Menopausal hormone therapy and risk of cholecystectomy: a prospective study based on the French E3N cohort

Antoine Racine MD MSc, Anne Bijon MSc, Agnès Fournier PhD, Sylvie Mesrine MD, Françoise Clavel-Chapelon PhD, Franck Carbonnel MD PhD, Marie-Christine Boutron-Ruault MD PhD

See related commentary by Liu on page 549 and at www.cmaj.ca/lookup/doi/10.1503/cmaj.130004

Abstract

Background: Studies in the United States and the United Kingdom have reported an increased risk of cholecystectomy among women exposed to menopausal hormone therapy, but with substantial heterogeneity between types of hormone treatments. We evaluated the risk of cholecystectomy associated with different regimens of menopausal hormone therapy in a large prospective cohort study.

Methods: Between 1992 and 2008, 70 928 menopausal women from the French E3N study cohort were sent questionnaires assessing their use of menopausal hormone therapy, medical history and lifestyle characteristics. The primary outcome was cholecystectomy. We analyzed the risk of cholecystectomy associated with use of menopausal hormone therapy using Cox proportional models, with age as time-scale.

Results: During follow-up, 45 984 (64.8%) of the participants were exposed to menopausal hormone therapy, and 2819 cholecystectomies were recorded. The use of menopausal hormone therapy was associated with an increased risk of cholecystectomy (adjusted hazard ratio [HR] 1.10, 95% confidence interval [CI] 1.01–1.20) compared with women who were not exposed to menopausal hormone therapy. The association was restricted to unopposed oral estrogen therapy (adjusted HR 1.38, 95% CI 1.14–1.67). Over 5 years, about 1 cholecystectomy in excess would be expected in every 150 women using oral estrogen therapy without progestogens, compared with women not exposed to menopausal hormone therapy.

Interpretation: The risk of cholecystectomy was increased among women exposed to oral estrogen menopausal hormone therapy, especially oral regimens without a progestagen. Complicated gallstone disease should be added to the list of potential adverse events to be considered when balancing the benefits and risks associated with menopausal hormone therapy.

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Correspondence to:
Antoine Racine,
antoine_racine@yahoo.fr

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Gallstone disease is common in developed countries,[1] and complications of gallstones represent a major reason for hospital admission and greatly contribute to health care costs and patient morbidity.[2] Among women, those over 50 years of age are at greatest risk of gallstone disease.[3] Other known risk factors are obesity, multiparity, dyslipidemia, hyperinsulinism, inappropriate dietary intake and genetic predisposition.[4–8] Studies in the United States and the United Kingdom have reported an increased risk of cholecystectomy among women exposed to menopausal hormone therapy.[9–14] No data are available in France, where menopausal hormone therapy regimens are different from those most commonly used in the US and UK (predominance of the transdermal over oral route, infrequent use of equine estrogens, and frequent use of progesterone and its isomer, dydrogesterone, as the progestagen component). In addition, the impact of progestagens used in menopausal hormone therapy regimens remains unclear with regard to gallstone risk.

We prospectively evaluated the risk for cholecystectomy among women exposed to different menopausal hormone therapy regimens in a French cohort study.

Methods

Study design

The Étude Épidémiologique de femmes de la Mutuelle Générale de l'Éducation Nationale (E3N) is a large prospective cohort study conducted in France to investigate hormonal and environmental factors involved in female diseases. The study design, population and collection of baseline data have been described previously.[15] In brief, 98 995 women insured by the

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national health insurance plan for teachers and coworkers were enrolled in 1990 and asked to complete a questionnaire every 2 years that addressed medical history, reproductive history, dietary habits, and anthropometry and lifestyle characteristics.[16] All participants gave informed consent, in accordance with the rules of the French National Commission for Data Protection and Privacy.

