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Menopausal hormone therapy use and risk of primary liver cancer in the Clinical Practice Research Datalink

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Abstract

Primary liver cancer occurs less commonly among women than men in almost all countries. This discrepancy has suggested that hormone levels and/or exogenous hormone use could have an effect on risk, although prior studies have reached inconsistent conclusions. Thus, the current study was conducted to examine the relationship between menopausal hormone therapy (MHT) use and development of liver cancer. A nested case-control study was conducted within the United Kingdom's Clinical Practice Research Datalink (CPRD). Controls were matched, at a 4-to-1 ratio, to women diagnosed with primary liver cancer between 1988 and 2011. A second match, based on whether the cases and controls had diabetes, was also conducted. Odds ratios (OR) and 95% confidence intervals (95%CI) for associations of MHT with liver cancer were estimated using conditional logistic regression adjusted for known risk factors. In the overall match, 339 women with liver cancer were matched to 1318 controls. MHT use was associated with a significantly lower risk of liver cancer (OR_{adj}=0.58, 95%CI=0.37–0.90) especially among users of estrogen-only MHT (OR_{adj}=0.44, 95%CI=0.22–0.88) and among past users (OR_{adj}=0.53, 95%CI=0.32–0.88). Among the matched cases (n=58) and controls (n=232) with diabetes, the odds ratios were similar to the overall analysis (OR_{adj}=0.57, 95%CI=0.09–3.53), but did not attain statistical significance. In the current study, MHT use, especially estrogen-only MHT use, was associated with a significantly lower risk of liver cancer. These results support the need of further investigation into whether hormonal etiologies can explain the variation in liver cancer incidence between men and women.

Keywords

Liver cancer; menopausal hormone therapy

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Introduction

In almost all countries, the incidence of primary liver cancer is higher among men than women [1]. Although some major risk factors, such as chronic infection with hepatitis B or hepatitis C viruses, excessive alcohol consumption, and cigarette smoking are more common among men, these factors do not entirely explain the male excess in incidence. Whether steroid hormones might be related to the gender discrepancy has been discussed for many years. Although some early animal experiments suggested that estrogens promoted hepatocarcinogenesis [2–4], others reported that ovariectomy enhanced the development of liver tumors [5, 6]. More recently, rodent experiments demonstrated the ability of estrogens to protect against diethylnitrosamine-induced liver cancer via inhibition of interleukin-6 production [7]. The results of these experiments suggest that menopausal hormone therapy (MHT) might affect the development of liver cancer in humans.

The relationship of MHT use to risk of cancer has been most extensively examined in respect to breast and gynecologic cancers. Increased risks of breast, endometrial and ovarian cancers have been well documented [8–10]. Some evidence also suggests that MHT may increase the risk of central nervous system tumors [11], and lung cancer [12]. In contrast, other studies suggest that MHT use decreases the risk of cancers of the colon and rectum, esophagus and stomach [13], and possibly, multiple myeloma [14]. The results of prior examinations of MHT use and liver cancer have been inconsistent, with some studies reporting decreased risks [15–17] and others reporting null associations [18, 19]. Many of the MHT-liver cancer studies, however, have been modest in size and have based their assessment of MHT exposure on questionnaire data rather than on prescription records. Thus, the current study sought to examine the MHT-liver cancer association in a large population with documented prescription data.

Material and Methods

A nested case-control study was conducted within the Clinical Practice Research Datalink (CPRD) of the United Kingdom (UK). The CPRD is a large, population-based, electronic medical records database that contains information on approximately 8.5% of the UK population. The UK National Health Service (NHS) provides universal coverage, therefore no segment of the population is excluded from the CPRD and the age and gender distributions are representative of the general UK population [20]. General practitioners (GPs) who contribute to the CPRD provide the data in an anonymous format for research purposes. All GPs have been trained to record demographic data, medical information, details of hospital stays and deaths. Diagnoses, physical findings, symptoms and administrative events, such as referrals to specialists, are recorded using Read codes. Detailed information is available for all medications prescribed. Several studies have examined the validity of the information recorded in the CPRD and indicate that the data are complete and accurate with regard to clinical illnesses diagnosed either by the GP or a specialist [21, 22]. Specifically, it has been demonstrated that more than 90% of information from manual medical records gets recorded electronically [21, 22] and approximately 95% of all electronically identified primary cancers are confirmed as incident cancers [23]. The base population for the current study included all women between the ages of 10 and 90 years in the CPRD between the years

