Fatal Breast Cancer Risk in Relation to Use of Unopposed Estrogen and Combined Hormone Therapy

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Abstract

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Purpose: Use of combined menopausal hormone therapy (CHT) is associated with an increased risk of developing breast cancer, but it remains unclear to what degree the increase in incidence translates into an increase in breast cancer mortality. We evaluated fatal breast cancer risk in relation to recency and duration of use of CHT and unopposed estrogen hormone therapy (EHT).

Methods: We conducted a large population-based nested case-control study in the Canadian province of Saskatchewan, where a population-based prescription drug database has existed since 1975. Cases (n = 1,288) were women who died of breast cancer in Saskatchewan between 1990-2008 at 50-79 years of age, and were eligible for Saskatchewan Prescription Drug Plan benefits for at least 5 years prior to their first primary breast cancer diagnosis (index date). Controls (n = 12,535) were matched to cases on duration of eligibility for health benefits prior to the index date and year of birth. Multivariate-adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were computed using unconditional logistic regression.

Results: Exclusive use of EHT was not associated with risk of fatal breast cancer, neither overall nor within categories of recency and duration of use (OR for current use versus never use = 1.05; 95% CI:

0.83-1.34). Use of CHT (includes women who had also used EHT) was also not associated with fatal breast cancer risk (OR for current use versus never use = 0.93; 95% CI: 0.67-1.28), except for a suggestion of an increased risk associated with current long-term use. However, the number of women in this category of use was small and the confidence intervals wide.

Conclusions: Consistent with several other studies, we observed no association between fatal breast cancer risk and use of EHT. Only a few studies have evaluated the association between fatal breast cancer risk and use of CHT, and collectively the results have been inconsistent. It remains to be seen whether women who take CHT are at an increased risk of dying from breast cancer.

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Introduction

Findings from meta-analyses of epidemiologic studies[1,2] and a Women's Health Initiative (WHI) randomized trial[3] leave little doubt that use of combined hormone therapy (CHT) is associated with an increased risk of developing breast cancer. In the two meta-analyses, the summary estimates of breast cancer risk associated with current use of CHT were 1.39 (95% CI: 1.12-1.72; 8 studies)[2] and 1.70 (95% CI: 1.36-2.13; 7 studies)[1] respectively. In the WHI randomized trial of women 50-79 years of age with an intact uterus, those assigned to CHT had a 24% increased risk of developing breast cancer (HR = 1.24; 95% CI: 1.01-1.54) compared to those assigned to placebo during a mean follow-up of 5.6 years.[3] Less clear however, is whether use of CHT is associated with an increased risk of death from breast cancer. In the WHI, women assigned to CHT had a 96% increased risk of death from breast cancer during a mean follow-up of 11.0 years (with a median duration of the intervention of 5.6 years).[4] However, the confidence interval (CI) was wide with a lower bound of 1.00 (hazard ratio [HR] = 1.96; 95% CI: 1.00-4.04; 37 breast cancer deaths).[4] In addition, because follow-up extended to 2009 and the intervention ended in 2002, some women who died of breast cancer may have been diagnosed during the intervention phase whereas others may have been diagnosed during the post-intervention phase; therefore it is not clear to what degree the risk estimate applies to current or past use of CHT. Further, duration-specific risk estimates were not reported. To our knowledge only two other studies have evaluated fatal breast cancer risk in users of CHT; one observed a decrease in risk[5] and the other no association.[6] In the British Million Women Study, fatal breast cancer risk was 22% greater in current hormone therapy (HT) users compared to nonusers (relative risk = 1.22; 95% CI: 1.05-1.41).[7] However, as with nearly all studies of the question of whether HT use in women without breast cancer is related to risk of dying from breast cancer, separate analyses were not conducted for CHT and unopposed estrogen hormone therapy (EHT).[7,8] In a separate WHI randomized trial of women 50-79 years of age without a uterus, those assigned to receive EHT had a 63% lower risk of fatal breast cancer (HR = 0.37;

95% CI: 0.13-0.91; 22 breast cancer deaths) compared to those assigned to placebo during a median follow-up of 11.8 years (with a median duration of the intervention of 7.2 years; follow-up extended to 2009 and the intervention ended in 2004).[9]

Although the prevalence of use of HT has declined dramatically since the early 2000's - for example, among women ≥40 years of age in the U.S. in 2009-2010, only 2.7% were taking EHT and 1.7% were taking CHT[10]- this still translates to large absolute number of women: in the U.S., 2.0 million for EHT and 1.3 million for CHT.[11] To better understand the relation between fatal breast cancer risk and use of CHT and EHT, we conducted a large population-based nested case-control study in the Canadian province of Saskatchewan, where a provincial Drug Plan has existed since September 1975. We evaluated fatal breast cancer risk in relation to recency and duration of use of CHT and EHT.

Methods

Saskatchewan has a publicly-funded health care system which is overseen by the Saskatchewan Ministry of Health. More than 99% of the population is eligible for provincial health benefits (about 1 million persons); excluded are individuals whose health care is fully funded through the federal government (e.g. the Royal Canadian Mounted Police).[12] Eligible individuals receive a unique lifetime health services number (HSN) which enables an individual's records to be linked across the various provincial population-based health services databases (included for the present study were: the population registry, vital statistics death registry, outpatient prescription drug database, hospital services database, and physician services database; and the Saskatchewan Cancer Agency's (SCA) cancer registry and Screening Program for Breast Cancer database).[12] Approximately 91% of persons eligible for Saskatchewan health benefits are also eligible for outpatient prescription drug benefits through its Drug Plan; persons not eligible are primarily First Nation peoples, who receive prescriptions drug benefits

through a federal program.[12] The underlying population from which cases and controls were drawn included only women eligible for the prescription drug benefits.

Study procedures were approved by the Saskatchewan Ministry of Health's Data Access Review Committee and a Saskatchewan research ethics board designated under the *Health Information Protection Act* of Saskatchewan. This study did not meet the definition of research involving human subjects under the U.S. Department of Health and Human Services Code of Federal Regulations, Title 45, Part 46-Protection of Human Subjects.

Case identification

Cases were women who died of breast cancer at 50-79 years of age during 1990-2008 (born 1911-1958), and who had continuous Drug Plan coverage for at least 5 years prior to their first primary breast cancer diagnosis (index date). Death from breast cancer (International Statistical Classification of Diseases, Ninth Revision[13] [ICD-9] 174 and International Classification of Disease for Oncology[14] [ICD-O] C50) was ascertained from the vital statistics death registry of Saskatchewan and the Saskatchewan cancer registry. Among 1,881 potentially eligible women, 17% (n = 316) did not have at least 5 years of continuous prescription drug coverage prior to the index date. Of the remaining 1,565 women, 29 did not have a record of a breast cancer diagnosis in the cancer registry (these women had been assigned an index date equal to their death date). These 29 women were excluded because in our analyses, receipt of HT was considered only until the first primary breast cancer diagnosis date (and the comparable date in the controls).

Control identification

Control women were enumerated from the population registry after excluding women not eligible for prescription drug benefits. For each case, 15 potential controls were randomly sampled,

with replacement, among women with the same birth year and the same duration of continuous health coverage as the case prior to the cases' breast cancer diagnosis date (index date). The potential controls were assigned the index date of their matched case. Following this step, a prior breast cancer diagnosis among the controls was ascertained from the cancer registry. Controls with a breast cancer diagnosis prior to the index date were excluded from the control pool, because our goal was to assess fatal breast cancer risk in relation to use of HT among women with no prior breast cancer diagnosis. For each case, 10 controls were randomly sampled, without replacement, from the remaining pool of controls.

