

Postmenopausal hormone replacement therapy and risk of acute pancreatitis: a prospective cohort study

Viktor Oskarsson MD, Nicola Orsini PhD, Omid Sadr-Azodi MD PhD, Alicja Wolk DMSc

ABSTRACT

Background: Several case reports have suggested that women's use of exogenous sex hormones is associated with acute pancreatitis; however, relevant epidemiologic data are sparse. We examined the association between postmenopausal hormone replacement therapy and risk of acute pancreatitis.

Methods: We conducted a prospective study involving 31 494 postmenopausal women (aged 48–83 yr) from the population-based Swedish Mammography Cohort. Participants completed a baseline questionnaire in 1997 assessing their use of hormone replacement therapy. We linked the cohort to the hospital-based Swedish National Patient Register to determine hospital admissions for acute pancreatitis through 2010. Relative risks (RRs) were calculated using Cox proportional hazard models.

Results: Over a total follow-up of 389 456 person-years, we identified 237 cases of inci-

dent acute pancreatitis. The age-standardized incidence rates per 100 000 person-years were 71 cases among women who had ever used hormone replacement therapy and 52 cases among women who had never used such hormones. Among ever users of hormone replacement therapy, the multivariable-adjusted RR of acute pancreatitis was 1.57 (95% confidence interval [CI] 1.20–2.05) compared with never users. The risk did not differ by current or past use, but it seemed to be higher among women who used systemic therapy (RR 1.92, 95% CI 1.38–2.66) and among those with duration of therapy of more than 10 years (RR 1.87, 95% CI 1.11–3.17).

Interpretation: Use of postmenopausal hormone replacement therapy was associated with increased risk of acute pancreatitis. Physicians should consider this potential increase in risk when prescribing such therapy.

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Correspondence to: Viktor Oskarsson, viktor.oskarsson@ki.se

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The clinical spectrum of acute pancreatitis varies from a mild, self-limiting illness to a severe or fatal disease.¹ Besides well-established risk factors such as alcohol abuse and gallstone disease,² the use of certain prescription drugs has been suspected as a cause of acute pancreatitis (as reviewed by Trivedi and Pitchumoni³ and by Nitsche and associates⁴). Hormone replacement therapy, which is widely used to relieve postmenopausal symptoms, may, according to several case reports,^{5–10} increase the risk of acute pancreatitis. Such an association has also been suggested for oral contraceptives.^{11–14} However, epidemiologic data on the association between use of exogenous sex hormones and risk of acute pancreatitis are sparse. One case-control study from Denmark showed no clear increase in risk with short-term (≤ 1 yr) use of postmenopausal hormone replacement therapy.¹⁵ Whether a longer duration of therapy increases the risk of acute pancreatitis has not been studied.

We sought to evaluate prospectively the association between hormone replacement therapy and risk of acute pancreatitis in a cohort of postmenopausal women.

Methods

Participants

The Swedish Mammography Cohort is a population-based prospective study conducted in central Sweden. From 1987 to 1990, all women born between 1914 and 1948 and living in Västmanland and Uppsala counties ($n = 90\,303$) were invited to participate in a mammography screening program and to complete a dietary questionnaire. Of these, 66 651 women (74%) returned a completed questionnaire. In 1997, a second questionnaire was sent to all surviving women ($n = 56\,030$), with questions on such lifestyle factors as diet, alcohol intake and smoking status, as well as questions on medications and medical history; here, the response rate was 70% ($n = 39\,227$).

For the current study, only those who completed the second questionnaire (in 1997) were eligible, given that hormone replacement therapy was not mentioned in the first questionnaire. Of these, we excluded women with an incorrect personal identity number, those with a history of cancer (except nonmelanoma skin cancer) or exocrine pancreatic disease, and those who, according to the questionnaire, were premenopausal (as previously defined¹⁶) or had missing information on hormone replacement therapy.

Ethics approval was granted by the Regional Ethical Review Board at Karolinska Institutet (Stockholm, Sweden), and return of a completed questionnaire was considered to imply informed consent.