1988 and 2011. The protocol for this study was approved by the NIH Human Research Protection Program and the Independent Scientific Advisory Committee of the CPRD.

Cases and Controls

The eligibility criteria for cases were: 1) female; 2) first time diagnosis of primary liver cancer (Read codes B150300, B150z00, B152.00); 3) no prior diagnosis of the cancers most likely to metastasize to the liver: lung, stomach, breast, colon or pancreatic cancer; and 4) no diagnosis of any other cancer (except non-melanoma skin cancer) in the 3 years prior to the index date. The index date was defined as the date of liver cancer diagnosis minus one year. All cases were required to have ≥2 years of recorded activity in the CPRD prior to the index date. Persons with any code for liver metastases were excluded from the study. Of the 339 cases included in the study, the majority (N=298, 88%) had supporting clinical codes that indicated presence of liver cancer such as diagnostic exams (biopsies), treatment (chemotherapy, radiotherapy, surgery), palliative care and referrals to specialty care. The minority (N=41, 12%) who had no supporting clinical codes were women who died shortly after the liver cancer diagnosis, prior to treatment, or women whose cancer diagnosis was solely recorded at the time of death.

Controls were matched to cases at a four-to-one ratio on age (same year of birth as case), general practice, index date (one year prior to case's diagnosis date) and number of years in the CPRD prior to the case's index date. Controls had to be free of any cancer (except non-melanoma skin cancer) prior to the index date of the matched case and were required to have >2 years of history in the CPRD prior to the case's index date. Only three controls could be identified for 22 of the cases, only two for 5 cases and only one for 2 cases, resulting in a total of 1318 controls overall.

In addition to the overall match, as second match that considered the presence of diabetes (type I and type II) was completed for the study, as diabetes is a known risk factor for liver cancer [24]. The inclusion and exclusion criteria were the same in the full match (comprised of all 339 cases and matched controls) and the diabetes status match. For the diabetes-matched analysis, controls with diabetes were matched to the 58 cases with diabetes, and controls without diabetes were matched to the 281 cases without diabetes. Other risk-factor based matches were not conducted based on the lack of a sufficient number of cases.

Exposure to Menopausal Hormone Therapy

For all analyses, MHT use was defined as having >2 MHT prescriptions recorded prior to the participant's index date. Non-use was defined as one or no MHT prescriptions prior to the index date. Current MHT use was defined as use that ended within 1 year prior to the index date, while past use was defined as use that ended >1 year prior to the index date. In addition to examining the relationship between any use of MHT and risk, we also examined use stratified on whether women had exclusively used estrogen-only MHT, exclusively used combination estrogen-progesterone therapy, or had used both.

Statistical analysis

Prior to initiating the statistical analysis, the distributions of all covariates were examined univariately by examining the percentiles and the largest and smallest values to identify potentially invalid values or outliers that may influence the results. For variables with missing values, 'unknown' categories were created for the analyses. Interactions between the major matching factors and covariates and MHT use were also estimated in the logistic regression models by including cross terms between the matching variables and covariates. Odds ratios (ORs) and 95% confidence intervals (95%CI) were calculated using conditional logistic regression to assess crude and adjusted risk estimates for the relationship of MHT use to liver cancer. Known liver cancer risk factors for which adjustment was made in the analysis included: body mass index (BMI), smoking, alcohol-related disorders (Supplementary Table 2), HBV and/or HCV infection, diabetes, and rare metabolic disorders (hemochromatosis, Wilson Disease, alpha-1 antitrypsin deficiency, porphyrias). Adjustment was also made for oophorectomy and hysterectomy status. As some evidence has suggested that aspirin [25] and anti-diabetic medications [26] might be related to liver cancer risk, adjustment was made for those exposures. In addition, adjustment was made for paracetamol use due to a statistically significantly increased risk noted in the univariate analysis. Finally, as statins have been reported to decrease risk of liver cancer in the CPRD population [27], analysis stratified on stain use was also conducted.