Ascertainment of menopausal hormone therapy use

Menopausal HT prescriptions dispensed to cases and controls prior to the index date were ascertained from the outpatient prescription drug database.[12] The database includes all outpatient prescriptions dispensed for drugs listed on the Saskatchewan Formulary.[12] In this study, EHT (estrogen alone) and CHT (estrogen plus progestogen) comprised prescriptions for oral or transdermal patch estrogens and progestogens. During the observation period, 1975-2008, women in Saskatchewan who were prescribed CHT were generally given separate prescriptions for the estrogen and progestogen component. Some women who took CHT may not have filled both prescriptions on the same day, therefore, an estrogen prescription was classified as a CHT prescription if there was a progestogen prescription within the prior 90 days or the subsequent 20 days (Among all CHT prescriptions, 80.4% had a progestogen dispensed on the same day as the estrogen.). All remaining estrogen prescriptions were classified as EHT.

The drug name, dispensing date, route of administration, strength and quantity were ascertained from the prescription database. Duration of use of EHT and CHT was estimated based on the quantity of estrogen dispensed. The estrogen component of EHT or CHT may be administered continuously (estrogen is taken daily) or cyclically (estrogen is taken daily except for 5-7 days per month

when no hormone is taken).[15,16] Therefore, 25 pills or one package of estrogen-containing transdermal patches (which contains a 4-week supply) were considered equivalent to one month of use. Dose was computed from strength assuming one pill (patch) was taken (worn) per day on pill-taking (patch-wearing) days.

We also determined whether the progestogen component of the CHT was administered continuously (progestogen is taken on all days when estrogen is taken) or sequentially (progestogen is taken only 7-20 of the days when estrogen is taken).[15] The ratio of the quantities of progestogen and estrogen dispensed (P:E) per CHT prescription was computed for the 80.4% of CHT prescriptions where the estrogen and progestogen were dispensed on the same day. To estimate the P:E ratio for the remaining 19.6% of CHT prescriptions where a progestogen was not dispensed on the same day as the estrogen, we computed episodes of CHT use. An episode of CHT use was a period wherein CHT was being regularly dispensed to the woman. The P:E ratio for the whole episode was assigned to those CHT prescriptions that were part of the episode but for which the progestogen was not dispensed on the same day as the estrogen. An episode of CHT use was computed by allowing no more than a 60 day gap between the end date for a given CHT prescription and the dispensing date of the subsequent CHT prescription. If the gap exceeded 60 days a new episode of CHT use was created. To determine the end date for each CHT prescription, 25 estrogen pills or one package of estrogen-containing transdermal patches were considered equivalent to one month of use. All CHT prescriptions with a P:E ratio <0.75 were classified as sequential therapy and all those with a P:E ratio ≥ 0.75 were classified as continuous therapy.

To determine the strength of the progestogen component for the 19.6% of CHT prescriptions that did not have a progestogen dispensed on the same day as the estrogen, we computed the average strength of progestogen dispensed during each episode of CHT use. It was then applied to those CHT

prescriptions that were part of the episode but did not have a progestogen dispensed on the same day as the estrogen. There were 153 CHT prescriptions (0.7% of the 20,967 CHT prescriptions; representing 40 women with ≥1 of these prescriptions) for which we could not determine the strength (or type) of the progestogen component because more than one type of progestogen was used during the episode. The 153 prescriptions were therefore not included in the analysis of risk in relation to type and strength of the progestogen component of CHT (Tables 4 and 5).

Ascertainment of potential confounders

Demographic information was ascertained from the population registry (duration of continuous health care coverage prior to the index date, residence in the index year, marital status in the index year, and receipt of income security benefits in the index year). Receipt of a hysterectomy prior to the index date was ascertained from the hospital services database and the physician services database. The hospital services database dates back to 1970 and includes procedure and diagnosis codes for all hospital inpatient stays and day surgeries for Saskatchewan beneficiaries.[12] The physician services database includes Saskatchewan physicians' claims for payment since 1975 (most Saskatchewan physicians are paid on a fee-for service basis).[12] We were unable to specifically ascertain receipt of bilateral oophorectomy because not all codes distinguished unilateral from bilateral oophorectomy. A diagnosis of cancer prior to the index date was ascertained from the cancer registry, going back to 1970 (the earliest year for which automated data were available). Receipt of screening mammogram in the 3 years prior to the index date was ascertained from the Screening Program for Breast Cancer database going back to 1990. The program began in select regions in 1990, and since 1993 women in the whole province who are eligible to receive a screening mammogram do so through the program. It offers mammography every year to eligible women with a first degree family history of breast cancer, and mammography every two years to those without a family history.[17] Women eligible for screening are

≥50 years of age, do not have symptoms of breast cancer such as breast lumps, do not have breast implants, and are not being actively followed-up for breast cancer (i.e. are not <5 years post breast cancer treatment or <5 years post diagnosis if no treatment was received).[17,18] Women 50-69 years of age are identified from the province's population registry and are mailed a letter of invitation to receive a screening mammogram.[17]

Analysis

Women who never had an HT prescription served as the reference group for all analyses. Ever use of EHT was defined as ≥2 prescriptions for EHT within a 6-month period, and ever use of CHT was defined as ≥2 prescriptions for CHT within a 6-month period. These definitions provided some assurance that women categorized as ever users of the specified HT did not include women who took little or none of the prescribed medication before discontinuing use. Women were categorized as current users of CHT or of EHT if they had at least 1 prescription for the specified HT within the 6 months prior to the index date. Former users were women whose last use of the specified HT was more than 6 months prior to the index date. Excluded from all analyses were women who had ≥1 HT prescription but did not meet our criteria for being "ever users" of EHT or "ever users" of CHT (248 cases and 2,818 controls). A total of 1,288 cases and 12,353 controls remained for analysis.

Unconditional logistic regression was used to compute odds ratios (ORs) and 95% CIs. For our main analyses of use of EHT and CHT we also computed ORs using conditional logistic regression. We observed similar results with both methods but the conditional logistic regression analysis of CHT use was based on less than half of the cases included in the unconditional logistic regression analysis, therefore we used unconditional logistic regression for all analyses. All ORs were adjusted for the following variables on which cases and controls were matched: duration of prescription drug coverage prior to the index date, year of birth, and index year. We additionally adjusted for variables that

changed the OR by ≥10% among the following: duration of continuous health care coverage prior to the index date, residence in the index year, marital status in the index year, receipt of income security benefits in the index year, receipt of a screening mammogram in the 3 years prior to the index date, hysterectomy prior to the index date, and a diagnosis of cancer prior to the index date. All variables were categorized as shown in Table 1. Only receipt of a screening mammogram in the 3 years prior to the index date and receipt of a hysterectomy prior to the index date met the criterion for confounding in any analyses. All analyses were adjusted for these two variables in addition to the matching variables. Tests for trend were conducted by modeling the categorical exposure variable as a single linear term in the logistic regression models. Women who did not have a prescription for any hormone therapy (the reference category) were excluded from the tests for trend. All analyses were conducted using Stata/SE 12.1 (StataCorp LP, College Station, Texas).

