ever OC users among HRT users were at greater risk than never-users (HR=1.84; 95% CI 1.51-2.26 vs. HR=1.36; 95% CI 1.11-1.66, respectively). Ever-users of C-HRT were at greater risk for breast cancer than E-HRT users (HR=2.19; 95% CI 1.76-2.73 vs. HR=1.25; 95% CI 1.03-1.51, respectively). Ever OC users in both regimen groups are generally at slightly greater risk for breast cancer than never OC users in the same HRT group. The largest difference in risk between OC never-users and ever-users in the same regimen and duration group was for long-term users of E-HRT (HR=1.15; 95% CI 0.79-1.66 vs. HR=1.70; 95% CI 1.19-2.42, respectively). The overall average duration of HRT use was 6.7 years, but 7.0

years for E-HRT users and 6.5 years for C-HRT users (data not shown). Generally, the women using HRT for longer duration were at greater risk for breast cancer than those who used it for shorter duration, whether OCs had formerly been used or not. The largest risk difference between the two duration subgroups in the same regimen group was for women who used E-HRT and were OC ever-users (HR=1.20; 95% CI 0.84-1.71 vs. HR=1.70; 95% CI 1.19-2.42, respectively).

Table 4a shows HR values of breast cancer for past and current HRT use for the 41.6% of HRT users who gave information on this aspect. HR values are shown for HRT users in general who gave information on this factor, as well as by OC use. Table 4b shows the same for the two regimen subgroups, in general and by OC use. The breast cancer risk is greater for current than past HRT users (HR=1.87; 95% CI 1.40-2.58 vs. HR=1.28; 95% CI 0.79-2.09), respectively, and greater for C-HRT users than E-HRT users. For current users of C-HRT and E-HRT, HR=1.61 (95% CI 1.24-2.09) vs. HR=1.55; (95% CI 1.01-2.38), respectively. There was no difference in HR between never and ever OC users among current or past HRT users, neither when viewing all HRT collectively nor E- and C-HRT individually.

DISCUSSION

Main findings

Although we did not find a statistically significant interaction between OC and HRT use on breast cancer risk, our findings indicate that HRT users who were former OC users had a somewhat higher risk of breast cancer than HRT users who had never used OCs.

The finding that there was an absence of interaction between OC and MPH use in our data is in agreement with results obtained in most other studies on this subject (66-68, 71-72). However, the absence of interaction is in contrast to the results of Norman *et al.*, who obtained a negative interaction between OC and HRT use (69). Indications of findings similar to Norman's were obtained in a study conducted by Dumeaux *et al.* (70). When comparing women ever using any exogenous sex hormones to those who had never used any, the highest risk was seen among those who used both. We found that the risk varied between HRT regimens, with a lower risk associated with estrogen unopposed HRT than combined HRT and a greater risk associated with continuous combined regimens than cyclic combined regimens (data not shown). A greater risk was usually associated with longer duration of use and with current use of HRT compared to short duration and past HRT use. These findings are in general agreement with other studies (49-51, 66-72).

Our finding that the greatest increase in breast cancer risk for ever-users compared to never OC users among users of the same HRT regimen was for estrogen unopposed HRT users unexpected and not in accordance with the main trend in this study, where greater risk was associated with combined HRT use. Our finding that a higher percentage of estrogen unopposed HRT users than

combined HRT users were current users may explain why their former use of OCs increased risk compared to those among them who never used OCs. The corresponding result for combined HRT users was that the difference in breast cancer risk between never and ever OC users was negligible. When investigating HR values according to whether HRT use was past or current, we were aware of the same trend; i.e., that combined HRT users are at greater risk than estrogen unopposed HRT users. Our results gave a weak indication that former use of OCs might reverse this trend. It has been proposed that OC use can enhance tumors already present in the breast when use commences. Estrogen is known to enhance tumor growth, and HRT use later in life may promote tumor growth even further (19, 28-32). Further research on the cellular and biochemical mechanisms involved in breast tumor formation is essential if we are to understand the action of exogenous sex hormones on breast cancer risk.