Study population

Of the 98 995 women in the E3N cohort, we included 70 928 in our study. We excluded those who had a history of cholecystectomy ($n = 4588$) or cancer other than basal cell skin carcinoma ($n = 4175$) before recruitment in that study, those without any menstrual period ($n = 28$), those who were not menopausal before the end of follow-up ($n = 6209$), those who did not answer the baseline questionnaire in 1992 ($n = 8117$) and the 4950 women who were lost to follow-up after inclusion. We defined baseline as January 1992 for women who were already menopausal by that date, or the date of the first questionnaire following their menopause. Women contributed person-years of follow-up until the date of cholecystectomy, the date of the last completed questionnaire or June 30, 2008 (the date at which the ninth questionnaire was sent to participants), whichever occurred first.

Data collection

Information on menopausal hormone therapy and other covariates was collected at inclusion in January 1992 and updated at the time of each subsequent questionnaire. For each episode of menopausal hormone therapy, the start date, duration and brand names of the products used were recorded, as described previously.[17] Data on other covariates were also updated during follow-up, except parity, breastfeeding, age at menarche and education level, which were recorded in the baseline questionnaire. Dietary data were collected in June 1993 with use of a validated questionnaire on diet history.[18,19]

Cholecystectomy and first diagnosis of gallstones, along with their respective dates, were self-reported by the participants. A validation study was performed on 3 random samples: 100 women with self-reported cholecystectomy, 100 who reported having untreated gallstones and 50 with no declaration of gallstone disease or cholecystectomy. These 250 women were sent a detailed questionnaire that requested documents relative to diagnostic and surgical procedures. Concordance between the documents and the self-reports of a history or absence of history of cholecystectomy was excellent (99%); concordance regarding gallstone disease was less satisfactory (67%) (Appendix 1, available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.121490/-/DC1). Thus, cholecystectomy was chosen as the primary outcome of our study.

Statistical analysis

We estimated the risk of cholecystectomy associated with exposure to menopausal hormone therapy using Cox proportional hazard models for left-truncated and right-censored data, with age as time-scale. Results are reported as hazard ratios (HRs) and 95% confidence intervals (CIs). Use of menopausal hormone therapy was analyzed as a time-dependent variable and dealt with prospectively: the information reported in questionnaires t and earlier was used to prospectively categorize participants for the period between completion of questionnaires t and $t + 1$. For women who did not answer questionnaire t, their status of exposure to menopausal hormone therapy was classified as missing for the period between the date when questionnaire t was sent to the participants and the date of completion of the subsequent questionnaire.

Menopausal hormone therapy was first categorized as a global exposure (never, past or current use) and then according to cumulative exposure to estrogen (oral estradiol, oral equine estrogens, transdermal estradiol, and other estrogens including vaginally or nasally administered estrogens) and progestagen (none, progesterone, pregnanes, norpregnanes and testosterone derivatives). If a woman received successively different regimens, she was simultaneously accounted for in the corresponding categories. For example, if at a given time a woman was both a current user of transdermal estradiol and a past user of oral estradiol, she contributed person-years to both categories. In the subgroup of women exposed to only one type of regimen, we analyzed the effect of duration of use (< 6 yr v. ≥ 6 yr [6 yr being the median]) among current users, and the recency of use (current v. past use; and time since last use according to the median, as < 11 yr v. ≥ 11 yr). Models were systematically adjusted for body mass index (BMI) (time-dependent: < 18.5, 18.5–22.5, 22.5–25, 25–30 and ≥ 30 kg/m^2), parity (0, 1, 2–3 and > 3 children), hypercholesterolemia and diabetes (time-dependent: no or yes), education level (secondary school, 1–3 yr of university and > 3 yr of university). We compared HRs using the Wald χ^2 test of homogeneity. Potential interactions between covariates and regimens of menopausal hormone therapy were explored in Cox models.