Sensitivity analyses

We sought to determine whether our finding on fatal breast cancer risk in relation to use of CHT differed when we used a different algorithm to ascertain prescriptions for CHT. For this sensitivity analysis, we evaluated fatal breast cancer risk in relation to the number progestogen prescriptions (oral or transdermal patch) dispensed prior to the index date. Ever use of progestogen was defined as ≥2 prescriptions for progestogen within a 6-month period. Excluded from this analysis were women (226 cases and 2,614 controls) who had ≥1 prescription for menopausal HT but were not ever users of estrogen (≥2 prescriptions for estrogen [oral or transdermal patch] within a 6-month period) or ever users of progestogen. A total of 1,310 cases and 12,739 controls remained for this analysis of risk in relation to number of progestogen prescriptions dispensed (Table 6).

There was a relatively brief period, July 1987-December 1988, when data on dispensed prescriptions were not available, due to an administrative change in the Saskatchewan's Drug Plan

during that time. We conducted a sensitivity analysis to estimate the impact of underascertainment of duration of HT use among ever users (Supplemental Tables 5 and 6). Women with ≥1 prescription for the specified type of HT (i.e. CHT or EHT) in the 3 months before and after this interval were classified as having taken the specified HT during the interval. Those with ≥1 prescription for the specified HT in the 3 months before or after the interval, but not both, were classified as having taken the specified HT for 9 months of the 18 month interval. The ORs associated with duration of use of EHT and CHT did not differ appreciably from the original analyses (Tables 2 and 3).

Some less commonly used menopausal hormones were listed on the Saskatchewan Formulary with restricted coverage during part of the observation period. These hormones included the transdermal patches (EHT [estradiol] and CHT [estradiol and norethindrone]) and micronized progesterone. If a drug is listed on the Formulary with restricted coverage, providers must apply to the Drug Plan for approval for individual patient coverage. If the application is not approved, or if an application is not made, the dispensing of the medication is not captured in the drug database. Micronized progesterone was added to the Formulary in July 1996, with restricted coverage. The transdermal patches were listed on the Formulary with restricted coverage in January 1997 or later (some were on the formulary without restriction prior to 1997). Our analyses of the specific formulation of CHT, conjugated estrogens (CE) plus medroxyprogesterone acetate (MPA), would not have been influenced by underascertainment of use of CHT transdermal patches (in which the progestogen component was norethindrone) or micronized progesterone. Our analyses of EHT use (whether specific to CE or not) could have been influenced by underascertainment of the restricted-coverage hormones as of July 1996. For example, an estrogen that was actually dispensed with micronized progesterone may have been misclassified as EHT (when it was really for CHT) because micronized progesterone prescriptions were not fully captured by the database. To estimate the impact of any misclassification of EHT use, we conducted an analysis of EHT use that was restricted to women with an index date before

July 1996 (no menopausal hormones were listed on the Formulary with restricted coverage prior to July 1996). The ORs in the restricted sample were similar to those from the whole study population (see Results and Supplemental Table 7).

Results

Cases were slightly more likely than controls to have resided in an urban region in the index year (52% versus 49%), to have never been married (7% versus 5%), to have received income security benefits in the index year (13% versus 9%), and to have had a prior cancer diagnosis (10% versus 8%) (Table 1). Controls were more likely than cases to have had a hysterectomy prior to the index date (22% versus 19%) and to have had a screening mammogram in the 3 years prior to the index date (25% versus 19%) (Table 1).

For our analysis of risk in relation to EHT use, we restricted ever users to women who were exclusive EHT users (i.e. they also did not have 2 or more prescriptions for CHT within a 6 month period) (Table 2). Among ever users of EHT, 83% were exclusive users. Exclusive ever use of EHT was not associated with risk (OR = 0.98; 95% CI: 0.84-1.15) (Table 2). There was no association with recency (Table 2) or with duration of use among current users (Table 2) or among former users (data not shown). Among exclusive ever users of EHT, 86% were ever users of CE (≥2 prescriptions for CE within a 6-month period). Risk was not related to use of CE whether evaluated by recency of use or duration of use among current and former users, for any dose of CE (0.3, 0.625, and >0.625-2.5 mg/day) (data not shown).

In our analysis of exclusive use of EHT that was restricted to women with an index date prior to July 1996 (852 cases and 8,362 controls), when no menopausal hormone was listed on the Formulary with restricted coverage, the ORs were similar to those from our analysis of the whole study population (Supplemental Table 7). For example, the respective ORs associated with ever use, current use and

former use were 0.92, 0.99, and 0.90 among women with an index date before July 1996, as compared to 0.98, 1.05, and 0.96 among women in the whole study population (Supplemental Table 7).

Among ever users of CHT, 51% were exclusive users (i.e. they also did not have 2 or more prescriptions for EHT within a 6 month period). Because about half of all ever users of CHT are excluded in an analysis restricted to exclusive users, and because EHT use was not related to risk, our analysis of CHT use included all ever users of CHT (Table 3). Ever use of CHT was not associated with risk (OR = 0.87; 95% CI: 0.69-1.09), and there was no association with recency (Table 3) nor with duration of use among former users (data not shown). Among current users, there was a suggestion of an increased risk with use of at least 10 years, OR = 2.12 (Table 3), but this association was statistically quite imprecise (95% CI: 0.79-5.67). In an exploratory analysis we evaluated risk associated with current use for each year of duration of use from >0-<1 year through ≥10 years, relative to never use. The pattern in the magnitude of the ORs suggested no excess risk until 8 years of use, from which point on the ORs were elevated (data not shown).

Among ever users of CHT, 84% were ever users of CE plus MPA (≥2 prescriptions for CE plus MPA within a 6-month period). Our findings on risk in relation to use of CE plus MPA (Table 4) were similar to those for use of CHT overall (Table 3). We also evaluated risk in relation to dose of MPA (Table 4). Risk was not associated with ever use of CE plus MPA or recency of use, for any dose of MPA (2.5-<5.0, 5.0-<10.0, and ≥10.0 mg/day) (Table 4). However, for all 3 MPA doses there was a suggestion of an increased risk with current use for ≥5 years (Table 4). Current use for <5 years was not associated with risk (Table 4). We also evaluated risk in relation to use of sequential and continuous CE plus MPA, and our findings (Table 5) were similar to those for use of CE plus MPA overall and to those for use of CHT overall.

We additionally evaluated risk in relation to recency and number of progestogen prescriptions dispensed (regardless of dispensed estrogen) (Table 6). Our findings were similar to those for use of CHT. Risk was not related to use of progestogen, except possibly for current long-term use. Women who were current users with ≥48 progestogen prescriptions had a 2.33-fold (95% CI: 1.06-5.12) increased risk of fatal breast cancer (Table 6).

Discussion

In this study, neither a history of use of CHT nor of EHT was associated with fatal breast cancer risk. When we evaluated risk by recency and duration, there also were no associations, except possibly for an increased risk associated with current long-term use of CHT. However, the number of women in this category of use was small and the confidence intervals wide.

These findings should be interpreted in the context of the limitations of this study. We were unable to measure or could only incompletely measure some potential confounding variables. The earliest year in which data on receipt of hysterectomy was available was 1970. To estimate the impact of residual confounding by hysterectomy, we conducted an analysis of ever use and recency of use that was restricted to the 33% of the study population who was 35 years of age or younger in 1970 (born ≥1935) and had health coverage between January 1970 and the index date (i.e. women for whom we likely had relatively complete information on receipt of hysterectomy) (Supplemental Tables 1 and 2). The ORs were similar in the whole versus the restricted sample. We also did not have information on receipt of bilateral oophorectomy, which has been associated with a decreased risk of developing breast cancer in women who receive the procedure before 40-45 years of age.[19,20] However, the prevalence of receipt of a bilateral oophorectomy before age 40-45 years was likely relatively low (e.g. it was only 5-8% among controls in these two large U.S. population-based breast cancer case-control studies).[19,20]

It is also possible that we did not have complete information on receipt of screening mammography. An organized screening mammogram program began in Saskatchewan in 1990 and was province-wide by 1993. The procedure was biennial and so by 1995 all women in Saskatchewan who were eligible to receive a screening mammogram (eligible age is ≥50 years) would have had the opportunity to be screened at least once. We conducted an analysis of ever use and recency of use that was restricted to women for whom we likely had relatively complete information on receipt of screening mammography in the recent past: all women with an index age <50 years, plus women with an index age ≥52 years, an index year ≥1995, and Saskatchewan health coverage between January 1993 and the index date (47% of the study population) (Supplemental Tables 3 and 4). Again, the ORs were similar in the whole versus the sample that was restricted on this basis.