Assessment of hormone replacement therapy

The questionnaire asked participants to report their use of hormone replacement therapy, whether such therapy was currently in progress, the duration of use and the indication for use (hot flashes or vaginal dryness, referred to hereafter as “systemic therapy” and “local therapy,” respectively). Self-reported use of hormone replacement therapy has been shown to be highly comparable with prescription data ($\kappa = 0.90$).¹⁷

Assessment of covariables

From the questionnaire, we obtained information on age at menopause, age at menarche, use of oral contraceptives, parity, education, smoking status, body mass index (BMI), waist circumference, alcohol intake and vegetable consumption. We obtained baseline history of cholelithiasis and diabetes mellitus from the Swedish National Patient Register and the Swedish National Diabetes Register, respectively. Additional information on diabetes was acquired from the questionnaire.

Outcome measure

We identified cases of incident acute pancreatitis (International Statistical Classification of Diseases and Related Health Problems, 10th revision [ICD-10] code K85) between Sept. 15, 1997, and Dec. 31, 2010, by linkage to the Swedish National Patient Register. We acquired information on other exocrine pancreatic diseases (ICD-10 codes K86–K87), cholelithiasis (ICD-10 code K80) and gallbladder surgery (Nordic Medico-Statistical Committee Classification of Surgical Procedures codes JKA20, JKA21, JKE00, JKE02, JKE12, JKE18 or JKB30) from the same register. Finally, we obtained information on pancreatic cancer (ICD-

10 code C25) and death from the Swedish National Cancer Registry and the Swedish National Cause of Death Register, respectively.

The Swedish National Patient Register covers nearly all hospital admissions in Sweden¹⁸ and was recently shown to have a positive predictive value of 98% (83% with strict criteria) for a recorded diagnosis of acute pancreatitis when validated by chart review.¹⁹ The register does not cover patients' contacts or visits in primary health care.

Statistical analysis

We calculated person-years from Sept. 15, 1997, to the date of either acute pancreatitis, other exocrine pancreatic diseases (including cancer), death or Dec. 31, 2010, whichever occurred first.

We used Cox proportional hazard models, with age as the time scale,²⁰ to estimate hazard ratios (referred to hereafter as relative risk [RR]) for acute pancreatitis associated with use of hormone replacement therapy. We classified participants as never users or ever users of hormone replacement therapy. We further classified ever users according to current use (no or yes), duration of use (< 5, 5–10 or > 10 yr) and type of therapy (local or systemic). In the analysis of type of therapy, we excluded women who reported having ever used both types of therapy. Furthermore, we modelled the association between duration of use and risk of acute pancreatitis using restricted cubic splines with knots at 10%, 50% and 90% of the distribution among ever users.²¹ We obtained a *p* value against the hypothesis of a linear association by testing the coefficient of the second spline transformation equal to 0. We tested the proportional hazards assumption (by scaled Schoenfeld residuals²²) and observed no significant deviations.

Multivariable analyses were adjusted for age at menopause (< 51 or ≥ 51 yr; median 51 yr), education (primary school, high school or university), smoking status (never, past [as < 10 or ≥ 10 pack-years] or current [as < 20 or ≥ 20 pack-years]), level of adiposity (BMI < 25, 25–29 or ≥ 30 or waist circumference < 80, 80–87 or ≥ 88 cm, depending on the model), alcohol intake (average [quartiles of grams per day] or per occasion [< 1, 1, 2–3 or ≥ 4 drinks, where 1 drink = 12 g of alcohol], depending on the model) and vegetable consumption (quartiles of servings per day). For each covariable, if necessary, we included an indicator level for missing data. We performed sensitivity analyses on complete case data and on multiple imputed data (30 datasets were imputed using chained equations).²³

We considered gallstone disease to be a mediator of the association of interest; thus, we

adjusted for baseline history of cholelithiasis (no or yes) only in a sensitivity analysis. We also performed analyses using non-gallstone-related acute pancreatitis as the outcome (defined as all K85 codes, except K85.1, without concurrent cholelithiasis or gallbladder surgery ≤ 3 months after the index episode²⁴).

