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EPIDEMIOLOGY

Fatal breast cancer risk in relation to use of unopposed estrogen and combined hormone therapy

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Abstract Use of combined hormone therapy (CHT) is associated with increased breast cancer incidence, but it is unclear whether this translates into increased breast cancer mortality. To address this question, we conducted a population-based nested case–control study in Saskatchewan, Canada, where a population-based prescription drug database has existed since 1975. We evaluated fatal breast cancer risk in relation to recency and duration of use of CHT and unopposed estrogen hormone therapy (EHT). A total of 1,288 cases and 12,535 controls were included in the analyses. Exclusive use of EHT was not associated with fatal breast cancer risk, either overall or within categories of recency or duration [odds ratio (OR) for current vs. never use = 1.1; 95 % confidence interval (CI) 0.8–1.3]. Use of CHT (includes women who had also used EHT) was also not associated with fatal breast cancer risk (OR for current vs. never use = 0.9; 95 % CI 0.7–1.3), except for a suggestion of an increased risk with current long-term use. Consistent with prior studies, we observed no increased risk of fatal breast cancer associated with use of EHT. To date only a few studies have evaluated fatal breast cancer risk in relation to use of CHT, and collectively the results are inconsistent.

Keywords Breast cancer · Estrogen · Progestin · Mortality · Menopause

Introduction

Findings from meta-analyses of observational studies [1–3] and a Women's Health Initiative (WHI) randomized trial [4] leave little doubt that use of combined hormone therapy (CHT) increases risk of developing breast cancer. Less clear, however, is whether use of CHT is associated with an increased risk of death from breast cancer. In the WHI randomized trial of women 50–79 years of age with an intact uterus, those assigned to CHT had a 1.96-fold (95 % confidence interval, CI 1.00–4.04) 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) [5]. In the WHI observational cohort study, the hazard ratio (HR) of fatal breast cancer associated with CHT use at baseline was 1.32 (95 % CI 0.90–1.93) during a mean

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follow-up of 11.3 years [6]. It is not clear to what degree these risk estimates apply to current or former use or to duration of use during the follow-up period. In a recent US case–control study, in which HT use was ascertained by in-person interview, no association was observed between fatal breast cancer risk and use of CHT [3]. In a separate WHI randomized trial of women 50–79 years of age without a uterus, those assigned to receive unopposed estrogen hormone therapy (EHT) had a 63 % lower risk of fatal breast cancer (HR = 0.37; 95 % CI 0.13–0.91) during a median follow-up of 11.8 years (with a median duration of the intervention of 7.2 years) [7]. In nearly all other studies of HT and fatal breast cancer, risk was not evaluated separately according to type of hormone therapy (CHT vs. EHT).

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 Saskatchewan, Canada, where a provincial prescription drug database has existed since September 1975. We evaluated fatal breast cancer risk in relation to recency and duration of use of CHT and EHT.

Materials and methods

Saskatchewan has a universal health care system funded by the provincial government and with leadership provided by the Saskatchewan Ministry of Health. More than 99 % of the population is eligible for health benefits (about 1 million persons); excluded are the individuals whose health care is fully funded through the federal government (e.g., the Royal Canadian Mounted Police) [8]. Eligible individuals receive a unique lifetime health services number which enables an individual's records to be linked across the various population-based health services databases [8]. Approximately 91 % of persons eligible for health benefits are also eligible for outpatient prescription drug benefits through the Saskatchewan Drug Plan; persons not eligible are primarily First Nation peoples, who receive prescriptions drug benefits through a federal program [8]. The underlying population from which study cases and controls were drawn included only women eligible for the Drug Plan.

Case identification

Cases were women who died of breast cancer at 50–79 years of age during 1990–2008, 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 [9] 174 and International and Statistical Classification of Diseases, Tenth Revision C50 [10]) was ascertained from the vital statistics death registry of Saskatchewan and the Saskatchewan Cancer Agency's cancer registry. Among 1,881 potentially eligible women, 17 % ($n = 316$) did not have at least 5 years of continuous Drug Plan 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 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