There are several strengths of this study, many of which arise from its population-based design. Unlike the in WHI, where only 17% of the women in the CHT arm were randomized to therapy within 5 years of menopause,[4] and only 20% of women in the EHT arm were randomized to therapy within 10 years of menopause,[9] women in this study were more likely to be taking EHT and CHT closer to the typical time of HT initiation, the onset of menopause. Evidence from the WHI suggests that the timing of HT initiation relative to menopause onset may be relevant to breast cancer incidence,[21] although it is not known how, if at all, it may be related to risk of fatal breast cancer. Cases and controls had relatively long periods of continuous prescription drug coverage prior to their index date (median = 17 years) which permitted us to evaluate risk in relation to long-term use of CHT and EHT. In the WHI, duration-specific estimates of fatal breast cancer risk were not presented, and the maximum duration of the intervention was approximately 9 years for the CHT trial[4] and 11 years for the EHT trial.[9] In addition, recall bias is not a concern because data on dispensed prescriptions were recorded prospectively. Further, selection bias is unlikely as the population registry made it possible to select controls from the underlying population from which the cases arose. Our study also includes an appreciably larger

number of women who died of breast cancer (n = 1,288) compared to any of the other prior studies of fatal breast cancer risk in relation to use of CHT (range of n: 37-278).[4-6] Although a potential concern is uncontrolled confounding by variables that could not be ascertained from the administrative databases, in a separate study of fatal breast cancer risk in relation to use of CHT and EHT, after adjusting for variables deemed *a priori* to be potential confounders (age at menopause, type of menopause, and receipt of a screening mammogram in the 2 years before the cases' breast cancer diagnosis and the comparable date in the controls), Norman et al. found no confounding (defined as a >5% change in the OR) by the following variables: body mass index, family history of breast cancer, education, marital status, parity, alcohol consumption, smoking status, number of pre-existing medical conditions, and use of oral contraceptives.[6] In the only other observational study of fatal breast cancer risk in relation to use of CHT and EHT, information was not available on potential confounders other than age.[5]

As mentioned above, other than the WHI CHT randomized trial, only two other studies have evaluated fatal breast cancer risk in relation to CHT use. In one, a Swedish study, the breast cancer mortality rate in a cohort of women with ≥1 CHT prescription (identified from pharmacy records) was compared to that of the general female population, after accounting for age. A decreased risk was observed in the cohort of women with ≥1 CHT prescription (relative risk = 0.6; 95% CI: 0.4-0.9).[5] However, the design of the study compromises the interpretation of the results. Women with prevalent breast cancer, in whom death from breast cancer is most likely to occur, were excluded from the cohort of CHT users, but not from the comparison cohort.[5] Thus, in the absence of a true association we would expect a lower breast cancer mortality rate to be observed in the cohort of CHT users. In the other, a U.S. study by Norman et al., current CHT use for ≥3 years was not associated with risk of fatal breast cancer (OR = 0.94; 95% CI: 0.59-1.48).[6] The data were from a case-control study of incident breast cancer in which cases were followed for death for 6 years after their diagnosis; CHT use (as ascertained by means of an interview) was compared in the subset of cases who died of breast cancer and the

original controls.[6] A potential concern with this study is the degree to which there was incomplete ascertainment of breast cancer deaths, primarily among women who, because of the presence of advanced disease, elected not to be interviewed.

In the WHI CHT trial, women assigned to receive CE plus MPA had an approximate 2-fold increased risk of fatal breast cancer.[4] In this trial, there also was an increased risk of incident breast cancer in women assigned to CHT that was greater for advanced-stage disease than for localized disease.[3] Yet, findings from observational studies tend to show that CHT use is more strongly associated with the development of tumors that have a relatively good prognosis, specifically, those that are estrogen receptor positive[22-25] and have lobular histology.[26,27] Some studies have also observed better case-fatality in women who took CHT prior to diagnosis.[28,29] Another consideration is that CHT use is associated with increased breast density,[30] and decreased sensitivity of mammography,[31] which may delay detection of tumors in these women.

Although few studies have evaluated fatal breast cancer risk separately for EHT and CHT use, several studies have evaluated HT use as a whole in relation to fatal breast cancer risk. In a 2002 systematic review of 10 such studies, HT use tended to be associated with a reduced risk (the reduction in risk was statistically significant in only two studies) or to not be associated with risk.[8] The time period during which the exposures occurred was generally before 1990 with some extension in some studies into the early 1990s.[8] The predominant form of HT during this time would have been EHT.[32] In the WHI EHT trial, a 63% (HR = 0.37; 95% CI: 0.13-0.91; 22 breast cancer deaths) decreased risk of fatal breast cancer was observed in women who were assigned to CE compared to those assigned to placebo.[9] As a whole, the findings from these studies, along with our own, are consistent with the hypothesis that EHT use is not associated with an increased risk of fatal breast cancer.

The current understanding of the association between use of CHT and fatal breast cancer risk may be augmented by examining the association in existing longitudinal studies of HT use in women without breast cancer who were followed for breast cancer mortality, provided data on CHT use are available.

Disclaimer

This Study is based in part on de-identified data provided by the Saskatchewan Ministry of Health. The interpretation and conclusions contained herein do not necessarily represent those of the Government of Saskatchewan or the Saskatchewan Ministry of Health.

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Table 1. Characteristics of women who died of breast cancer and control women.

	Cases (n =1,288)		Controls (n = 12,535)	
	n	%	n	%
Health care coverage as of 1970 (the earliest year in which data were available from any database)				
Covered in 1970	1,122	87.1	10,900	87.0
Covered after 1970	166	12.9	1,635	13.0
Duration of continuous health care coverage prior to index date (years)[1,2]				
5-9	35	2.7	343	2.7
10-14	132	10.3	1,294	10.3
15-19	265	20.6	2,645	21.1
20-24	371	28.8	3,602	28.7
25-29	262	20.3	2,479	19.8
30-39	223	17.3	2,172	17.3
Mean (standard deviation)	22.4 (6.8)		22.3 (6.8)	
Median (interquartile range)	22.1 (17.8-27.4)		22.0 (17.8-27.3)	
Duration of continuous prescription drug coverage prior to index date (years)[1,3]				
5-9	151	11.7	1,478	11.8
10-14	293	22.8	2,914	23.3
15-19	377	29.3	3,637	29.0
20-24	261	20.3	2,500	19.9
25-29	165	12.8	1,587	12.7
30-33	41	3.2	419	3.3
Mean (standard deviation)	17.4 (6.4)		17.3 (6.4)	
Median (interquartile range)	17.0 (12.8-22.1)		16.9 (12.7-22.0)	
Year of birth				
1911-1919	153	11.9	1,432	11.4
1920-1929	389	30.2	3,762	30.0
1930-1939	414	32.1	4,081	32.6
1940-1949	249	19.3	2,480	19.8
1950-1957	83	6.4	780	6.2
Index year[1]				
1980-1984	121	9.4	1,182	9.4
1985-1989	268	20.8	2,697	21.5
1990-1994	378	29.4	3,640	29.0
1995-1999	279	21.7	2,675	21.3
2000-2004	193	15.0	1,843	14.7
2005-2008	49	3.8	498	4.0