We performed several sensitivity analyses to account for changes in use of hormone replacement therapy during the follow-up period. First, we censored the analysis after 2003 because of the expected decrease in use following publication of findings from the Women's Health Initiative.²⁵ Second, we restricted the analysis to women older than 60 years, because women not taking hormone replacement therapy by that age would be unlikely to initiate such treatment later. Finally, we restricted the analysis of duration of use to past users, because their reported duration of use was unlikely to have changed.

We performed all analyses with Stata 12.1 (StataCorp, Tex.). Statistical tests were 2-sided with a 0.05 significance level.

Results

Of the 39 227 women who completed the questionnaire in 1997, a total of 31 494 postmenopausal women were included in the analysis (Figure 1). During the follow-up period (1997–2010; 389 456 person-years), we identified 237 cases of incident acute pancreatitis. The period prevalence of cholelithiasis was higher among those in whom acute pancreatitis occurred than among those without the disease (133/237 [56%] v. 4142/31 257 [13%]).

At baseline, 13 113 (42%) of the women were current users of hormone replacement therapy, and 3660 (12%) were past users. Among current users, 6795 (52%) used systemic therapy, 4148 (32%) used local therapy and 2170 (17%) used both therapies. Past and current users were more likely to be well educated than never users (Table 1). In addition, compared with never users and past users, current users were younger, had lower BMI, were less likely to be current smokers and tended to have a higher alcohol intake. Past users were more likely to have a history of cholelithiasis.

We observed a positive association between use of hormone replacement therapy and risk of acute pancreatitis (Table 2). Incidence rates, directly standardized to the cohort's age distribution, were 71 cases per 100 000 person-years among women who had ever used hormone replacement therapy and 52 cases per 100 000 person-years among women who had never used such hormones. Ever users had a multi-

variable-adjusted RR of acute pancreatitis of 1.57 (95% confidence interval [CI] 1.20–2.05) compared with never users. The overall fraction of missing data was 21% in the multivariable model. Results based on complete case data (RR 1.64, 95% CI 1.22–2.20) and multiple imputed data (RR 1.51, 95% CI 1.16–1.97) were similar. Controlling for waist circumference²⁶ and amount of alcohol consumed per occasion,²⁷ rather than BMI and average alcohol intake, did not materially change the results (RR 1.53, 95% CI 1.17–2.01), nor were the results altered by further adjustment for age at

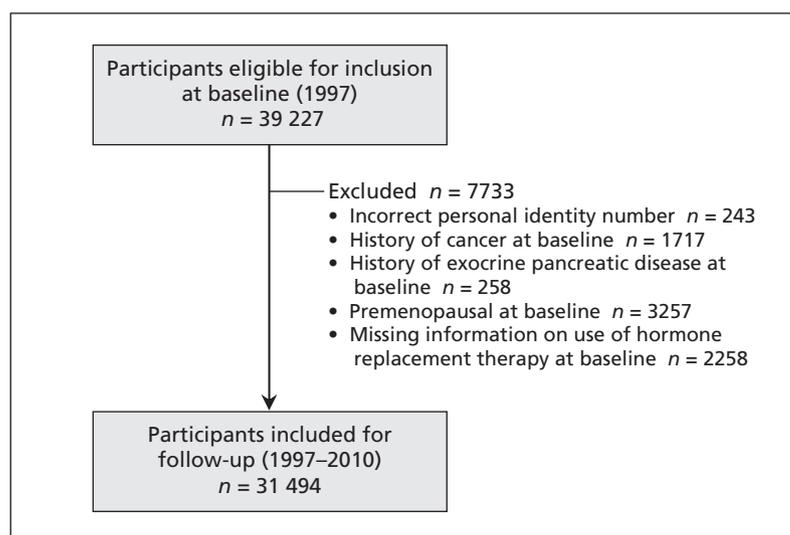


Figure 1: Flow chart for participants in the Swedish Mammography Cohort whose data were used in an analysis of acute pancreatitis in relation to postmenopausal hormone replacement therapy.