Controls were enumerated from the population registry after excluding women not eligible for the Drug Plan. 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. Controls with a breast cancer diagnosis prior to the index date, ascertained from the cancer registry, were excluded from the control pool, because our goal was to assess fatal breast cancer risk in relation to HT use among women with no prior breast cancer diagnosis. For each case, 10 controls were randomly sampled 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 Drug Plan database [8]. The database includes all outpatient prescriptions dispensed for drugs listed on the Saskatchewan Formulary [8]. In this study, EHT and CHT comprised prescriptions for oral or transdermal patch estrogens and progestogens. During the study period, 1975–2008, women in Saskatchewan who were prescribed CHT were generally given separate prescriptions for estrogen and progestogen components. Therefore, an estrogen prescription was classified as a CHT prescription if a progestogen was dispensed 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, dosage form (e.g., tablet, transdermal patch, etc.), 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. Twenty-five estrogen pills or one package of estrogen-containing transdermal patches (which

contains a 4-week supply) were considered equivalent to 1 month of use. Dose was computed from strength assuming that one pill (or patch) was taken (worn) per day on pill-taking (patch-wearing) days. Details on the computation of specific CHT regimens (e.g., combined vs. sequential) are described in Online Resource 1.

Ascertainment of potential confounders

Demographic information from the index year was ascertained from the population registry (residence, marital status, and receipt of income security benefits). Receipt of a hysterectomy prior to the index date was ascertained from the hospital services and physician services databases. 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 [8]. The physician services database includes physicians' claims for payment since 1975 (most Saskatchewan physicians are paid on a fee-for-service basis) [8].

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 with automated data). Receipt of screening mammogram in the 3 years prior to the index date was ascertained from the Screening Program for Breast Cancer database. 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 2 years to those without a family history [11]. Eligible women are those who are ≥50 years of age, who do not have symptoms of breast cancer such as breast lumps, and who do not have breast implants [11, 12].

Statistical analysis

Women who never had any HT prescription served as the reference group for all analyses. Ever use was defined as ≥2 prescriptions for the specified HT within a 6-month period. This definition provided some assurance that women categorized as ever users did not include women who took little or no medication before discontinuing use. Current users were women who had a 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 the analyses were women who had ≥1 HT prescription but did not meet our criteria for being "ever users" of EHT or 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. All ORs were adjusted for variables on which cases and controls were matched: duration of health care coverage prior to the index date, year of birth, and index year. We additionally adjusted for variables (categorized as shown in Table 1) that changed the OR by ≥10 %: receipt of a screening mammogram in the 3 years prior to the index date and receipt of a hysterectomy prior to the index date. Tests for trend were conducted by modeling the categorical exposure variable as a single linear term in the 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, TX).

Sensitivity analyses

We conducted several sensitivity analyses. (1) We sought to determine whether our finding on fatal breast cancer risk in relation to CHT use differed when we used a different algorithm to ascertain prescriptions for CHT. To do so, we evaluated risk in relation to number of progestogen prescriptions dispensed prior to the index date (regardless of dispensed estrogen; Table 5).

(2) 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 Drug Plan. We estimated the impact of underascertainment of duration of HT use among ever users. 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 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 HT for 9 months of the 18 month interval. We found that the ORs associated with duration of use of EHT and CHT did not differ appreciably from the original analyses (data not shown).

(3) Some less commonly used menopausal hormones (transdermal patches and micronized progesterone) were listed on the Formulary with restricted coverage during part of the observation period. Providers had the option to apply to the Drug Plan for approval for patient coverage for these medications. If an application was not made or not approved, then the dispensing of the medication was not captured in the Drug Plan database. Micronized progesterone had restricted coverage from July 1996–2008, and the transdermal patches from January 1997 or later through 2008. Our analyses of the specific formulation of CHT, conjugated estrogens (CEs) plus medroxyprogesterone

Table 1 Characteristics of study 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)[a,b]				
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)[a,c]				
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[a]				
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
Age in index year (years)[a]				
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[a]				
Urban (population >100,000)	485	37.7	4,536	36.2
Small urban[d]	183	14.2	1,598	12.8
Rural	618	48.0	6,372	50.8
Unknown[e]	2	0.2	29	0.2
Marital status in index year[a]				
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[e]	2	0.2	29	0.2
Receipt of government income security benefits in index year[a,f]				
None	1,120	87.0	11,328	90.4
Any	166	12.8	1,178	9.4
Unknown[e]	2	0.2	29	0.2
Receipt of a screening mammogram in the 3 years prior to the index date[a,g]	249	19.3	3,189	25.4
Age ≥50 years in index year (1,120 cases/10,846 controls)[a,h]	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[a,i]	238	18.5	2,709	21.6
Cancer diagnoses prior to index date[a,j]				
None	1,166	90.5	11,552	92.2
Any	122	9.5	983	7.8

[a] The index date/year is the date of the first primary breast cancer diagnosis for cases and the comparable date for controls

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

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

[d] Includes communities with a regional hospital

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

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

[g] 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

[h] One case received a screening mammogram before age 50

[i] 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

[j] 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

acetate (MPA), would not have been influenced by underascertainment of CHT transdermal patches (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). Therefore, we conducted an analysis of risk in relation to recency and duration of EHT use that was restricted to women with an index date before July 1996 (no menopausal hormones were on the Formulary with restricted coverage before July 1996). The ORs in the restricted sample were similar to those based on the whole study population (data not shown).