We examined other potential confounders, including physical activity, previous use of oral

contraceptives, type of menopause (artificial or natural), age at menopause, age at menarche, age at first pregnancy, history of hysterectomy, history of breastfeeding and history of benign thyroid disease. For the 61 026 women with available dietary data, models were also adjusted for intake of polyunsaturated fatty acids, simple sugars, dietary fibre, alcohol and coffee (in quartiles). Covariates were included in the final adjusted model if they were significantly associated with risk of cholecystectomy or if they changed the estimate associated with ever use of menopausal hormone therapy by more than 10%. Missing data for adjustment variables were imputed by means of a multiple imputation procedure.[20] We explored potential interactions between use of menopausal hormone therapy and covariates by including an interaction term in the models.

We calculated incident rates of cholecystectomy according to the various regimens of menopausal hormone therapy. Absolute risks were calculated among women who never used menopausal hormone therapy (reference) and in the treatment groups, considering the multivariable models.

All statistical tests were 2-sided, and statistical significance was set at the 0.05 level. We used SAS version 9.2 (SAS Institute, Inc., Cary, North Carolina) to perform all analyses.

Results

Overall, 70 928 women were included; the mean follow-up period was 11.5 years, for a total of 819 889 person-years of follow-up. During the study period, 45 984 (64.8%) of the women reported ever using menopausal hormone therapy. The baseline characteristics of the participants are shown in Table 1 according to their exposure menopausal hormone therapy. Overall, 78 435 courses of treatment with menopausal hormone therapy were recorded (Table 2). The main route of estrogen administration was transdermal. Most of the estrogens were in combined formulations with progestagens. Oral equine estrogens use was infrequent.

During follow-up, 2819 incident cholecystectomies were recorded. There was a positive association between risk of cholecystectomy and increasing BMI, higher parity, hypercholesterolemia, diabetes and education level (data not

Table 1: Baseline characteristics of 70 928 participants from the E3N cohort, by use of menopausal hormone therapy during follow-up

Characteristic	Use of menopausal hormone therapy*		Type of regimen used		
	Never *n* = 18 694	Ever *n* = 45 984	Transdermal estrogen *n* = 33 584	Oral estrogen *n* = 16 736	Other estrogen *n* = 6 709
Length of follow-up, yr, mean (IQR)	10.5 (5.8–15.9)	12.1 (7.9–16.2)	12.6 (10.1–16.4)	11.9 (10.9–16.3)	12.0 (7.9–16.3)
Age, yr, mean ± SD	56.4 ± 4.7	53.9 ± 4.1	53.8 ± 4.0	53.2 ± 3.9	53.7 ± 4.0
Education level ≥ high school,† no. (%)	15 986 (85.5)	41 181 (89.6)	30 049 (89.5)	15 119 (90.3)	6 075 (90.6)
BMI,† kg/m², mean ± SD	23.3 ± 3.7	22.4 ± 2.8	22.4 ± 2.8	22.2 ± 2.7	22.3 ± 2.7
Parity,† mean ± SD	1.8 ± 1.2	1.8 ± 1.1	1.8 ± 1.1	1.8 ± 1.1	1.8 ± 1.1
Hypercholesterolemia, no. (%)	623 (3.3)	1 318 (2.9)	997 (3.0)	393 (2.3)	188 (2.8)
Diabetes mellitus, no. (%)	262 (1.4)	281 (0.6)	213 (0.6)	77 (0.5)	31 (0.5)
Hysterectomy, no. (%)	3 011 (16.1)	9 404 (20.5)	7 476 (22.3)	2 965 (17.7)	1 225 (18.3)
History of gallstone disease not requiring surgery, no. (%)	341 (1.8)	749 (1.6)	563 (1.7)	257 (1.5)	94 (1.4)
Physical activity,† MET-h/wk, mean ± SD	44.2 ± 28.5	42.0 ± 26.2	41.7 ± 25.9	41.9 ± 26.4	41.6 ± 25.5
Artificial menopause,†‡ no. (%)	1 741 (9.3)	3 936 (8.6)	3 047 (9.1)	1 323 (7.9)	505 (7.5)
Ever use of oral contraceptives, no. (%)	9 310 (49.8)	29 602 (64.4)	21 371 (63.6)	11 774 (70.4)	4 588 (68.4)
History of breastfeeding† no. (%)	10 965 (58.7)	27 741 (60.3)	20 195 (60.1)	10 158 (60.7)	4 079 (60.8)