Table 1: Characteristics of 31 494 postmenopausal women in the Swedish Mammography Cohort, by use of HRT at baseline (1997)

Characteristic*†	Use of HRT		
	Never	Past	Current
No. of women	14 721	3 660	13 113
Age, yr, mean \pm SD	64 \pm 9	64 \pm 9	60 \pm 8
Age at menopause ≥ 51 yr, %	48	47	46
University education, %	14	18	22
Current smoker, %	21	21	17
BMI ≥ 30 , %	12	12	9
Alcohol intake, g/d, mean	5	5	6
Vegetable consumption, servings/d, mean	3	3	3
History of cholelithiasis, %	9	11	9

Note: BMI = body mass index, HRT = hormone replacement therapy, SD = standard deviation.
*Values (except age) are standardized to the age distribution (≤ 51 , 52–56, 57–61, 62–66, 67–71, 72–76, and ≥ 77 yr) of the study population.

†Means and percentages were calculated for women with known values. Data were missing on age at menopause for 4 415 women, on education for 193, on BMI for 591, on smoking for 611, on alcohol intake for 1219 and on vegetable consumption for 237.

menarche (< 13, 13 or > 13 yr), parity (0, 1–2 or > 2), oral contraceptive use (never or ever) and history of diabetes (no or yes) (RR 1.58, 95% CI 1.21–2.08). The risk of acute pancreatitis did not differ by current or past use of hormone replacement therapy but seemed to be higher among women who used systemic therapy (RR 1.92, 95% CI 1.38–2.66) and among

those with duration of therapy of more than 10 years (RR 1.87, 95% CI 1.11–3.17) (Table 2). Among women who had used systemic therapy for more than 10 years ($n = 945$, including 14 cases of acute pancreatitis), the RR was 2.44 (95% CI 1.38–4.31). The restricted cubic spline analysis yielded no strong evidence against the hypothesis of a linear association between dura-

Table 2: Risk of acute pancreatitis associated with use of postmenopausal HRT (1997–2010)

HRT	No. of women	No. of cases/person-years	Age-adjusted RR (95% CI)	Multivariable RR (95% CI)*
Never users	14 721	98/178 430	1.00 (ref)	1.00 (ref)
Ever users	16 773	139/211 026	1.41 (1.08–1.83)	1.57 (1.20–2.05)
Current use				
No	3 660	36/45 144	1.49 (1.01–2.18)	1.58 (1.07–2.32)
Yes	13 113	103/165 882	1.38 (1.04–1.83)	1.56 (1.17–2.09)
Duration of use, y†				
< 5	5 937	46/75 238	1.45 (1.01–2.07)	1.59 (1.10–2.29)
5–10	3 463	32/43 797	1.53 (1.02–2.29)	1.73 (1.14–2.61)
>10	1 372	17/16 648	1.62 (0.97–2.71)	1.87 (1.11–3.17)
Type of therapy used‡				
Local	4 307	38/53 099	1.21 (0.83–1.76)	1.37 (0.94–2.00)
Systemic	9 115	75/116 419	1.66 (1.21–2.28)	1.92 (1.38–2.66)

Note: CI = confidence interval, HRT = hormone replacement therapy, ref = reference group, RR = relative risk.
 *Derived from a Cox proportional hazards model with age as time scale and with adjustment for age at menopause (< 51 or ≥ 51 yr), education (less than high school, high school or university), smoking status (never, past [as < 10 or ≥ 10 pack-years] or current [as < 20 or ≥ 20 pack-years]), body mass index (< 25, 25–29 or ≥ 30), alcohol intake (quartiles [g/d]) and vegetable consumption (quartiles [servings/d]).
 †Sum of categories is less than the total of 16 773 women who were ever users because data on duration of use were missing for 6001 women (including 44 cases).
 ‡Categories refer to women who were exposed exclusively to either systemic therapy or local therapy. In addition, 3351 women (including 26 cases) reported having ever used both types of therapy.