Results

Cases were slightly more likely than controls to have resided in an urban region in the index year, never had been married, received income security benefits in the index year, and had a prior cancer diagnosis (Table 1). Controls were more likely than cases to have had a hysterectomy prior to the index date and a screening mammogram in the 3 years prior to the index date.

Among ever users of EHT, 83 % were exclusive users. Exclusive ever use of EHT was not associated with risk (OR = 1.0; 95 % CI 0.8–1.2), and risk did not vary by recency (Table 2) or by duration of use among former (data not shown) and current users (Table 2). Among exclusive ever users of EHT, 86 % were ever users of CE. Risk was not related to use of CE, and it did not vary by recency or by duration of use among current and former users, for any dose (0.3, 0.625, and >0.625–2.5 mg/day; data not shown).

Among ever users of CHT, 51 % were exclusive users. 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 = 0.9; 95 % CI 0.7–1.1), and risk did not vary by recency or by duration of use among former users (data not shown). Among current users, there was a suggestion of an increased risk with use of ≥10 years, OR = 2.1, but this association was statistically imprecise (95 % CI 0.8–5.7).

Among ever users of CHT, 84 % were ever users of CE plus MPA. Our findings on risk in relation to use of CE plus MPA overall (Table 4), by dose of MPA (Online Resource 2), and for sequential and continuous regimens (Online Resource 3), were similar to those for use of CHT overall.

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

Regimens	Cases (n = 1,288)		Controls (n = 12,535)		OR[i]	95 % CI
	n	%[h]	n	%[h]		
Exclusive EHT use						
Never[a]	911	76.9	8,500	74.9	1.0	Ref.
Ever[b]	274	23.1	2,845	25.1	1.0	0.8, 1.2
Duration[e]						
>0–<1 year	40	7.1	947	8.4	0.9	0.7, 1.1
1–<3 years	126	6.9	786	6.9	1.1	0.8, 1.4
3–<5 years	39	3.3	356	3.1	1.2	0.8, 1.6
5–<10 years	48	4.1	487	4.3	1.0	0.8, 1.4
10–<15 years	16	1.4	180	1.6	0.9	0.6, 1.6
≥15 years	5	0.4	89	0.8	0.6	0.3, 1.5
Recency of exclusive EHT use						
Never[a]	911	76.9	8,500	74.9	1.0	Ref.
Current[b,c]	96	8.1	978	8.6	1.1	0.8, 1.3
Duration[f]						
>0–<5 years	47	4.0	480	4.2	1.0	0.8, 1.4
5–<10 years	32	2.7	295	2.6	1.2	0.8, 1.7
≥10 years	17	1.4	203	1.8	0.9	0.5, 1.5
Former[b,d]	178	15.0	1,867	16.5	1.0	0.8, 1.1
Time since last use[g]						
>6 months–<5 years	70	5.9	710	6.3	1.0	0.8, 1.3
≥5 years	108	9.1	1,157	10.2	0.9	0.7, 1.2

OR odds ratio, *CI* confidence interval

[a] No prescription for any hormone therapy

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

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

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

[e] P for trend excluding never users = 0.875

[f] P for trend excluding never users = 0.554

[g] P for trend (time since last use) excluding never users = 0.505

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

[i] ORs were adjusted for duration of health care 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

Our findings on risk in relation to number of progestogen prescriptions dispensed were also similar to those for use of CHT. Risk was not related to use of progestogen,

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

Regimens	Cases (n = 1,288)		Controls (n = 12,535)		OR[j]	95 % CI
	n	%[i]	n	%[i]		
CHT use						
Never[a]	911	89.8	8,500	87.7	1.0	Ref.
Ever[b]	103	10.2	1,190	12.3	0.9	0.7, 1.1
Duration[e]						
>0–<1 year	34	3.4	424	4.4	0.8	0.6, 1.2
1–<3 year	32	3.2	344	3.6	0.9	0.6, 1.4
3–<5 years	12	1.2	172	1.8	0.7	0.4, 1.2
5–<10 years	20	2.0	199	2.1	1.0	0.6, 1.7
≥10 years	5	0.5	51	0.5	1.0	0.4, 2.6
Recency of CHT use						
Never[a]	911	89.8	8,500	87.7	1.0	Ref.
Current[b,c]	47	4.6	498	5.1	0.9	0.7, 1.3
Duration[f,h]						
>0–<5 years	28	2.8	355	3.7	0.8	0.5, 1.2
5–<10 years	14	1.4	119	1.2	1.2	0.7, 2.1
≥10 years	5	0.5	24	0.2	2.1	0.8, 5.7
Former[b,d]	56	5.5	692	7.1	0.8	0.6, 1.1
Time since last use[g]						
>6 months–<5 years	37	3.6	407	4.2	0.9	0.6, 1.3
≥5 years	19	1.9	285	2.9	0.7	0.4, 1.1