Note: BMI = body mass index, E3N = Étude Épidémiologique de femmes de la Mutuelle Générale de l'Éducation Nationale, IQR = interquartile range, MET-h/wk = metabolic equivalent hours per week, SD = standard deviation.
*Data on use of menopausal hormone therapy were missing for 6 250 women, including 211 who reported undergoing cholecystectomy during follow-up.
†Data were missing on education level for 2 841 women, on BMI for 76, on parity for 523, on physical activity for 779, on status of artificial menopause for 1 229 and on breastfeeding for 523 women.
‡Artificial menopause due to bilateral oophorectomy or to a specific medical condition (induced by radiation or a drug).

shown). Data on the use of menopausal hormone therapy were available for 2608 women who underwent cholecystectomy. Compared with women who never used menopausal hormone therapy, those who ever used it had an increased risk of cholecystectomy (adjusted HR 1.10, 95% CI 1.01–1.20) (Table 3). The association was restricted to use of oral estrogens (adjusted HR 1.16, 95% CI 1.06–1.27). Other types of regimens were not associated with an increased risk. Risk was significantly higher with oral estrogens than with transdermal estrogens ($p = 0.03$). Risk was also significantly higher with oral estrogens used alone (unopposed estrogens) than with oral estrogens combined with a progestagen ($p = 0.03$) (Table 3). When we looked at the difference in risk of cholecystectomy by type of oral estrogen, the risk was significantly higher with oral equine estrogens alone than with oral equine estrogens combined with a progestagen ($p = 0.01$). We found no significant difference between women who used oral estradiol therapy alone and those who used oral equine estrogens alone ($p = 0.4$) or oral estradiol with a progestagen ($p = 0.2$) (Table 4).

In the sensitivity analysis in which we included women exposed to only one type of menopausal hormone therapy during follow-up (25 654 [55.8%] of 45 984 who ever used such therapy), the risk of cholecystectomy was associated with use of unopposed oral estradiol therapy (adjusted HR 1.83, 95% CI 1.18–2.86) and use of unopposed oral equine estrogen therapy (adjusted HR 1.90, 95% CI 1.17–2.11) compared with women who never used menopausal hormone therapy (Table 5). Other types of regimens were not associated with an increased risk of cholecystectomy. Among current users of unopposed oral estrogen therapy, we found no difference in risk by duration of exposure (< 6 yr v. ≥ 6 yr; $p = 0.6$). We

Table 2: Types of regimens of menopausal hormone therapy used

Regimen	No. (%) of treatments*
Transdermal estrogen	48 846 (62.3)
Without progestagen	9 488 (12.1)
With progesterone	20 534 (26.2)
With pregnane derivative	6 449 (8.2)
With norpregnane derivative	11 370 (14.5)
With testosterone derivative	518 (0.7)
With other progestagen	487 (0.6)
Oral estrogen	22 880 (29.2)
Estradiol	21 498 (27.4)
Without progestagen	1 713 (2.2)
With progesterone	4 940 (6.3)
With pregnane derivative	7 121 (9.1)
With norpregnane derivative	2 775 (3.5)
With testosterone derivative	4 822 (6.1)
With other progestagen	127 (0.2)
Oral equine estrogen	1 382 (1.8)
Without progestagen	585 (0.7)
With progesterone	219 (0.3)
With pregnane derivative	311 (0.4)
With norpregnane derivative	193 (0.2)
With testosterone derivative	45 (0.1)
With other progestagen	29 (0.04)
Other estrogen	6 709 (8.6)

*Each course of menopausal hormone therapy is counted separately. The total courses of treatment was 78 435 among 45 984 women.