In addition to the full-match and the diabetes-match, two sensitivity analyses were conducted. The first analysis was restricted to cases with clinical codes for treatment of liver cancer (e.g., surgery, chemotherapy, or palliative care) and their matched controls. The second analysis used an index date of 2 years, rather than 1 year, prior to the case's date of diagnosis. All statistical tests were 2-sided; p-values less than 0.05 were considered statistically significant.

Results

Table 1 displays the characteristics of the 339 liver cancer cases and 1318 controls included in the analysis, and the univariate analyses of covariates. Cases and controls were matched on sex, index date, birth year, and length of enrollment in CPRD prior to index date, thus there were no differences in these factors. Not unexpectedly, cases were significantly more likely than controls to be current smokers, have had an alcohol-related condition (as defined by Supplementary Table 2), be infected with HBV or HCV, have chronic liver disease (as defined by Supplementary Table 1), have a rare metabolic disorder, use paracetamol, and to have type I or type II diabetes. Cases, however, were more likely than controls to have low body mass index.

Table 2 displays the relationship of MHT use to liver cancer. MHT use (2 or more prescriptions) was associated with a significantly lower risk (OR_{adj}=0.58, 95%CI=0.37–0.90). Women who received 2–9 prescriptions were at significantly lower risk (OR_{adj}=0.46, 95%CI=0.24–0.89), while women who had received 10 or more prescriptions were at non-significantly lower risk (OR_{adj}=0.66, 95%CI=0.40–1.10). Analysis of MHT by formulation found that a significant low risk was restricted to users of estrogen-only MHT (OR_{adj}=0.44, 95%CI=0.22–0.88), although there was a non-significant lower risk among users of

estrogen-progesterone MHT (OR_{adj}=0.63, 95%CI=0.37–1.09) and among women who had used both estrogen-only MHT and combined estrogen-progesterone MHT (OR_{adj}=0.73, 95%CI=0.26–2.06). Stratification by recency of use found that the significantly lower risk was restricted to past users (OR_{adj}=0.53, 95%CI=0.32–0.88), although there was a non-significant risk reduction among current users as well (OR_{adj}=0.72, 95%CI=0.36–1.40).

The results of the analysis restricted to non-users of statins are displayed in Table 3. The results were very similar to the results in the overall population. There was an inverse association between MHT use and liver cancer (OR_{adj}=0.55, 95%CI=0.32–0.92), which was particularly notable in the estrogen-only MHT users (OR_{adj}=0.34, 95%CI=0.14–0.85). Among statin users, the inverse association between MHT use and liver cancer was strong (OR_{adj}=0.18, 95%CI=0.02–1.70), but not statistically significant, perhaps due to the inclusion of only 8 case and 56 control women who were MHT users (data not shown).

Shown in Table 4 **are** the results of the analysis that matched cases to controls based on diabetes status. Among the women without diabetes, the results were very similar to the overall results in that there was an inverse association between MHT use and liver cancer (OR_{adj}=0.49, 95%CI=0.30–0.80), which was particularly notable in the estrogen-only MHT users (OR_{adj}=0.41, 95%CI=0.20–0.84) and the past users (OR_{adj}=0.52, 95%CI=0.25–0.86). Among the women with diabetes, although the point estimates were similar to those in the analysis of women without diabetes (OR_{adj}=0.57, 95%CI=0.09–3.53), the results did not attain statistical significance, but were based on small numbers (n=58).