OR odds ratio, *CI* confidence interval

[a] No prescription for any hormone therapy

[b] At least two prescriptions for CHT within a 6-month period

[c] 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)

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

[e] P for trend excluding never users = 0.362

[f] P for trend excluding never users = 0.046

[g] P for trend (time since last use) excluding never users = 0.219

[h] OR comparing current users for ≥5 years to never users = 1.4 (95 % CI 0.8, 2.2)

[i] 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

[j] ORs were adjusted for duration of health care 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

except possibly for current long-term use (Table 5). Women who were current users with ≥48 progestogen prescriptions had a 2.3-fold (95 % CI 1.1–5.1) increased risk of fatal breast cancer (Table 5).

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

Regimens	Cases (n = 1,288)		Controls (n = 12,535)		OR[g]	95 % CI
	n	%[f]	n	%[f]		
Never[a]	911	91.2	8,500	89.5	1.0	Ref.
Ever[b]	88	8.8	993	10.5	0.9	0.7, 1.1
Current[b,c]	40	4.0	396	4.2	1.0	0.7, 1.4
Duration[e]						
>0–<5 years	22	2.2	280	2.9	0.8	0.5, 1.2
≥5 years	18	1.8	116	1.2	1.6	0.9, 2.6
Former[b,d]	48	4.8	597	6.3	0.8	0.6, 1.1

OR odds ratio, *CI* confidence interval

[a] No prescription for any hormone therapy

[b] At least two prescriptions for CE plus MPA within a 6-month period

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

[d] Last prescription for CE plus MPA was >6 months prior to the index date

[e] P for trend excluding never users = 0.071

[f] Denominator 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

[g] ORs were adjusted for duration of health care 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

Discussion

In this study, neither a history of use of EHT nor of CHT was associated with fatal breast cancer risk. Risk was also not related to recency or duration of use, except possibly for an increased risk with current long-term use of CHT. However, the number of women in this category of use was small.

These findings should be interpreted in the context of the limitations of this study. Only incomplete measures were available for some potential confounding variables. The earliest year in which data on receipt of hysterectomy were available was 1970. To estimate the impact of residual confounding by hysterectomy status, we conducted an analysis of ever use and recency of use that was restricted to the 33 % of the study population who were 35 years of age or younger in 1970 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). The ORs were similar in the whole versus the restricted sample. We also did not have information on

Table 5 Risk of fatal breast cancer in relation to use of progestogen

Regimens	Cases (n = 1,310)		Controls (n = 12,739)		OR[i]	95 % CI
	n	%[h]	n	%[h]		
Progestogen use						
Never[a]	911	87.6	8,500	86.0	1.0	Ref.
Ever[b]	129	12.4	1,384	14.0	0.9	0.8, 1.1
Number of prescriptions[e]						
2–11	77	7.4	816	8.3	0.9	0.7, 1.2
12–23	23	2.2	287	2.9	0.8	0.5, 1.2
24–47	20	1.9	214	2.2	1.0	0.6, 1.5
≥48	9	0.9	67	0.7	1.3	0.7, 2.7
Recency of progestogen use						
Never[a]	911	87.6	8,500	86.0	1.0	Ref.
Current[b,d]	54	5.2	532	5.4	1.0	0.7, 1.4
Number of prescriptions[f]						
2–11	20	1.9	215	2.2	0.9	0.6, 1.4
12–23	13	1.3	152	1.5	0.8	0.5, 1.5
24–47	13	1.3	131	1.3	1.0	0.6, 1.8
≥48	8	0.8	34	0.3	2.3	1.1, 5.1
Former[b,d]	75	7.2	852	8.6	0.9	0.7, 1.1
Time since last use[g]						
>6 months–<5 years	41	3.9	436	4.4	0.9	0.7, 1.3
≥5 years	34	3.3	416	4.2	0.8	0.6, 1.2