Table 3: Incidence of cholecystectomy and risk associated with use of menopausal hormone therapy

Variable	No. of women*	No. who had cholecystectomy*	Age-adjusted HR (95% CI)	Multivariate HR† (95% CI)
Never used menopausal hormone therapy	18 694	824	1.00 (ref)	1.00 (ref)
Ever used menopausal hormone therapy	45 984	1 784	1.01 (0.93–1.10)	1.10 (1.01–1.20)
Oral estrogen	16 736	625	1.10 (1.00–1.20)	1.16 (1.06–1.27)‡
Oral estrogen alone	2 229	118	1.36 (1.03–1.65)	1.38 (1.14–1.67)§
Oral estrogen with progestagen	15 645	555	1.03 (0.93–1.13)	1.09 (0.99–1.20)
Transdermal estrogen	33 584	1 300	0.97 (0.89–1.04)	1.01 (0.94–1.10)
Transdermal estrogen alone	9 488	361	1.06 (0.95–1.19)	1.04 (0.93–1.17)
Transdermal estrogen with progestagen	30 444	1 165	0.93 (0.87–1.01)	0.99 (0.91–1.07)
Other estrogen	6 709	187	1.01 (0.87–1.17)	1.03 (0.89–1.20)

Note: CI = confidence interval, HR = hazard ratio, ref = reference group.
*Data on use of menopausal hormone therapy were missing for 6 250 women, including 211 who reported undergoing cholecystectomy during follow-up.
†Adjusted for body mass index, parity, hypercholesterolemia, diabetes and educational level.
‡$p = 0.03$ for comparison of oral estrogen v. transdermal estrogen; $p = 0.2$ for comparison of oral estrogen v. other estrogen.
§$p = 0.03$ for comparison of oral estrogen alone v. oral estrogen with progestagen.

also found no difference when we compared current and past use ($p = 0.2$) and time since last use (< 11 yr v. ≥ 11 yr; $p = 0.6$). Among progestagen users, there was no difference in risk by type of progestagen ($p = 0.6$) (data not shown). There was no interaction between exposure to menopausal hormone therapy and BMI, parity, period of follow-up (before v. after 2003), presence of hypercholesterolemia or diabetes, hysterectomy or history of gallstones at baseline (data not shown). Among women for whom dietary data were available, additional adjustment for dietary intake did not modify the findings (data not shown).

Among women who had undergone cholecystectomy during follow-up, those exposed to oral estrogens ($n = 625$) were younger at the time of cholecystectomy ($p < 0.001$), leaner ($p < 0.001$) and less likely to have a history of gallstones at baseline ($p < 0.001$) than women with no exposure to menopausal hormone therapy ($n = 824$). They were also somewhat less likely to be nulliparous ($p = 0.09$) (data not shown).

The absolute risk of cholecystectomy was 49 per 10 000 person-years among women who reported ever using menopausal hormone therapy and 35 per 10 000 person-years among those who reported no exposure. From these rates, over 5 years, about 1 cholecystectomy in excess would be expected in every 150 women using oral estrogen therapy without a progestagen, compared with women not exposed to menopausal hormone therapy.

Interpretation

In this large French prospective cohort study, we found that the risk of cholecystectomy was increased among women exposed to oral estrogen regimens for menopausal hormone therapy, especially oral regimens without a progestagen. Other types of menopausal hormone therapy were not associated with an increased risk of cholecystectomy.