Strengths and limitations

The main strength of this study is that it is a large population-based cohort study based on data collected over a thirty-year period. The CDC cohort databank contains information from the majority of Icelandic women of screening age since the establishment of the databank in 1964. Therefore, we believe that we have obtained a valid picture of the situation for Icelandic women. Of the 96,000 women who visited the CDC during the study period, we limited our study group to those aged 40 years and over who answered questions about their ever/never use of OCs and HRT. We used data that they gave in their most recent visit to the CDC so as to have the most recent information possible. Another strength of this study is that the Icelandic population is ethnically homogenous. Finally, the Icelandic personal identification number makes

follow-up of subjects easy and loss to follow-up negligible. A further strength is that we were able to distinguish between HRT regimens and describe the effects of duration of use for 82% of HRT users, as well as the effects of current use, albeit only for 42% of HRT users.

There were several limitations in this study. First, there were no data available on menopausal status, type of menopause, or age at menopause for our subjects. As a result, we did not make restrictions based on the menopausal status of our subjects, as was done in most of the similar studies mentioned above (66-72). We compensated for this by restricting the study group to women aged 40 years and older. Data on regimens may not have been very accurate and were obtained only for the regimen with the longest duration of use; hence the effects of combined use of various regimens were not analyzed. Only 62% of the women gave information on regimen, and we restricted the cohort to the 90% of them who used the three most common HRT regimens. We believe it is important to investigate different HRT regimens, as estrogen unopposed HRT and combined HRT are chemically very different and have been shown to have different effects on their users (44).

Furthermore, questions on the time elapsed since OC and HRT were used and initiation and discontinuation of their use were not included in the questionnaires; therefore, this information was not available. The average time lag of eight years for the entire cohort between the age when data were given and the end of the study also limits the study because it is likely that HRT was used during this time. Consequently, our duration information is likely to be underestimated. In addition, the time lag is, on average, 2.4 years shorter for the women who developed breast cancer than for the entire cohort.

The number of visits made to the CDC during the study period was higher for women who developed breast cancer (Table 1). There was a decrease in risk with an increasing number of visits to the CDC. We had expected that the breast cancer cases might have visited the CDC more often before diagnosis because women might be prompted to do so after becoming aware of something unusual in their breast. Counteracting this would be the fact that the life expectancy of breast cancer patients is lower, leading to fewer visits. Also, there may be a difference between the women who visit the CDC regularly and those who come seldom. Therefore, when carrying out our Cox regression analyses, we adjusted for the number of visits to the CDC giving data. Other potential confounders for which we adjusted were birth year, age at giving data, parity, number of births, and age at first birth. Age at menarche was unexpectedly higher in the women who developed breast cancer, presumably because of their belonging to older birth cohorts and the fact that the age at menarche declined in the first half of the twentieth century (16).

Conclusions

Exogenous sex hormone use increases breast cancer risk in Icelandic women. Although we did not find a statistically significant interaction between OC and HRT use, we found that HRT users who were former OC users were at greater risk of breast cancer if they used estrogen unopposed HRT regimens for five years or longer. The main finding, though, was that former OC use had only a modest effect on breast cancer risk in HRT users. In addition, the women who used combined HRT regimens were at greater risk of breast cancer than those who used estrogen unopposed HRT regimens and longer duration of HRT use was associated with greater risk of breast cancer.

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TABLES

Table 1 Summary of covariates in the cohort and in the women who developed breast cancer (BC)

Covariate	cohort (N=31,430)	BC (n=1,182)	[a]HR (95% CI)*
birth year, mean (range)	1945 (1891-1968)	1936 (1904-1967)	0.94 (0.93-0.94)
birth year group, n (%)			
1891-1919	1,482 (4.7)	91 (7.7)	
1920-1939	10,037 (31.9)	648 (54.8)	
1940-1959	15,371 (48.9)	419 (35.4)	
1960-1988	4,540 (14.4)	24 (2.0)	
[b]age when giving data mean (range)	54.1 (39-90)	56.6 (40-79)	0.89 (0.88, 0.90)
age at exit, mean (range)	62.1 (40-102)	62.2 (40-92)	0.83 (0.82-0.84)
person-years, mean, (SD)	14.8 (9.31)	12.0 (8.1)	
age at menarche mean (range)	13.21 (9-23)	13.24 (9-19)	0.93 (0.89, 0.98)
missing, n	66	2	
parous, n (%)	29,588 (94.1)	1,075 (90.9)	0.76 (0.61, 0.95)
missing, n	347	17	
number of children, mean (range)	3.0 (0-20)	2.9 (0-11)	0.89 (0.86, 0.92)
1 - 3, n(%)	18,699 (59.5)	685 (58.0)	
> 3, n(%)	11,252 (35.8)	407 (34.4)	
missing, n	1,617	27	
[c]age at first birth, mean (range)	22.9 (13-54)	23.4 (15-45)	1.03 (1.02, 1.04)[b]
missing, n	431	20	
[d]Number of visits mean (range)	1.88 (1-7)	1.92 (1-5)	0.82 (0.76, 0.88)