The results of the sensitivity analysis restricted to cases with supporting clinical codes (87.9%) and their controls did not differ from that in the overall analysis (OR_{adj}=0.56, 95%CI=0.35–0.92). Similarly, the sensitivity analysis that was based on an index date of 2 years post-diagnosis, rather than 1 year, resulted in findings very similar to the main analysis (OR_{adj}=0.59, 95%CI=0.48–0.72).

Discussion

In the large CPRD cohort, MHT use was associated with a significantly lower risk of liver cancer. The relationship was significant, in particular, among past MHT users and among users of estrogen-only MHT. The inverse association was similar among women with diabetes, a risk factor for liver cancer, and women without diabetes. The inverse association was also similar when the analysis was restricted to non-users of statins, thus indicating that MHT use was not acting as a surrogate for statin use.

A stronger relationship with past-MHT use than current use is not surprising as the mean age of liver cancer diagnosis in the current study was 68.1 years and women are more likely to be prescribed MHT around the time of menopause (i.e. around age 50 years). Even so, there was a lower risk of liver cancer with current use (OR_{adj}=0.72, 95%CI=0.36–1.40) which was not significantly different from the risk associated with past use (OR_{adj}=0.53, 95%=0.32–0.88).

In the current analysis, estrogen-only therapy was more strongly related to risk reduction than was estrogen-progesterone therapy. The explanation for this difference is not certain,

but may be related to a deleterious effect of progesterone on the liver. An alternative explanation could be that what appeared to be an effect of estrogen-only MHT was really an effect of hysterectomy as only women with hysterectomies are offered estrogen-only MHT. This explanation is unlikely, however, as univariate analyses in the current study not did identify associations between hysterectomy and liver cancer. It is also possible that the difference between estrogen-only and estrogen-progesterone MHT is a chance finding based on small numbers.

Prior findings have suggested that MHT use might reduce liver cancer risk as MHT has been inversely associated with fatty liver disease, liver enzyme levels and the development of diabetes in post-menopausal women [28–30]. In line with these observations are the results of studies conducted in Sweden [16], Italy [15, 17] and Taiwan [31]. Both the Italian study (OR=0.2, 95%CI=0.1–0.8) [15, 17] and the Taiwanese study (OR=0.46, 95%CI=0.27–0.79) [31] reported significant inverse associations. Similar findings were reported by the Swedish study (SIR=0.7, 95%CI=0.4–1.2) [16] although the results did not attain statistical significance. In contrast, two studies from the U.S. each reported no association [18, 19]. The reason that the study results vary is not clear, but may be related to differences in formulations of the various types of MHT by country, and/or differences in ascertainment (questionnaire, prescription records) of MHT use. Only the current study and the study from Sweden [16] relied on prescription records. None of the studies had information on whether women took the medication, but it seems more likely that women with multiple refills took the medication than did women with only one prescription. For this reason, in the current study, the referent group included both women who had only one MHT prescription and women who had no prescriptions.

The mechanism by which exogenous estrogens might reduce the risk of liver cancer is not well understood. In murine models of chemically induced liver tumors, subcutaneous estradiol implantation has been reported to decrease the development of both preneoplastic foci and liver tumors [32]. As estradiol implantation in the spleen does not have a similar effect, estradiol may not have a direct effect on the liver itself. In subsequent experiments, evidence suggested that estradiol might be acting via its ability to stimulate prolactin production by the pituitary gland. In chemically-treated mice that had been ovariectomized, implantation of pituitary glands led to increased levels of prolactin and reduction in the number of preneoplastic foci [33]. There is also evidence that after diethylnitrosamine-induction of liver tumors, inflammatory signaling, primarily interleukin-6 (IL-6) expression, is reduced by estrogens [7]. As reported by Naugler et al., male rodents had higher levels of IL-6 expression after diethylnitrosamine dosing than did females. Estrogen treatment of the males prior to DEN-initiation, however, reduced IL-6 expression to the levels seen in females [7]. Whether the results of the animal experiments are applicable to humans, however, is not yet known.