Table 3: Sensitivity analyses for risk of acute pancreatitis associated with use of postmenopausal HRT

Sensitivity analysis	No. of women	No. of cases/person-years	Multivariable RR (95% CI)*
Follow-up until end of 2003			
Never user	14 721	43/89 916	1.00 (ref)
Ever user	16 773	57/103 756	1.52 (1.00–2.29)
Women aged > 60 yr			
Never user	9 080	76/105 441	1.00 (ref)
Ever user	7 362	78/88 606	1.42 (1.03–1.97)
Women not currently using HRT†			
Never user	14 721	98/178 430	1.00 (ref)
Past user with duration < 5 y	2 124	14/26 440	1.16 (0.66–2.04)
Past user with duration ≥ 5 y	918	10/11 305	1.62 (0.84–3.13)

Note: CI = confidence interval, HRT = hormone replacement therapy, ref = reference group, RR = relative risk.
 *Adjusted for the same covariables as the multivariable model (Table 2): age at menopause (< 51 or ≥ 51 yr), education (less than high school, high school or university), smoking status (never, past [as < 10 or ≥ 10 pack-years] or current [as < 20 or ≥ 20 pack-years]), body mass index (< 25, 25–29 or ≥ 30), alcohol intake (quartiles [g/d]) and vegetable consumption (quartiles [servings/d]).
 †Sum of categories is less than the total number of women not currently using HRT because data on duration of use were missing for 618 women (including 12 cases).

tion of hormone replacement therapy and risk of acute pancreatitis ($p = 0.37$). The RR for each 2 years of added use was 1.09 (95% CI 1.04–1.14).

Adjustment for baseline history of cholelithiasis did not change the association between ever having used hormone replacement therapy and risk of acute pancreatitis (RR 1.57, 95% CI 1.20–2.06). The association was also maintained when we used non-gallstone-related acute pancreatitis as the outcome: based on 43 cases in never users and 72 cases in ever users, the RR for ever having used hormone replacement therapy was 1.96 (95% CI 1.32–2.90).

Overall, the association with ever having used hormone replacement therapy did not change appreciably in the sensitivity analyses (where follow-up was censored or additional restrictions were applied) (Table 3). Also, as in the main analysis, the risk of acute pancreatitis seemed to increase with duration of use.

Interpretation

In this prospective cohort study, use of postmenopausal hormone replacement therapy was associated with increased risk of acute pancreatitis. Physicians should consider this potential increase in risk when prescribing this type of therapy.

Except for case reports,^{5–10} the epidemiologic data on the association between postmenopausal hormone replacement therapy and acute pancreatitis are sparse. Only 1 case–control study ($n = 1054$ cases of acute pancreatitis),¹⁵ which used data from prescription databases and hospital registers in Denmark, has examined the risk of acute pancreatitis associated with current and past use of hormone replacement therapy (defined as a prescription for such therapy within 1–90 or 91–365 days, respectively). That study showed a borderline significant association with past, but not current, use of combined estrogen and progestin preparations (odds ratio 1.6, 95% CI 1.0–2.5). No association was observed with estrogen-only preparations. Although there was adjustment for the occurrence of diseases related to alcohol and gallstones, the study did not adjust for other potential confounders, such as smoking²⁸ and adiposity.²⁶ Moreover, it did not consider an association with a longer duration of hormone replacement therapy, which limits the comparison with our study.