	Cases (n =1,288)		Controls (n = 12,535)	
	n	%	n	%
Age in index year (years)[1]				
30-39	5	0.4	43	0.3
40-49	163	12.7	1,646	13.1
50-59	396	30.8	3,941	31.4
60-69	465	36.1	4,454	35.5
70-79	259	20.1	2,451	19.6
Year of breast cancer death				
1990-1994	374	29.0	n/a	n/a
1995-1999	320	24.8	n/a	n/a
2000-2004	335	26.0	n/a	n/a
2005-2008	259	20.1	n/a	n/a
Age in year of breast cancer death (years)				
50-54	146	11.3	n/a	n/a
55-59	174	13.5	n/a	n/a
60-64	206	16.0	n/a	n/a
65-69	238	18.5	n/a	n/a
70-74	252	19.6	n/a	n/a
75-79	272	21.1	n/a	n/a
Residence in the index year[1]				
Urban (population >100,000)	485	37.7	4,536	36.2
Small urban[4]	183	14.2	1,598	12.8
Rural	618	48.0	6,372	50.8
Unknown[5]	2	0.2	29	0.2
Marital status in index year[1]				
Single, never married	90	7.0	577	4.6
Married or common law	861	66.9	8,739	69.7
Divorced, separated, widow, or other	335	26.0	3,190	25.5
Unknown[5]	2	0.2	29	0.2
Receipt of government income security benefits in index year[1,6]				
None	1,120	87.0	11,328	90.4
Any	166	12.8	1,178	9.4
Unknown[5]	2	0.2	29	0.2

	Cases (n =1,288)		Controls (n = 12,535)	
	n	%	n	%
Receipt of a screening mammogram in the 3 years prior to the index date[1,7]	249	19.3	3,189	25.4
Age ≥50 years in index year (1,120 cases/10,846 controls)[1,8]	248	22.1	3,189	29.4
Index year				
1980-1990 (316 cases/3,101 controls)	0	0.0	0	0.0
1990-1992 (217 cases/2,121 controls)	27	12.4	224	10.6
1993-1999 (368 cases/3,491 controls)	141	38.3	1,707	48.9
2000-2008 (219 cases/2,133 controls)	80	36.5	1,258	59.0
Receipt of hysterectomy prior to index date[1,9]	238	18.5	2,709	21.6
Cancer diagnoses prior to index date[1,10]				
None	1,166	90.5	11,552	92.2
Any	122	9.5	983	7.8

[1]The index date is the date of the first primary breast cancer diagnosis for cases and the comparable date for controls.

[2]The start date for health care coverage was the initiation of coverage with Saskatchewan Health or January 1, 1970, whichever occurred later.

[3]The start date for prescription drug coverage was initiation of health care coverage with Saskatchewan Health or September 1, 1975 (when the Drug Plan was introduced), whichever occurred later.

[4]Includes communities with a regional hospital.

[5]Demographic variable information from the population registry was not available for the index year.

[6]Includes various income security programs for low-income families and individuals.

[7]The Screening Program for Breast Cancer data were available as of 1990, when the program began in select regions of the province. The program became province-wide in 1993. Eligible age for receipt of a screening mammogram was ≥50 years.

[8]One case received a screening mammogram before age 50.

[9]Ascertained from: (1) procedure codes from hospital inpatient stays and day surgeries as of 1970 or initiation of health care coverage, whichever occurred later; and (2) Saskatchewan physician billing codes as of 1975 or initiation of health care coverage, whichever occurred later.

[10]Ascertained from the Saskatchewan Cancer Agency's cancer registry going back to 1970 (the earliest year in which automated data were available). By design no case or control had a breast cancer diagnosis prior to the index date.

Table 2. Risk of fatal breast cancer in relation to exclusive use of unopposed estrogen hormone therapy (EHT).

	Cases (n = 1,288)		Controls (n = 12,535)			
Regimen	n	%[1]	n	%[1]	OR[6]	95% CI
	Exclusive EHT Use					
Never[2]	911	76.9	8,500	74.9	1.00	Ref.
Ever[3]	274	23.1	2,845	25.1	0.98	0.84-1.15
Duration[7]						
>0-<1 year	40	7.1	947	8.4	0.88	0.69-1.12
1-<3 years	126	6.9	786	6.9	1.06	0.83-1.35
3-<5 years	39	3.3	356	3.1	1.15	0.81-1.63
5-<10 years	48	4.1	487	4.3	1.04	0.76-1.43
10-<15 years	16	1.4	180	1.6	0.94	0.56-1.60
≥15 years	5	0.4	89	0.8	0.62	0.25-1.54
Per 1 year					0.98	0.94-1.02
	Recency of Exclusive EHT Use					
Never[2]	911	76.9	8,500	74.9	1.00	Ref.
Current[3,4]	96	8.1	978	8.6	1.05	0.83-1.34
Duration[8]						
>0-<5 years	47	4.0	480	4.2	1.04	0.75-1.43
5-<10 years	32	2.7	295	2.6	1.16	0.79-1.70
≥10 years	17	1.4	203	1.8	0.91	0.54-1.51
Per 1 year					0.96	0.91-1.01
Per 1 year after ≥5 years of use					0.93	0.85-1.01
Former[3,5]	178	15.0	1,867	16.5	0.96	0.80-1.14
Time since last use[9]						
>6 months-<5 years	70	5.9	710	6.3	1.01	0.78-1.31
≥5 years	108	9.1	1,157	10.2	0.93	0.75-1.15

OR, odds ratio; CI, confidence interval

[1]Denominator does not include 103 cases and 1,190 controls who had ≥2 prescriptions for combined hormone therapy within a 6-month period.

[2]No prescription for any hormone therapy.

[3]At least 2 prescriptions for EHT within a 6-month period and never had ≥2 prescriptions for combined hormone therapy within a 6-month period.

[4]At least 1 prescription for EHT within the 6 months prior to the index date (date of breast cancer diagnosis in cases and comparable date in controls).

[5]Last prescription for EHT was >6 months prior to the index date.

[6]ORs were adjusted for duration of prescription drug coverage prior to the index date, year of birth, index year (year of breast cancer diagnosis in cases and comparable year in controls), receipt of a

screening mammogram in the 3 years prior to the index date and receipt of a hysterectomy prior to the index date.

[7]P-value for trend excluding never users = 0.859

[8]P-value for trend excluding never users = 0.558

[9]P-value for trend (time since last use) excluding never users = 0.522

Table 3. Risk of fatal breast cancer in relation to use of combined hormone therapy (CHT).