Our findings are in agreement with those from previous reports of an increased risk of cholecystectomy associated with menopausal hormone therapy.[9–14] Associations with unopposed oral estrogen therapy were stronger in other studies, such as the Million Women Study and the Women's Health Initiative,[9,12] than in ours. However, we observed stronger associations when we restricted the analysis to women exposed to a single treatment type, which suggests a diluting effect by the multiplicity of types of menopausal hormone therapy in our population compared with other studies. We did not observe any increased risk of cholecystectomy associated with transdermal estrogen use, which is in partial agreement with a weaker association with transdermal compared with oral estrogen use reported in the Million Women Study.[9]

We found no association between oral estrogen use and cholecystectomy risk when the regimens included a progestagen. These results contrast with those from previous studies where the risk was not modified by progestagens.[9,12] However, the types of progestagens were more diverse in our study than in the Women's Health Initiative,[12] in which only medroxy-progesterone acetate was used, or the Million Women Study, in which progestagens were essentially norpregnanes or medroxy-progesterone. We cannot exclude that differences in the progestagen molecules used could account for differences in the associations observed between our study and previous reports.

Beyond the specificities of the menopausal hormone therapy regimens, some differences in the characteristics of the study populations could explain the different findings. However, we observed no confounding effect on the risk of cholecystectomy between use of menopausal hormone therapy and known acquired risk factors for gallbladder disease. Hereditary factors[21–23] and specific

Table 4: Incidence of cholecystectomy and risk associated with use of oral estrogen menopausal hormone therapy

Variable	No. of women*	No. who had cholecystectomy*	Age-adjusted HR (95% CI)	Multivariate HR† (95% CI)
Never used menopausal hormone therapy	18 694	824	1.00 (ref)	1.00 (ref)
Ever used oral estrogen therapy	16 736	625	1.06 (0.96–1.16)	1.16 (1.06–1.27)
Estradiol alone	1 713	77	1.25 (0.99–1.57)	1.27 (1.01–1.60)‡
Estradiol with progestagen	15 261	533	1.03 (0.93–1,13)	1.10 (0.99–1.21)
Equine estrogen alone	585	44	1.48 (1.09–2.00)	1.53 (1.11–2.11)§
Equine estrogen with progestagen	599	23	0.95 (0.67–1.34)	0.68 (0.43–1.09)

Note: CI = confidence interval, HR = hazard ratio, ref = reference group.
*Data on use of menopausal hormone therapy were missing for 6 250 women, including 211 who reported undergoing cholecystectomy during follow-up.
†Adjusted for body mass index, parity, hypercholesterolemia, diabetes and education level.
‡$p = 0.2$ for comparison of estradiol alone v. estradiol with progestagen; $p = 0.4$ for comparison of estradiol alone v. equine estrogen alone.
§$p = 0.01$ for comparison of equine estrogen alone v. equine estrogen with progestagen.

genetic polymorphisms[24] that modulate the risk of gallstone disease and the hepatic response to estrogen exposure could account for some of the differences observed across populations.

Unlike the Million Women Study, we studied only surgically treated gallstone disease because concordance was not sufficient regarding untreated gallstone disease in the validation study. Therefore, some symptomatic gallstone disease may have gone undiagnosed, which may have resulted in some degree of outcome misclassification and therefore a weakening of the associations observed.

Pharmacologic data are consistent with epidemiologic studies: estrogens modify lipid metabolism, increase biliary cholesterol secretion and saturation,[22–27] and promote precipitation of cholesterol in the bile. Estrogens reduce gallbladder motility, which increases bile crystallization[26] and contributes to gallstone formation. The transdermal route of administration bypasses involvement of the liver and thus does not increase biliary cholesterol saturation, which could account for the lower risk of complicated gallstone disease associated with transdermal estradiol use than with oral estradiol use.[27] Hepatobiliary effects of progestagens have been explored to a lesser extent than those of estrogens.[26]

The E3N cohort study has assessed the impact of menopausal hormone therapy on several outcomes, including breast cancer,[17,28] diabetes onset,[29] thromboembolic events[30] and asthma.[31] Unlike most reports from cohort studies in which exposure to menopausal hormone therapy is assessed only at baseline, data on the use of menopausal hormone therapy and covariates in the E3N cohort were updated every 2 years during the follow-up period. These updates allowed us to determine the use of menopausal hormone therapy more precisely, reduced misclassification bias and allowed a better adjustment of models. In our study, less than 5% of women had missing data on covariates, and loss to follow-up was uncommon. The size of the cohort, the large number of events and the long follow-up period conferred a high statistical power; however, power was reduced in subgroup analyses, especially when we restricted exposure to a small proportion of women. Thus, the lack of interaction between exposure and other covariates may have been due to reduced statistical power for those analyses.

