ORIGINAL STUDY

Interaction between postmenopausal hormone therapy and diabetes on cataract

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Abstract

Objective: We investigated whether postmenopausal hormone therapy (HT) use interacts with diabetes, a risk factor for several age-related eye diseases.

Methods: A cross-sectional analysis of women involved in the Canadian Longitudinal Study on Aging was performed. The random sample comprised of 15,320 community-dwelling women between ages 45 and 85 years old sampled from areas adjacent to 11 data collection centers across Canada. Information on menopausal status and HT were collected by self-report. Data on diabetes and eye disease were obtained by self-report of a physician diagnosis. Multivariable logistic regression was used.

Results: After adjusting for demographic, lifestyle, and health variables, a multiplicative interaction was identified such that HT use for 10 years or more was associated with a much higher odds of a report of cataract in women with type 2 diabetes (odds ratio = 2.44, 95% confidence interval 1.49, 3.99) but not in long-term HT users with no diabetes (odds ratio = 1.03, 95% confidence interval 0.87, 1.21) (interaction term *P* value = 0.013). HT use was not associated with glaucoma or macular degeneration.

Conclusions: Long-term HT use and type 2 diabetes interact in their relationship with cataract. This novel finding should be confirmed. If confirmed, women with type 2 diabetes should be informed that long-term HT use increases their risk of cataract.

Key Words: Cataract – Canadian Longitudinal Study on Aging – Diabetes – Glaucoma – Hormone therapy.

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Much research has been done on whether there is a relationship between postmenopausal hormone therapy (HT) and age-related eye disease but little consensus exists. Several studies found a protective association between HT use and cataract.[1-4] Some studies, particularly more recent and longitudinal ones, have, however, found either no association or a harmful association between HT use and cataract or cataract surgery.[5-9] A lack of consensus also exists for age-related macular degeneration with some studies finding a protective effect of HT use while others report no association.[10-12] Similarly, several studies have reported a protective association between HT use and glaucoma or intraocular pressure[13-16] but not all[12] or only in certain subgroups.[17]

The frequency of use and reasons for taking HT have changed over the last 20 years since the publication of the principal results from the Women's Health Initiative trial in 2002.[18] That trial found that HT use could increase a woman's risk of certain cancers, heart disease, and stroke, but that HT could be used safely for the short-term relief of menopausal symptoms. Prescriptions for HT decreased sharply upon the publication of these results.[19]

Many reasons could exist regarding why results on the relationship between HT and age-related eye disease are so inconsistent. One reason could be due to undetected interaction in prior studies. Our hypothesis was that HT may act differently in the eye depending on the presence of diabetes, a consistent risk factor for cataract and glaucoma and an inconsistent risk factor for age-related macular degeneration, and which has increased in prevalence over the last 20 years.[20] Most studies are not large enough to have the statistical power to examine interaction. The Canadian Longitudinal Study on Aging is a large, national study of 15,320 women that has sufficient power to examine the interaction between HT and diabetes.

METHODS

Study design and sample

Baseline data from the Comprehensive Cohort of the Canadian Longitudinal Study on Aging (CLSA), which include 15,320 community-dwelling women aged 45 to 85 years, were used for this analysis.[21] Exclusion criteria included living in an institution or on a First Nations reserve or settlement, being a full-time member of the Canadian Armed Forces, being unable to speak French or English, and having overt cognitive impairment (unable to understand the study or answer basic questions about themselves). The Comprehensive Cohort participants underwent both a home interview and a face-to-face interview and exam at 1 of 11 Data Collection Sites (DCS) between 2012 and 2015.