	Cases (n = 1,288)		Controls (n = 12,535)			
Regimen	n	%[1]	n	%[1]	OR[6]	95% CI
	CHT Use					
Never[2]	911	89.8	8,500	87.7	1.00	Ref.
Ever[3]	103	10.2	1,190	12.3	0.87	0.69-1.09
Duration[7]						
>0-<1 year	34	3.4	424	4.4	0.80	0.56-1.15
1-<3 year	32	3.2	344	3.6	0.93	0.64-1.36
3-<5 years	12	1.2	172	1.8	0.68	0.37-1.24
5-<10 years	20	2.0	199	2.1	1.04	0.64-1.69
≥10 years	5	0.5	51	0.5	0.99	0.39-2.54
Per 1 year					1.06	0.97-1.15
	Recency of CHT Use					
Never[2]	911	89.8	8,500	87.7	1.00	Ref.
Current[3,4]	47	4.6	498	5.1	0.93	0.67-1.28
Duration[8,10]						
>0-<5 years	28	2.8	355	3.7	0.77	0.52-1.15
5-<10 years	14	1.4	119	1.2	1.18	0.66-2.08
≥10 years	5	0.5	24	0.2	2.12	0.79-5.67
Per 1 year of use					1.23	1.08-1.39
Per 1 year after ≥5 years of use					1.44	1.12-1.86
Former[3,5]	56	5.5	692	7.1	0.82	0.61-1.10
Time since last use[9]						
>6 months-<5 years	37	3.6	407	4.2	0.92	0.64-1.31
≥5 years	19	1.9	285	2.9	0.67	0.41-1.09

OR, odds ratio; CI, confidence interval

[1]Denominator does not include 274 cases and 2,845 controls who had ≥2 prescriptions for unopposed estrogen within a 6-month period but never had ≥2 prescriptions for CHT within a 6-month period were excluded.

[2]No prescription for any hormone therapy.

[3]At least 2 prescriptions for CHT within a 6-month period.

[4]At least one prescription for CHT within the 6 months prior to the index date (date of breast cancer diagnosis in cases and comparable date in controls).

[5]Last prescription of CHT was >6 months prior to the index date.

[6]ORs were adjusted for duration of prescription drug coverage prior to the index date, year of birth, index year (year of breast cancer diagnosis in cases and comparable year in controls), receipt of a screening mammogram in the 3 years prior to the index date and receipt of a hysterectomy prior to the index date

[7]P-value for trend excluding never users = 0.342

[8]P-value for trend excluding never users = 0.047

[9]P-value for trend (time since last use) excluding never users = 0.268

[10]OR comparing current users for ≥5 years to never users = 1.34 (95% CI: 0.81-2.20)

Table 4. Risk of fatal breast cancer in relation to use conjugated estrogens (CE) plus medroxyprogesterone acetate (MPA), by dose of MPA.

	Cases (n = 1,288)		Controls (n = 12,535)			
Regimen	n	%	n	%	OR[9]	95% CI
	Use of CE (0.3-2.5 mg/day) plus MPA (2.5-<5.0 mg/day)[1]					
Never[2]	911	96.2	8,500	95.5	1.00	Ref.
Ever[3]	36	3.8	396	4.5	0.91	0.63-1.32
Current[3,4]	23	2.4	197	2.2	1.17	0.74-1.85
Duration[10]						
>0-<5 years	15	1.6	157	1.8	0.97	0.56-1.67
≥5 years	8	0.8	40	0.4	1.97	0.90-4.30
Former[3,5]	13	1.4	199	2.2	0.65	0.36-1.17
	Use of CE (0.3-2.5 mg/day) plus MPA (5.0-<10.0 mg/day)[6]					
Never[2]	911	94.8	8,500	93.1	1.00	Ref.
Ever[3]	50	5.2	631	6.9	0.80	0.59-1.09
Current[3,4]	10	1.0	141	1.5	0.70	0.36-1.33
Duration[11]						
>0-<5 years	5	0.5	112	1.2	0.44	0.18-1.09
≥5 years	5	0.5	29	0.3	1.64	0.63-4.29
Former[3,5]	40	4.2	490	5.4	0.83	0.59-1.17
	Use of CE (0.3-2.5 mg/day) plus MPA (10.0 mg/day)[7]					
Never[2]	911	96.9	8,500	97.0	1.00	Ref.
Ever[3]	39	3.1	266	3.0	1.05	0.71-1.57
Current[3,4]	8	0.9	58	0.7	1.28	0.61-2.70
Duration[12]						
>0-<5 years	6	0.6	54	0.6	1.02	0.43-2.39
≥5 years	2	0.2	4	0.0	5.33	0.96-29.60
Former[3,5]	21	2.2	208	2.4	0.99	0.62-1.58
	Use of CE (0.3-2.5 mg/day) plus MPA (2.5-10.0 mg/day)[8]					
Never[2]	911	91.2	8,500	89.5	1.00	Ref.
Ever[3]	88	8.8	993	10.5	0.88	0.69-1.13
Current[3,4]	40	4.0	396	4.2	0.99	0.70-1.40
Duration[13]						
>0-<5 years	22	2.2	280	2.9	0.77	0.49-1.20
≥5 years	18	1.8	116	1.2	1.56	0.93-2.61
Per 1 year					1.23	1.07-1.41
Per 1 year after ≥5 year of use					1.39	1.06-1.83
Former[3,5]	48	4.8	597	6.3	0.81	0.59-1.11

OR, odds ratio; CI, confidence interval

[1]Denominator of calculated percentages does not include 341 cases and 3,639 controls who had ≥2 prescriptions for unopposed estrogen therapy within a 6-month period or ≥2 prescriptions for combined hormone therapy within a 6-month period but never had ≥2 prescriptions for CE (0.3-2.5 mg/day) plus MPA (2.5-<5.0 mg/day) within a 6-month period.
[2]No prescription for any hormone therapy.
[3]At least 2 prescriptions for the specified dose of CE plus MPA within a 6-month period.
[4]At least 1 prescription for CE plus MPA in the specified dose within the 6 months prior to the index date (date of breast cancer diagnosis in cases and comparable date in controls).
[5]Last prescription for CE plus MPA in the specified dose was >6 months prior to the index date.
[6]Denominator of calculated percentages does not include 327 cases and 3,404 controls who had ≥2 prescriptions for unopposed estrogen therapy within a 6-month period or ≥2 prescriptions for combined hormone therapy within a 6-month period but never had ≥2 prescriptions for CE (0.3-2.5 mg/day) plus MPA (5.0-<10.0 mg/day) within a 6-month period.
[7]Denominator of calculated percentages does not include 348 cases and 3,769 controls who had ≥2 prescriptions for unopposed estrogen therapy within a 6-month period or ≥2 prescriptions for combined hormone therapy within a 6-month period but had never had ≥2 prescriptions for CE (0.3-2.5 mg/day) plus MPA (10.0 mg/day) within a 6-month period.
[8]Denominator of calculated percentages does not include 289 cases and 3,042 controls who had ≥2 prescriptions for unopposed estrogen therapy within a 6-month period or ≥2 prescriptions for combined hormone therapy within a 6-month period but never had ≥2 prescriptions for CE plus MPA within a 6-month period.
[9]ORs were adjusted for duration of prescription drug coverage prior to the index date, year of birth, index year (year of breast cancer diagnosis in cases and comparable year in controls), receipt of a screening mammogram in the 3 years prior to the index date and receipt of a hysterectomy prior to the index date.
[10]P-value for trend excluding never users = 0.161
[11]P-value for trend excluding never users = 0.013
[12]P-value for trend excluding never users (not adjusted for receipt of hysterectomy because 0 exposed cases had a prior hysterectomy) = 0.729
[13]P-value for trend excluding never users = 0.085

Table 5. Risk of fatal breast cancer in relation to use of sequential and continuous conjugated estrogen (CE) plus medroxyprogesterone acetate (MPA).