Limitations

Our study has limitations. Exposure to menopausal hormone therapy and the occurrence of cholecystectomy were self-reported. However, the study population was composed mostly of highly adherent and educated women. To limit record bias regarding use of menopausal hormone therapy, we used a booklet with colour photographs and names of all of the relevant products marketed in France. Regarding the outcome, the validation study showed excellent concordance between self-reports and validated reports of cholecystectomy. Thus, missing data and case misclassification are unlikely to explain our findings. Nevertheless, because the medical indication for cholecystectomy was available only for the small sample of women in the validation study, it is difficult to conclude whether menopausal hormone therapy promotes gallstones per se or its complications. Extrapolation of our

Table 5: Sensitivity analysis of risk of cholecystectomy associated with menopausal hormone therapy restricted to women exposed to only one type of regimen

Variable	No. of women*	No. who had cholecystectomy*	Multivariate HR† (95% CI)
Never used menopausal hormone therapy	18 694	824	1.00 (ref)
Oral estradiol alone	277	20	1.83 (1.18–2.86)‡
Oral estradiol with progestagen	5 930	232	1.18 (0.89–1.55)
Oral equine estrogen alone	157	17	1.90 (1.17–2.11)§
Oral equine estrogen with progestagen	91	10	1.64 (0.88–3.06)
Transdermal estrogen alone	2 166	101	1.20 (0.97–1.47)¶
Transdermal estrogen with progestagen	15 481	674	1.05 (0.95–1.16)
Other estrogen	1 552	38	0.93 (0.67–1.29)

Note: CI = confidence interval, HR = hazard ratio, ref = reference group.
*Data on use of menopausal hormone therapy were missing for 6 250 women, including 211 who reported undergoing cholecystectomy during follow-up.
†Adjusted for body mass index, parity, hypercholesterolemia, diabetes and educational level.
‡$p = 0.06$ for comparison of oral estradiol alone v. oral estradiol with progestagen; $p = 0.9$ for comparison of oral estradiol alone v. oral equine estrogen alone; $p = 0.08$ for comparison of oral estradiol alone v. oral transdermal estrogen alone; $p = 0.02$ for comparison of oral estradiol alone v. other estrogen.
§$p = 0.7$ for comparison of oral equine estrogen alone v. oral equine estrogen with progestagen.
¶$p = 0.3$ for comparison of transdermal estrogen alone v. transdermal estrogen with progestagen.

findings to the general population should be done with caution, because the study population comprised women insured by France's national health insurance plan for teachers and coworkers, a cohort with a higher mean education level than in the overall French population.

Conclusion

The risk of cholecystectomy was increased among women exposed to oral estrogen menopausal hormone therapy, especially oral regimens without a progestagen. Complicated gallstone disease should be added to the list of potential adverse events to be considered when balancing the benefits and risks associated with menopausal hormone therapy.

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Affiliations: From the Institut national de la santé et de la recherche médicale (INSERM), the Centre for Research in Epidemiology and Population Health and Université Paris Sud (Racine, Bijon, Fournier, Mesrine, Clavel-Chapelon, Carbonnel, Boutron-Ruault), Villejuif, France; and the Department of Hepatogastroenterology (Racine, Carbonnel), Hôpital Bicêtre, Assistance Publique Hôpitaux de Paris, Université Paris-Sud, Le Kremlin Bicêtre, France

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