The comprehensive cohort participants represent a random sample of community-dwelling adults within a 25 to 50 km radius of 1 of the 11 DCS (Victoria, Vancouver, Surrey, Calgary, Winnipeg, Hamilton, Ottawa, Montreal, Sherbrooke, Halifax, St. John's) in 7 Canadian provinces recruited from either provincial health databases or random digit dialing. Each randomly chosen eligible person recruited from a provincial health registry was sent a consent form to sign and return. For those recruited through random digit dialing, a random sample of landline telephone numbers was selected for a given geographic area. Once a call was answered, eligibility was established, and consent was obtained. Stratified sampling was used to ensure adequate representation of various demographic groups. Strata within a province were defined according to age group, sex, and distance from the DCS. Sampling weights were developed to ensure generalizability of the samples and to control for nonresponse bias. Research ethics boards in seven provinces approved the CLSA project. In addition, the Research Ethics Board of the Ottawa Hospital Research Network approved this specific

work. Research followed the tenets of the Declaration of Helsinki. Written informed consent was obtained from all participants. The CLSA study design and methods have been previously described by Raina et al[21] elsewhere.

Age-related eye disease

Participants were asked if they had ever been told by a doctor that they had the following eye diseases: cataract, glaucoma, or macular degeneration. Cataract, glaucoma, and macular degeneration were deemed present if a participant answered ''yes'' to the former question.

Menopause and postmenopausal hormone therapy variables

Menopausal status was assessed by the following question: ''Have you gone through menopause, meaning that your menstrual periods stopped for at least one year and did not restart?'' Women who answered ''yes'' were classified as naturally postmenopausal.[22] Individual age at natural menopause was reported in response to the following question: ''How old were you when your menstrual periods stopped for at least one year and did not re-start?'' Answers were recorded as age in years. Age at natural menopause and menopause type were computed into a new categorical variable that encompassed the following groups: women with premature menopause (menopause occurred <40 y), early natural menopause (menopause occurred naturally between ages 40 and 44 y), normal natural menopause (menopause occurred naturally between ages 45 and 54 y), late natural menopause (menopause occurred naturally ≥55 y),[23] and those who reported hysterectomy. To avoid small numbers, categories for premature menopause and early natural menopause were collapsed and labeled as having early natural menopause.

Ever use of postmenopausal HT was captured by the following question: ''Have you ever used any hormone replacement therapy, sometimes called HRT, for any reason?'' A new HT use variable was created using the following variables: age at the time of interview, duration of HT use, and age at initiation of HT. Women using HT when interviewed were defined as current users, women who had used HT in the past were labeled as past users, whereas those who had never taken HT were labeled as never users. Duration of HT use was categorized as never, less than 10, or 10 years or more. This cut off was chosen because it gives a fairly equal distribution among the different categories.

Covariates

Sociodemographic variables included age at time of interview, province of residence, and ethnicity classified as white versus non-white, where non-white included Aboriginal, South Asian, Chinese, Hispanic, Arab, and Black individuals. Additional sociodemographic information included the self-report of the highest education level, marital status, and annual household income in Canadian dollars. Participants were asked whether they had ever smoked at least 100 cigarettes and if they still smoked. Participants reported

whether a doctor had diagnosed them with diabetes, borderline diabetes, or high blood sugar. Those who answered affirmatively were asked the type of diabetes with choices being type 1, type 2, or neither. Participants were asked if they had ever been diagnosed with hypertension or high blood pressure. Seated, resting blood pressure was also measured using a random-zero sphygmomanometer; the average of the last two out of three readings was used. Hypertension was defined as self-reported diagnosis of hypertension, or a systolic blood pressure greater than 140 mm Hg or diastolic blood pressure greater than 90 mm Hg. Height and weight were measured and used to calculate body mass index in kg/m^2.

Statistical analyses

Our primary outcome was cataract given the majority of HT research is with this outcome.[1] Glaucoma and macular degeneration were secondary outcomes. Characteristics are presented as percentages for categorical variables and mean $\pm$ SE for continuous variables. Because age is a major risk factor for all outcome variables, age-adjusted logistic regression analyses were first done to examine relationships between HT use and each outcome. Multiple logistic regression was then used to analyze the association between HT use and each outcome after adjustment for sociodemographic, lifestyle, and clinical covariates. Potential confounders were chosen because they were thought to be important to the outcomes based on previous literature.[24-27] Interaction was assessed in two ways: by stratification to qualitatively assess homogeneity of effects and, if present, by the inclusion of an interaction term to test for statistical significance. Odds ratios (OR) and 95% confidence intervals (CIs) were presented. Statistical significance for all analyses was defined as $P < 0.05$. All analyses were conducted using Stata version 15.0 (StataCorp, College Station, TX). Sample weight and strata information that account for the complex study design were used.