We excluded women (226 cases and 2,614 controls) who had ≥1 HT prescription but were not ever users of estrogen (≥2 prescriptions for estrogen within a 6-month period) or ever users of progestogen (≥2 prescriptions for progestogen within a 6-month period). A total of 1,310 cases and 12,739 controls remained for analysis

OR odds ratio, *CI* confidence interval

[a] No prescription for any hormone therapy

[b] At least two prescriptions for progestogen within a 6-month period

[c] 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)

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

[e] P for trend excluding never users = 0.444

[f] P for trend excluding never users = 0.157

[g] P for trend (time since last use) excluding never users = 0.440

[h] 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

[i] ORs were adjusted for duration of health care 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

receipt of bilateral oophorectomy, which has been associated with a decreased risk of breast cancer in women who receive the procedure before 40–45 years of age [13, 14]. 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 % in these two large US population-based studies) [13, 14].

Information on receipt of screening mammography may also have been incomplete. A biennial organized screening mammogram program was present in the whole province by 1993. Thus, by 1995, all women in 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 health care coverage since January 1993 (47 % of the study population). Again, the ORs were similar in the sample that was restricted on this basis.

Although a potential concern is uncontrolled confounding by variables that could not be ascertained from the databases, one prior study of fatal breast cancer risk in relation to use of CHT reported which variables, ascertained by in-person interview, met a specified criterion for confounding (>5 % change in the OR) [3]. Norman et al. [3] found that 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), there was no confounding by body mass index, family history of breast cancer, education, marital status, parity, alcohol consumption, smoking status, number of preexisting medical conditions, and use of oral contraceptives.

There are several strengths of this study, many of which arise from its population-based design. Women in the present study were likely taking HT around the onset of menopause, whereas in the WHI trials, only 17 % of women were randomized to CHT within 5 years of menopause [5], and only 20 % of women were randomized to EHT within 10 years of menopause [7]. The timing of HT initiation relative to menopause onset may be relevant to breast cancer incidence [15], although it is not known how it may be related to fatal breast cancer risk. Cases and controls also had relatively long periods of continuous prescription drug coverage prior to their index date (median = 17 years). Information on HT use was ascertained from prospectively recorded Drug Plan data and therefore was not influenced by case/control status or subject to recall errors. Selection bias is unlikely as all eligible cases identified from the databases were included, and the population registry made it possible to select controls from the underlying population from which the cases arose.

Other than the WHI randomized trial [5] and WHI observational study [6], only two studies [3, 16] 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 [16]. A decreased risk was observed in the cohort of CHT users (relative risk = 0.6; 95 % CI 0.4–0.9) [16]. However, the design of the study compromises the interpretation of the results. Women with prevalent breast cancer were excluded from the cohort of CHT users, but not from the comparison cohort [16]. Thus, in the absence of a true association one would expect a lower breast cancer mortality rate in the cohort of CHT users. In the other, mentioned above, by Norman et al. [3], current CHT use for ≥3 years was not associated with fatal breast cancer risk (OR = 0.94; 95 % CI 0.59–1.48).

In the WHI CHT trial, the increase in breast cancer incidence in women assigned to CHT was greater for advanced-stage disease than for localized disease [4]. CHT use is associated with increased breast density [17], and decreased sensitivity of mammography [18], which may delay tumor detection. Yet findings from observational studies, including the WHI observational study, tend to show that CHT was more strongly associated with the development of tumors that have a relatively good prognosis, specifically, those that are estrogen receptor positive [6, 19–22]. Some studies have also observed better case-fatality in women who took CHT prior to diagnosis [23, 24]. The magnitude of the increased risk of fatal breast cancer associated with CHT use in the WHI randomized trial [5] was not seen in other studies which controlled for potential confounders [3, 6]. It remains to be seen whether the disparity in the results across studies is due to chance or to the presence of residual confounding in the nonrandomized studies.

Although few studies have evaluated fatal breast cancer risk separately for EHT and CHT, several have evaluated HT use overall in relation to fatal breast cancer risk. Ten such studies were identified in a 2002 systematic review; HT use tended to be associated with a reduced risk (statistically significant in only two studies) or to not be associated with risk [25]. The exposures generally occurred before 1990 with some extension in some studies into the early 1990s [25]. The predominant form of HT during this time would have been EHT [26]. In the WHI EHT trial of women 50–79 years of age without a uterus, a 63 % decreased risk of fatal breast cancer (HR = 0.37; 95 % CI 0.13–0.91) was observed in women assigned to CE 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) [7]. 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 initially enrolled without breast cancer, who were then followed for breast cancer mortality, provided data on CHT use are available.

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Conflict of interest The authors declare that they have no conflict of interest.

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