[a]Birth year and age when data was given were obtained with a bivariate Cox regression analysis with these two covariates. HR for age attained, which is the age of the women on their date of exit from the study, was only adjusted for age at giving data. Other covariates were adjusted for birth year and age when data was given. [b]Data are from questionnaires answered during the women's most recent visit to the CDC after 1979 and after they reached age 40. [c]This covariate was observed for parous women only. [d]Number of visits to the CDC after 1979 in which data was given.

Table 2 Adjusted hazard ratios for breast cancer according to exogenous sex hormone never/ever (-/+) use

Hormone use	n cohort (%)	n BC (%)	[a]HR (95%CI)
[b]OC use			
OC	9,636 (30.7)	498 (42.1)	1.0 (ref.)
+OC	21,794 (69.3)	684 (57.9)	**1.36** (1.17-1.58)
[b]HRT use			
-HRT	22,316 (71)	719 (48.6)	1.00 (ref.)
+HRT	9,114 (29)	463 (30.6)	**1.45** (1.28-1.64)
OC use/HRT use			
- OC/-HRT (ref.)	7,290 (23.2)	348 (29.4)	1.0 (ref.)
+OC/-HRT	15,026 (47.8)	371 (31.4)	**1.28** (1.06-1.55)
-OC/+HRT	2,346 (7.5)	150 (12.7)	**1.36** (1.11-1.66)
+OC/+HRT	768 (21.5)	13 (26.5)	**1.84** (1.51-2.26)

[a]Adjusted for birth year, age when giving data, number of visits to CDC when giving data, age at menarche, parity, number of births, age at first birth. [b]HRs are based on data from users of estrogen unopposed (E-HRT) and combined (C-HRT) regimens of hormone replacement therapy and non-users of HRT.

Table 3 Adjusted hazard ratios for breast cancer according to HRT regimens and duration of use, exclusively and by OC use.

			Never OC		Ever OC	
Hormone use	**n cohort /BC**	**[a]HR (95% CI)**	**n**	**HR (95% CI)**	**n**	**HR(95% CI)**
-HRT/-OC (ref.)	7,290/348	1.00				
[b]Ever HRT	9,114/463	1.56 (1.33-1.83)	2,346	1.36 (1.11-1.66)	6,768	1.84 (1.51-2.26)
<5 years	3,362/198	1.43 (1.17-1.74)	873	1.37 (1.06-1.79)	2,489	1.55 (1.21-1.99)
5+ years	4,070/200	1.73 (1.41-2.13)	1,085	1.45 (1.09-1.92)	2,985	2.04 (1.57-2.64)
missing	1,682/65					
Ever E-HRT	3,749/189	1.25 (1.03-1.51)	1,299	1.11 (0.87-1.42)	2,450	1.46 (1.13-1.88)
<5 years	1,380/89	1.19 (0.93-1.53)	533	1.22 (0.89-1.67)	847	1 (0.84-1.71)
5+ years	1,696/78	1.38 (1.06-1.80)	573	1.15 (0.79-1.66	1,123	1.70 (1.19-2.42)
missing	673/22	2				
[d]Ever C-HRT	5,365/274	2.19 (1.76-2.73)	1,047	2.02 (1.49-2.72)	4,318	2.15 (1.69-2.12)
<5 years	1,982/109	1.87 (1.43-2.44)	340	1.84 (1.19-2.82)	1,642	1.87(1.39-2.52)
5+ years	2,374/122	2.19 (1.67-2.87)	512	2.13 (1.41-3.21)	1,862	2.14 (1.59-2.87)
missing	1009/43					

[a]Adjusted for birth year, age when giving data, number of visits giving data, age at menarche, parity, number of births and age at first birth. [b]HRs are based on data from users of estrogen unopposed (E-HRT) and combined (C-HRT) regimens of hormone replacement therapy (HRT). [c]This category consists of both cyclic and continuous combined hormone replacement therapy regimens.