Sensitivity analyses were done excluding the following groups to determine whether the results changed: (1) women with a previous diagnosis of breast, ovarian, or endometrial cancers ($n = 1,180$), these conditions can mask the true age at menopause; (2) women who used HT before the reported onset of menopause ($n = 740$), HT can mask the true age at menopause; (3) women who reported an age of more than 62 years ($n = 72$) at natural menopause, these values may be erroneous.

RESULTS

Some women were excluded from the analysis. Premenopausal women were excluded from the analysis since we were focusing on postmenopausal HT use ($n = 2,557$). Women who did not know or refused to report if they had undergone menopause ($<1\%$, $n = 103$) were also excluded. After these exclusions, 12,660 women remained for analysis. Women are compared by their use of HT in Table 1. There were 186 (1.5%) women who did not report data on HT use. Long-term users of HT were older than nonusers. Other large differences were that long-term HT users were more likely to be white, to be living

TABLE 1. *Comparison of women by duration of use of menopausal hormone therapy*

N = 12,474	No HT Mean (SE) or % n = 7,156	HT<10 y Mean (SE) or % n = 3,401	HT ≥10 y Mean (SE) or % n = 1,917
Age, y (n = 12,474)	61.3 (0.1)	63.7 (0.2)	69.7 (0.2)
Ethnicity			
White (n = 11,881)	93.6	95.9	97.2
Non-white (n = 593)	6.4	4.1	2.8
Marital status			
With partner (n = 7,138)	67.4	69.9	59.8
No partner (n = 5,333)	32.6	30.1	40.2
Education			
More than bachelor's (n = 2,098)	18.0	17.5	13.9
Bachelor's degree (n = 2,669)	23.0	22.5	16.9
Less than bachelor's (n = 7,684)	59.1	60.1	69.2
Household income			
≥$100,000 (n = 3,034)	32.1	29.7	18.1
$50,000-$100,000 (n = 4,033)	32.4	34.3	33.3
$20,000-$50,000 (n = 3,443)	22.5	22.8	31.4
<$20,000 (n = 895)	5.5	5.0	8.0
Refused/do not know (n = 1,069)	7.5	8.2	9.2
Menopausal age and type			
Early (n = 1,156)	8.2	10.6	15.7
Normal (n = 6,931)	64.5	57.3	35.3
Late (n = 1,595)	12.7	12.0	7.3
Surgical (n = 2,437)	14.6	20.1	41.7
Smoking			
Never (n = 6,139)	50.7	47.7	46.3
Former (n = 5,254)	39.3	45.0	47.0
Current (n = 1,038)	10.0	7.3	6.7
Body mass index, (n = 12,413)	28.1 (0.1)	27.5 (0.1)	27.5 (0.1)
Doctor visit in last year			
No (n = 900)	10.0	5.6	4.2
Yes (n = 11,020)	90.0	94.4	95.8
High blood pressure			
No (n = 7,615)	67.1	63.5	53.2
Yes (n = 4,797)	32.9	36.5	46.8
Diabetes			
No (n = 10,334)	84.3	85.1	83.8
Type 1 (n = 66)	0.6	0.6	0.3
Type 2 (n = 1,066)	7.9	7.4	9.3
Neither type 1 or 2 (n = 871)	7.1	7.0	6.7

HT, hormone therapy; SE, standard error.

with a partner, to have lower education and household income, to have surgical or early menopause, to have visited the doctor in the last year, and to report high blood pressure.