Because hormone replacement therapy may increase the risk of gallbladder disease,²⁹ the observed association between hormone replacement therapy and acute pancreatitis could, in principle, be mediated by gallstones. However,

the association remained when we adjusted for cholelithiasis, as well as when we used non-gallstone-related acute pancreatitis as the outcome, which suggests that hormone replacement therapy might have additional effects that may explain our findings. Most case reports on estrogen-induced pancreatitis have reported concurrent hypertriglyceridemia.^{7–12,14} Use of hormone replacement therapy may elevate triglycerides,³⁰ which, even at moderately elevated levels, have been associated with increased risk of acute pancreatitis.³¹ The role of triglycerides in the pathogenesis of acute pancreatitis is not fully understood, but a key event is thought to be accumulation of free fatty acids in the pancreas after hydrolysis of triglycerides by pancreatic lipase.³¹ Exogenous estrogen may also have deleterious effects on the pancreas by itself, as some case reports have reported estrogen-induced pancreatitis in the absence of gallstones and hypertriglyceridemia.^{5,6,13} Experimental studies have identified estrogen-binding proteins in the pancreas,³² and upregulation of these proteins has been observed in the serum of patients with acute pancreatitis.³³ Moreover, administration of high-dose estrogen has been reported to decrease the cholecystokinin-stimulated secretion of amylase in rats.³⁴ Impaired secretion of pancreatic enzymes is considered an important event in the initial pathogenesis of acute pancreatitis.³⁵

In other population-based Swedish studies based on data from the mid-1990s, oral estradiol combined with testosterone-like progestins was reported to be predominantly used as systemic therapy,^{36,37} whereas oral estriol and vaginal estriol, dienestrol or estradiol were reported to be equally used as local therapy. Our finding that local therapy was associated with lower increase in risk of acute pancreatitis may therefore be due to local administration of estrogens of low dose or low potency. There are no contemporary data that might explain our finding that the risk was sustained among past users of hormone replacement therapy or that the risk seemed to increase with duration of use. These findings, though speculative, may suggest that exogenous estrogen induces some persistent change in the pancreas for which the duration of exposure may be important.

The strengths of our study were its prospective design, high response rate, virtually complete follow-up and adjustment for several potential confounders. The incidence of acute pancreatitis was also similar to that reported in Sweden as a whole.³⁸ For example, for 1998 to 2003, the incidence rate per 100 000 women (aged 70–79 yr) was 73 cases in Sweden and 68 cases in our analytical cohort.

Limitations

The information on hormone replacement therapy was self-reported, which may have led to some degree of nondifferential misclassification. However, self-reporting of hormone replacement therapy has been shown to be highly comparable with prescription data,¹⁷ and the prevalence of hormone replacement therapy in our study was similar to that previously reported from Sweden for that period.³⁶ Given the length of follow-up in our study, and given that the exposure was assessed only once, it is likely that the participants changed their use of hormone replacement therapy. We used several sensitivity analyses to evaluate whether this may have biased our findings, and the results did not depart substantially from those obtained in the main analysis. A second limitation was the lack of information on preparation, dose and route of administration of the hormone replacement therapy. Third, the cases were identified by register diagnosis, which may not have been entirely correct. However, the Swedish National Patient Register has been shown to be highly accurate for the diagnosis of acute pancreatitis,¹⁹ and this accuracy should not differ by use of hormone replacement therapy. To minimize misclassification with other exocrine pancreatic diseases, we used such diseases (including cancer) as censoring events. Finally, although we adjusted for several potential confounders, there may have been unmeasured or residual confounding.

Conclusion

Use of postmenopausal hormone replacement therapy was associated with increased risk of acute pancreatitis. The role of the preparation, dose and route of administration of hormone replacement therapy merits further investigation. If these findings are confirmed by other studies, the risk of acute pancreatitis should be considered when hormone replacement therapy is prescribed.

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Affiliations: Unit of Nutritional Epidemiology (Oskarsson, Orsini, Sadr-Azodi, Wolk), Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden; Unit of Upper Gastrointestinal Research, Department of Molecular Medicine and Surgery (Sadr-Azodi), Karolinska Institutet, Stockholm, Sweden; Centre for Clinical Research Sörmland (Sadr-Azodi), Uppsala University, Eskilstuna, Sweden

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