	Cases (n = 1,288)		Controls (n = 12,535)			
Regimen	n	%	n	%	OR[7]	95% CI
	Recency of Use of Sequential CE plus MPA[1]					
Never[2]	911	93.4	8,500	92.3	1.00	Ref.
Ever[3]	64	6.6	707	7.7	0.90	0.68-1.19
Current[3,4]	19	1.9	175	1.9	1.06	0.65-1.72
Duration[8]						
>0-<5 years	13	1.3	142	1.5	0.89	0.50-1.58
≥5 years	6	0.6	33	0.4	1.85	0.76-4.46
Per 1 year					1.20	0.97-1.50
Former[3,5]	45	4.6	532	5.8	0.85	0.61-1.17
Time since last use[9]						
>6 months-<5 years	20	2.1	284	3.1	0.71	0.45-1.13
≥5 years	25	2.6	248	2.7	1.01	0.65-1.56
	Recency of Use of Continuous CE plus MPA[6]					
Never[2]	911	95.6	8,500	94.4	1.00	Ref.
Ever[3]	42	4.4	508	5.6	0.83	0.59-1.17
Current[3,4]	24	2.5	223	2.5	1.08	0.69-1.68
Duration[10]						
>0-<5 years	18	1.9	178	2.0	1.02	0.61-1.68
≥5 years	6	0.6	45	0.5	1.30	0.54-3.12
Per 1 year					1.14	0.89-1.45
Former[3,5]	18	1.9	285	3.2	0.64	0.39-1.04
Time since last use[11]						
>6 months-<5 years	17	1.8	188	2.1	0.91	0.54-1.52
≥5 years	1	0.1	97	1.1	0.10	0.01-0.74

OR, odds ratio; CI, confidence interval

[1]Denominator of calculated percentages does not include 313 cases and 3,328 controls who had ≥2 prescriptions for EHT or ≥2 prescriptions for CHT but never had ≥2 prescriptions for sequential CE plus MPA within a 6-month period.

[2]No prescription for any hormone therapy.

[3]At least 2 prescriptions for the specified regimen of CE plus MPA within a 6-month period.

[4]At least 1 prescription for the specified regimen of CE plus MPA within the 6 months prior to the index date (date of breast cancer diagnosis in cases and comparable date in controls).

[5]Last prescription for the specified regimen of CE plus MPA was >6 months prior to the index date.

[6]Denominator of calculated percentages does not include 335 cases and 3,527 controls who had ≥2 prescriptions for EHT or ≥2 prescriptions CHT but never had ≥2 prescriptions for continuous CE plus MPA within a 6-month period.

[7]ORs were adjusted for duration of prescription drug coverage prior to the index date, year of birth, index year (year of breast cancer diagnosis in cases and comparable year in controls), receipt of a screening mammogram in the 3 years prior to the index date and receipt of a hysterectomy prior to the index date.

[8]P-value for trend excluding never users = 0.783

[9]P-value for trend (time since last use) excluding never users = 0.289

[10]P-value for trend excluding never users = 0.441

[11]P-value for trend (time since last use) excluding never users = 0.038

Table 6. Risk of fatal breast cancer in relation to use of progestogen.

	Cases (n = 1,310)		Controls (n = 12,739)			
Regimen	n	%[1]	n	%[1]	OR[6]	95% CI
			Progestogen use			
Never[2]	911	87.6	8,500	86.0	1.00	Ref.
Ever[3]	129	12.4	1,384	14.0	0.92	0.75-1.14
Number of prescriptions[7]						
2-11	77	7.4	816	8.3	0.94	0.73-1.21
12-23	23	2.2	287	2.9	0.78	0.50-1.20
24-47	20	1.9	214	2.2	0.94	0.58-1.52
≥48	9	0.9	67	0.7	1.33	0.65-2.72
			Recency of Progestogen use			
Never[2]	911	87.6	8,500	86.0	1.00	Ref.
Current[3,4]	54	5.2	532	5.4	1.00	0.74-1.35
Number of prescriptions[8]						
2-11	20	1.9	215	2.2	0.90	0.57-1.44
12-23	13	1.3	152	1.5	0.84	0.47-1.50
24-47	13	1.3	131	1.3	0.99	0.55-1.78
≥48	8	0.8	34	0.3	2.33	1.06-5.12
Former[3,5]	75	7.2	852	8.6	0.87	0.67-1.13
Time since last use[9]						
>6 months -<5 years	41	3.9	436	4.4	0.94	0.67-1.32
≥5 years	34	3.3	416	4.2	0.81	0.56-1.17

OR, odds ratio; CI, confidence interval

[1]Denominator does not include 270 cases and 2,855 controls who had ≥2 prescriptions for estrogen within a 6-month period but never had ≥2 prescriptions for progestogen within a 6-month period

[2]No prescription for any hormone therapy.

[3]At least 2 prescriptions for progestogen within a 6-month period.

[4]At least one prescription for progestogen within the 6 months period to the index date (date of breast cancer diagnosis in cases and comparable date in controls).

[5]Last prescription for progestogen was >6 months prior to the index date.

[6]ORs were adjusted for duration of prescription drug coverage prior to the index date, year of birth, index year (year of breast cancer diagnosis in cases and comparable year in controls), receipt of a screening mammogram in the 3 years prior to the index date and receipt of a hysterectomy prior to the index date.

[7]P-value for trend excluding never users = 0.439

[8]P-value for trend excluding never users = 0.192

[9]P-value for trend (time since last use) excluding never users = 0.486

Appendix 1. Sensitivity Analyses

1) Incomplete ascertainment of hysterectomy status.

We likely have relatively complete information on receipt of a hysterectomy among women who were 35 years of age or younger in 1970 and were covered by Saskatchewan Health between January 1970 and the index date (33% of the study population). Hysterectomy data from the Hospital Services database dates back to 1970.

Supplemental Table 1. Risk of fatal breast cancer in relation to exclusive use of unopposed estrogen hormone therapy (EHT) among the whole study population and among women ≤35 years of age in 1970 (born ≥1935) who were covered by Saskatchewan Health between January 1970 and the index date

	Whole study population (1,288 cases/12,535 controls)		Women ≤35 years of age in 1970 who were covered by Saskatchewan Health between January 1970 and the index date (426 cases/4,196 controls)	
Regimen	OR	95% CI	OR	95% CI
	Exclusive Use of EHT			
Never	1.00	Ref.	1.00	Ref.
Ever	0.98	0.84-1.15	1.10	0.80-1.51
Current	1.05	0.83-1.34	1.07	0.71-1.62
Former	0.96	0.80-1.14	1.12	0.77-1.63

Supplemental Table 2. Risk of fatal breast cancer in relation to use of combined hormone therapy (CHT) among the whole study population and among women ≤35 years of age in 1970 (born ≥1935) who were covered by Saskatchewan Health between January 1970 and the index date

	Whole study population (1,288 cases/12,535 controls)		Women ≤35 in 1970 who were covered by Saskatchewan Health between January 1970 and the index date (426 cases/4,196 controls)	
Regimen	OR	95% CI	OR	95% CI
	Use of CHT			
Never	1.00	Ref.	1.00	Ref.
Ever	0.87	0.69-1.09	0.86	0.63-1.19
Current	0.93	0.67-1.28	1.07	0.71-1.62
Former	0.82	0.61-1.10	0.70	0.46-1.08

2) Incomplete ascertainment of receipt of a screening mammogram.

An organized screening mammogram program began in Saskatchewan in 1990 and was province-wide by 1993. The procedure was biennial and so by 1995 all women in Saskatchewan who were eligible to receive a screening mammogram (eligible age is ≥50 years) would have had the opportunity to be screened at least once. We conducted an analysis of ever use and recency of use that was restricted to women for whom we likely had relatively complete information on receipt of screening mammography in the recent past: women with an index age <50 years, plus women with an index age ≥52 years, an index year ≥1995, and Saskatchewan Health coverage between January 1993 and the index date (47% of the study population).