Women are compared by their self-report of a diagnosis of cataract in Table 2. Women with a report of cataract were older than those without. Other large differences included that women living with a partner, with less education and household income, who had late or surgical menopause, who visited a doctor in the last year, or who had high blood pressure or type 1 or 2 diabetes were more likely to report cataract.

After age adjustment, HT duration was associated with a report of cataract with women who used HT for less than 10 years (OR = 1.18, 95% CI = 1.05, 1.32) and having used HT for 10 years or more (OR = 1.16, 95% CI = 1.01, 1.32) being statistically significantly more likely to report cataract than never HT users. Also, women who were past HT users were 1.20 times statistically significantly more likely to report cataract (95% CI = 1.07-1.34) while current use was not associated. Women with a surgical menopause were more

TABLE 2. *Comparison of women by report of cataract*

	No cataract % or mean (SE) n = 7,767	Report of cataract % or mean (SE) n = 4,658
Age	59.7 (0.1)	70.6 (0.1)
Ethnicity		
White	67.8	32.1
Non-white	70.9	29.1
Marital status		
With partner	73.0	27.0
No partner	58.0	42.1
Education		
More than bachelor's	72.5	27.5
Bachelor's degree	72.7	27.3
Less than bachelor's	65.2	34.8
Household income		
≥$100,000	81.8	18.2
$50,000-$100,000	68.9	31.2
$20,000-$50,000	57.0	43.0
<$20,000	54.6	45.4
Refused/do not know	56.9	43.1
Menopausal age and type		
Early	71.7	28.3
Normal	69.6	30.4
Late	62.9	37.1
Surgical	62.1	38.0
Smoking		
Never	67.3	32.7
Former	66.9	33.1
Current	78.4	21.6
Body mass index, kg/m^2	27.7 (0.1)	28.1 (0.1)
Doctor visit in last year		
No	79.1	20.9
Yes	67.2	32.9
High blood pressure		
No	74.3	25.7
Yes	57.0	43.0
Diabetes		
No	70.2	29.8
Type 1	56.7	43.3
Type 2	51.7	48.4
Neither type 1 or 2	64.5	35.5

SE, standard error.

likely to report having cataract (OR = 1.17, 95% CI = 1.03, 1.34) compared to women with a natural menopause between ages 45 and 54 years.

The multivariable-adjusted associations between HT duration, menopausal age and type, and cataract are presented in Table 3. Women who used HT for less than 10 years had a significantly greater odds of cataract (OR = 1.23, 95% CI = 1.09, 1.38) compared to women who never used HT, whereas those who used for 10 or more years had a borderline association (OR = 1.15, 95% CI 0.99, 1.33). Surgical menopause was not associated with cataract after full adjustment. Other variables statistically significantly associated with cataract were older age, non-white ethnicity, not living with a partner, former smoking, type 1 diabetes, type 2 diabetes, diabetes that is neither type 1 or type 2, and body mass index ($P < 0.05$).

A multiplicative interaction was identified (Table 4, Fig. 1) such that HT duration of 10 or more years was associated with a much higher odds of a report of cataract in women with type 2 diabetes (OR = 2.44, 95% CI 1.49, 3.99) but not in women with no diabetes (OR = 1.03, 95% CI 0.87, 1.21) (interaction term P value = 0.013). There was no interaction for use less

TABLE 3. *Multiple regression analysis of hormone therapy, menopausal age and type, and cataract*

	Number of cases	Report of cataract adjusted odds ratio[a]	95% CI
HT duration			
Never	2,225	1.00	Reference
<10 y	1,301	1.23	1.09, 1.38
≥10 y	1,028	1.15	0.99, 1.33
Menopausal age and type			
Early	2,303	1.01	0.84, 1.22
Normal	420	1.00	Reference
Late	629	0.98	0.85, 1.14
Surgical	1,104	1.08	0.94, 1.25
Age, per 1 y	4,658	1.17	1.16, 1.18
Ethnicity			
White	4,450	1.00	Reference
Non-white	208	1.33	1.04, 1.70
Marital status			
With partner	2,195	1.00	Reference
No partner	2,463	1.13	1.01, 1.27
Smoking			
Never	2,319	1.00	Reference
Former	2,035	1.11	1.00, 1.24
Current	287	1.14	0.92, 1.41
Diabetes			
None	3,631	1.00	Reference
Type 1	34	2.71	1.39, 5.29
Type 2	560	1.70	1.41, 2.04
Neither type 1 or 2	363	1.24	1.02, 1.51
Body mass index, per 1 kg/m^2	4,658	1.01	1.00, 1.02