Table 4a Adjusted HRs for breast cancer according to past and current use of all HRT and by OC use

HRT use	n (%)	[a]HR (95% CI)
-OC/-HRT	7,290 (23.2)	1.00 (ref.)
all HRT	9,114	**1.56** (1.28-1.64)
[b]past + current	3,790 (41.6)	**1.75** (1.31-2.35)
past	1,048 (27.6)	1.28 (0.79-2.09)
current	2,742 (72.3)	**1.87** (1.40-2.58)
-OC/+all HRT	2,346 (25.7)	**1.36** (1.11-1.66)
past + current	782 (33.3)	**1.71** (1.14-2.58)
[c]past	225 (28.8)	1.23 (0.53-2.85)
current	557 (71,2)	**1.86** (1.19-2.89
+OC/+HRT	6,768 (74.3)	**1.84** (1.51-2.26)
past + current	3,008 (44.4)	**1.74** (1.26-2.39
past	823 (27.4)	1.32 (0.75-2.31
current	2,185 (72.6))	**1.87** (1.33-2.62)

Adjusted for birth year, age when giving data, number of visits giving data, age at menarche, parity, number of births and age at first birth. Percentages for (past + current) use are for the number of women in the group who gave information about past and current use. cPercentages for pastand current use individually are for the number of women in the (past +current) group who are in each subgroup.

Table 4b Adjusted HRs for breast cancer according to past and current HRT use by regimen and OC use

HRT use	n (%)	HR (95% CI)
-OC/-all HRT	7,290 (23.2	1.00 (ref.)
all E-HRT	3,749 (41.1)	1.25 (1.03-1.51)
past + current	1,378 (36.8)	1.33 (0.88-2.01)
past	298 (21,6)	0.67 (0.24-1.84)
current	1,080 (78.4)	1.55 (1.01-2.38)
-OC/+E-HRT	1,299 (34.6)	1.11 (0.87-1.42)
past + current	311 (23.9)	1.40 (0.73-2.66)
Past	85 (27.3)	1.30 (0.40-4.16
Current	226 (72.7)	1.47 (0.70-3.08)
+OC/+ E-HRT	2,450 (65.4)	1.46 (1.13-188)
past + current	1,067 (43.6)	1.33 (0.83-2.13)
Past	213 (20.0)	0.30 (0.04-2.00)
Current	854 (80.0)	1.60 (0.99-2.59)

[a]Adjusted for birth year, age when giving data, number of visits giving data, age at menarche, parity, number of births and age at first birth. [b]Percentages for (past + current) use are for the number of women in the group who gave information about past and current use. [c]Percentages for pastand current use individually are for the number of women in the (past +current) group who are in each subgroup.

Table 4b Adjusted HRs for breast cancer according to past and current HRT use by regimen and OC use (continued)

HRT use	n (%)	HR (95% CI)
-OC/-all HRT	7,290 (23.2	1.00 (ref.)
all C-HRT	5,365 (58.9)	1.80 (1.55-2.11)
past + current	2,412 (45.0)	1.61 (1.24-2.09))
past	750 (31.1)	1.32 (0.82-2.13)
current	1,662 (68.9)	1.61 (1.24-2.09)
-OC/+C-HRT	1,047 (19.5)	2.02 (1.49-2.72)
past + current	471 (45.0)	1.91 (1.20-3.06)
Past	140 (29.7))	1.18 (0.37-3.77)
Current	331 (70.3)	2.06 (1.25-3.39)
+OC/+ C-HRT	4,318 (80.5)	2.15 (1.69-2.73)
past + current	1,941 (45.0)	2.02 (1.42-2.86)
Past	610 (31.4)	1.84 (1.03-3.29))
Current	1,331(68.6)	2.06 (1.41-3.00)

[a]Adjusted for birth year, age when giving data, number of visits giving data, age at menarche, parity, number of births and age at first birth. [b]Percentages for (past + current) use are for the number of women in the group who gave information about past and current use. [c]Percentages for pastand current use individually are for the number of women in the (past +current) group who are in each subgroup.