Supplemental Table 3. Risk of fatal breast cancer in relation to exclusive use of unopposed estrogen hormone therapy (EHT) among whole study population and among women with an index age <50 years, and women with an index age ≥52 years, an index year ≥1995, and Saskatchewan Health coverage between January 1993 and the index date.

	Whole study population (1,288 cases/12,535 controls)		Women with an index age <50 years and women with an index age ≥52 years, an index year ≥1995, and Saskatchewan Health coverage between January 1993 and the index date (600 cases/5,875 controls)	
Regimen	OR	95% CI	OR	95% CI
	Exclusive Use of EHT			
Never	1.00	Ref.	1.00	Ref.
Ever	0.98	0.84-1.15	0.99	0.77-1.27
Current	1.05	0.83-1.34	0.99	0.70-1.42
Former	0.96	0.80-1.14	0.99	0.75-1.31

Supplemental Table 4. Risk of fatal breast cancer in relation to use of combined hormone therapy (CHT) among whole study population and among women with an index age <50 years, and women with an index age ≥52 years, an index year ≥1995, and Saskatchewan Health coverage between January 1993 and the index date.

	Whole study population (1,288 cases/12,535 controls)		Women with an index age <50 years and women with an index age ≥52 years, an index year ≥1995, and Saskatchewan Health coverage between January 1993 and the index date (600 cases/5,875 controls)	
Regimen	OR	95% CI	OR	95% CI
	Use of CHT			
Never	1.00	Ref.	1.00	Ref.
Ever	0.87	0.69-1.09	0.91	0.69-1.20
Current	0.93	0.67-1.28	1.05	0.72-1.54
Former	0.82	0.61-1.10	0.82	0.58-1.15

3) During July 1987-December 1988 prescription data were not available due to an administrative change in the Prescription Drug Plan during that time.

We conducted a sensitivity analysis to estimate the impact of underascertainment of duration of HT use among ever users. For this analysis, women with ≥1 prescription for the specified type of HT (i.e. CHT or EHT) in the 3 months before and after this interval were classified as having taken the specified HT during the interval. Those with ≥1 prescription for the specified HT in the 3 months before or after the interval, but not both, were classified as having taken the specified HT for 9-months of the 18 month interval.

Supplemental Table 5. Risk of fatal breast cancer in relation to exclusive use of unopposed estrogen hormone therapy (EHT)

	Original analysis		Sensitivity analysis	
Regimen	OR	95% CI	OR	95% CI
	Exclusive Use of EHT			
Never	1.00	Ref.	1.00	Ref.
Ever	0.98	0.84-1.15		
Duration				
>0-<6 months	0.91	0.65-1.27	0.90	0.63-1.27
6 months-<3 years	0.98	0.80-1.20	0.98	0.80-1.21
3-<5 years	1.15	0.81-1.63	1.08	0.77-1.53
5-<10 years	1.04	0.75-1.43	1.02	0.74-1.41
10-<15 years	0.94	0.55-1.60	1.14	0.71-1.82
≥15 years	0.61	0.25-1.54	0.58	0.25-1.35
	Recency of Exclusive Use of EHT			
Never	1.00	Ref.	1.00	Ref.
Current	1.05	0.83-1.34		
Duration				
>0-<5 years	1.04	0.75-1.43	1.05	0.76-1.46
5-<10 years	1.16	0.79-1.70	1.11	0.75-1.65
≥10 years	0.91	0.54-1.51	0.96	0.60-1.55
Former	0.96	0.80-1.14		
Time since last use by duration				
>6 months-<5 years	1.01	0.78-1.31		
>0 to <5 years	1.06	0.79-1.42	1.04	0.77-1.39
≥5 years	0.84	0.49-1.45	0.93	0.56-1.55
≥5 years	0.94	0.75-1.17		
>0 to <5 years	0.94	0.75-1.17	0.93	0.75-1.16
≥5 years	0.69	0.28-1.72	0.79	0.34-1.84

Supplemental Table 6. Risk of fatal breast cancer in relation to use of combined therapy (CHT)

Regimen	Original analysis		Sensitivity analysis	
	OR	95% CI	OR	95% CI
	Use of CHT			
Never	1.00	Ref.	1.00	Ref.
Ever	0.87	0.69-1.09		
Duration				
>0-<6 months	0.87	0.69-1.09	0.75	0.43-1.31
6 months-<3 years	0.82	0.49-1.38	0.90	0.67-1.23
3-<5 years	0.87	0.64-1.19	0.69	0.39-1.22
5-<10 years	0.68	0.37-1.24	0.96	0.59-1.58
≥10 years	1.04	0.64-1.68	1.16	0.49-2.75
	Recency of Use of CHT			
Never	1.00	Ref.	1.00	Ref.
Current	0.93	0.67-1.28		
Duration				
>0-<5 years	0.77	0.52-1.15	0.78	0.52-1.16
5-<10 years	1.18	0.66-2.08	1.15	0.65-2.03
≥10 years	2.12	0.79-5.67	2.04	0.77-5.43
Former	0.82	0.61-1.10		
Time since last use by duration				
>6 months-<5 years	0.92	0.64-1.31		
>0 to <5 years	0.97	0.66-1.43	0.98	0.77-5.43
≥5 years	0.71	0.31-1.66	0.70	0.67-1.44
≥5 years	0.67	0.41-1.09		
>0 to <5 years	0.72	0.44-1.17	0.72	0.44-1.17
≥5 years	0	-	0	-

4) To estimate the impact of any underascertainment of EHT use that may have resulted from some hormones being listed on the Formulary with restricted coverage (i.e. their use may not have been captured in the drug database), we conducted an analysis of fatal breast cancer risk in relation to use of EHT that was restricted to women with an index date before July 1996 (no menopausal hormones were listed on the Formulary with restricted coverage prior to July 1996).

Supplemental Table 7. Risk of fatal breast cancer in relation to use of unopposed estrogen therapy (EHT) among the whole study population and among only women with an index date before July 1996.

	Whole study Population (1,288 cases/ 12,535 controls)[1]		Women with an index date before July 1996 (852 cases/ 8,362 controls)[2]	
Regimen	OR	95% CI	OR	95% CI
	Exclusive Use of EHT			
Never	1.00	Ref.	1.00	Ref.
Ever	0.98	0.84-1.15	0.92	0.76-1.12
Duration				
>0-<5 year	0.99	0.84-1.17	0.90	0.73-1.11
5-<10 years	1.03	0.75-1.42	1.16	0.77-1.75
≥10 years	0.83	0.52-1.33	0.68	0.30-1.58
	Recency of Exclusive Use of EHT			
Never	1.00	Ref.	1.00	Ref.
Current	1.05	0.83-1.34	0.99	0.72-1.36
Duration				
>0-<5 years	1.04	0.76-1.44	0.90	0.59-1.38
≥5 years	1.06	0.77-1.46	1.09	0.70-1.70
Former	0.96	0.80-1.14	0.90	0.72-1.12
Time since last use by duration				
>6 months-<5 years	1.01	0.78-1.31	0.89	0.63-1.24
≥5 years	0.93	0.75-1.15	0.91	0.70-1.19

[1]Data on dispensations of some menopausal hormones (transdermal patches and micronized progesterone) were incompletely ascertained from July 1996-December 2008.

[2]No menopausal hormones were listed on the Saskatchewan Formulary with restricted coverage prior to July 1996.