CI, confidence interval; HT, hormone therapy.
[a]Adjusted for all variables in table in addition to education, household income, visit to a doctor in the last year, high blood pressure, and province.

than 10 years as both ORs in those with and without type 2 diabetes were around 1.2. There was no interaction with diabetes that was neither type 1 nor type 2 and we did not have adequate numbers of people with type 1 diabetes (n = 66) to examine interaction specifically in that group.

In addition to HT duration, both past (OR = 1.18, 95% CI 1.06, 1.33) and current use of HT (OR = 1.23, 95% CI 1.01, 1.50) were associated with cataract after multivariable

TABLE 4. *Stratified analysis of hormone therapy and cataract by type 2 diabetes status*

Strata	Number of cases	HT duration	Report of cataract OR[a]	95% CI
No diabetes n = 10,137				
	1,704	Never	1.00	Reference
	1,038	<10 y	1.21	1.07, 1.39
	806	≥10 y	1.03	0.87, 1.21
Type 2 diabetes n = 1,052				
	281	Never	1.00	Reference
	142	<10 y	1.15	0.78, 1.71
	122	≥10 y	2.44[b]	1.49, 3.99

CI, confidence interval; HT, hormone therapy; OR, odds ratio.
[a]Also adjusted for age at menopause, age, ethnicity, education, household income, marital status, smoking, seen doctor in last year, high blood pressure, BMI, and province.
[b]Interaction term P value for type 2 diabetes and HT duration ≥10 Years = 0.013.
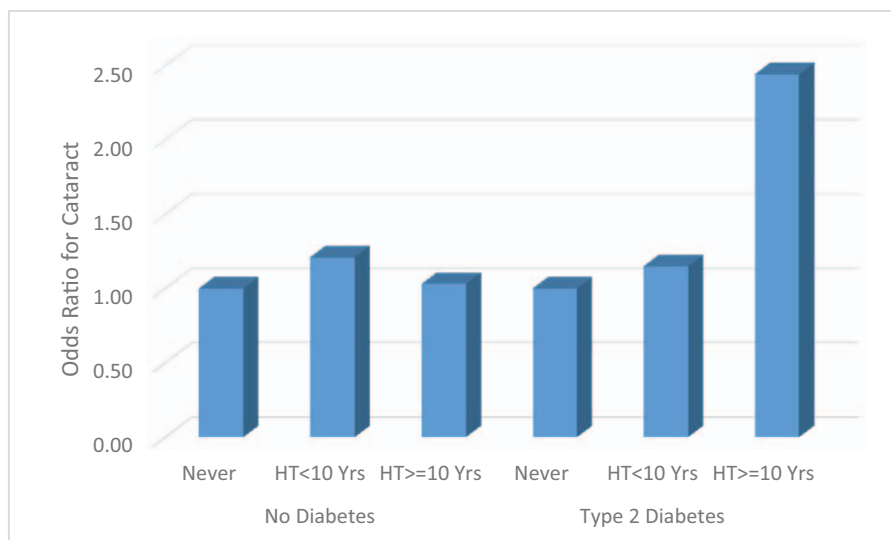
FIG. 1. Interaction between hormone therapy duration and type 2 diabetes in their relationship with report of cataract. Long-term hormone therapy users with type 2 diabetes have a much higher odds of cataract. HT, hormone therapy.

adjustment. No interactions with diabetes were, however, found. There were no statistically significant associations between HT duration or HT use with our secondary outcomes: glaucoma and macular degeneration. HT use for less than 10 years (OR = 1.05, 95% CI 0.85, 1.30) and HT use of 10 years or more (OR = 1.07, 95% CI 0.83, 1.37) were not associated with glaucoma. HT use of less than 10 years (OR = 1.20, 95% CI 0.96, 1.50) and HT use of 10 years or more (OR = 1.01, 95% CI 0.79, 1.30) were also not significantly associated with macular degeneration. No interactions were detected.

In sensitivity analyses, results were essentially the same after the exclusion of women with breast, endometrial, and ovarian cancers (n = 1,180), who reported using HT before the onset of menopause (n = 740), or who reported implausible ages at natural menopause (n = 72).

DISCUSSION

In this large, representative sample of Canadian women, HT use in general was weakly associated with the report of cataract. This is, however, the first article to report an interaction between long-term HT use and type 2 diabetes in their relationship with cataract. Long-term HT users with type 2 diabetes had a 2.44-fold higher odds of reporting cataract than those who never used HT but had type 2 diabetes. This finding is important because results from the Women's Health Initiative trial and others have indicated that HT use could reduce the risk of developing type 2 diabetes.[18,28,29] Our results indicate that having type 2 diabetes and using HT for a long period of time could potentially harm the lens of the eye. Other researchers should attempt to confirm this finding and to examine whether HT use interacts with type 2 diabetes in relation to other health conditions besides cataract. Although cataract is a treatable condition, it is nonetheless associated with adverse outcomes like motor vehicle collision and depression.[30,31]

It is unknown why HT use could be harmful to the lens, especially in those with type 2 diabetes. Estrogen and progesterone receptors are present throughout the eye.[32,33] One possible mechanism could be through inflammatory factors such as C-reactive protein. Some studies have found that both HT use[34,35] and type 2 diabetes[36] can increase levels of inflammatory factors such as C-reactive protein, which may be related to cataract.[37]

Although most prior studies have found HT use to be related to a lower odds of cataract,[1-4] a few have reported findings similar to ours that HT use is related to a higher odds of cataract or cataract surgery.[5,6,23] One study by Lindblad et al[5] found very similar results as ours. In a prospective study of more than 30,000 postmenopausal women in Sweden, HT usage over 10 years was associated with a higher risk of cataract extraction (relative risk = 1.20, 95% CI 1.06, 1.36) after multivariable adjustment. Ever using HT was also associated with cataract extraction in the Age-Related Eye Disease Study cohort study (hazard ratio = 1.22, 95% CI 1.04, 1.43).[23] In a cohort of 14,337 Chinese women, Tian et al[6] also found that women who had ever used HT had a higher odds of having cataract (OR = 1.61, 95% CI 1.05, 24.7).

A strength of this research is the use of a large, representative, population-based sample of women from across Canada, which allowed us to have adequate statistical power to detect modestly sized interaction ORs. Another strength is the abundant data available to adjust for confounding. There are some limitations to our research, however. First, eye disease was self-reported rather than ascertained through an ophthalmological examination. Second, information on HT and menopause were collected by self-report and we did not have information on the type of HT, the delivery mode of HT, age of menarche, or prior oral contraception use. HT preparations can vary in their use of estrogen, progestin, and selective estrogen receptor modulators. Furthermore, there are different types of estrogens and

progestins in the various preparations which may lead to different potencies and mechanisms of action. These different preparations may have varying effects on the eye.[14,38] Prior associations between oral contraception use and glaucoma[39] and cataract[4,40] have been reported, although null findings have been reported as well.[41] Third, the cross-sectional nature of the study does not allow us to disentangle the temporality of HT use, type 2 diabetes, and the onset of eye disease.

CONCLUSION

In conclusion, our results indicated that women who are long-term users of HT with type 2 diabetes had a 2.44 higher odds of cataract than women who never used HT with type 2 diabetes. These findings should be confirmed by prospective studies with longitudinal data on diabetes, HT use, and cataract. If confirmed, women with type 2 diabetes taking HT for 10 or more years should be counseled that they may be at a higher risk of cataract.

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