The current study had several major strengths including being one of the largest observational liver cancer studies, to date, in a western population. The study was conducted using a large, well-established, validated, longitudinal primary-care database that is known for accuracy of diagnoses, including cancer diagnoses, and completeness of pharmacy data. All information on diseases and drug exposures in the CPRD is recorded in the absence of a

study hypothesis, thus the current study was not susceptible to recall bias. In addition, exposure was ascertained using medical record data that extended back an average of >12 years before the index date. All analyses were adjusted for a range of potential confounders, including BMI, smoking, alcohol abuse, HBV/HCV, diabetes, liver disease, oophorectomy, hysterectomy and paracetamol use. By excluding cases and controls with <2 years of history in their medical record before the index date, the risk of incorrectly classifying MHT use was minimized. In addition, the study was conducted in a country that has universal health care coverage, thus decreasing the chance that the results were biased due to failure to consider socio-economic status. Finally, sensitivity analyses were conducted that yielded findings consistent with the overall outcome.

In contrast with its strengths, the current study also had several limitations. Although previous validation studies have reported that cancer diagnoses in the CPRD are accurate and complete [23], it is possible that some secondary liver cancers were erroneously included as verification of diagnoses via linkage to a cancer registry was not undertaken. To minimize this possibility, the current study excluded prior cancer diagnoses (except non-melanoma skin cancer) in at least the 3 years prior to the liver cancer diagnosis. In addition, the majority of the cases (87.9%) had clinical codes consistent with a liver cancer diagnosis in their records. In a sensitivity analysis restricted to these cases and their matched controls, no material differences in results from the total population were found. As we did not link to a cancer registry, we were unable to confirm the histology of the cases, although the great majority of primary liver cancers in most populations are hepatocellular carcinomas. In addition, it is likely that ascertainment of HBV and HCV status was not complete as persons can be infected without being aware of it, and race and ethnicity are not recorded uniformly in CPRD, so these variables could not be included as covariates. The majority (84%) of the UK population, however, is white, so any extrapolation to persons of other racial/ethnic groups should be done cautiously. Finally, the current study used existing records to examine an MHT-liver cancer relationship, so was only able to adjust for conditions as they were recorded in the database. A prospective study design would have permitted the more precise capture of medical conditions, but such a study would be prohibitively large and costly given that liver cancer is a rare outcome. For this reason, prospective cohort studies of MHT use have rarely been able to examine liver cancer as an outcome.

In conclusion, the results of the current study suggest that the use of MHT, particularly estrogen-only MHT, may protect against the development of liver cancer.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Impact Statement

The pronounced gender discrepancy in the risk of primary liver cancer has suggested that steroid hormone levels and/or exogenous hormone use could be related to risk. In this study, the authors found a lower risk of liver cancer in association with menopausal hormone therapy (MHT) use which was particularly evident among users of estrogen-only MHT. These results support the need for future research into a hormonal mechanism in liver cancer.

Table 1

Characteristics of liver cancer cases and controls and univariate effects in relation to liver cancer

	Cases N=339 (%)	Controls N=1318 (%)	Univariable OR[a] (95% CI)
Index Year			
1991–1994	19 (5.6)	76 (5.8)	†
1995–1999	46 (13.6)	179 (13.6)	†
2000–2004	74 (21.8)	290 (22.0)	†
2005–2010	200 (59.0)	773 (58.7)	†
Years in CPRD prior to index date			
Mean ± SD	11.0 ± 5.6	11.3 ± 5.5	†
Age at index date (years)			
<40	17 (5.0)	68 (5.2)	†
40–49	19 (5.6)	76 (5.8)	†
50–59	46 (13.6)	181 (13.7)	†
60–69	75 (22.1)	294 (22.3)	†
70–79	104 (30.7)	409 (31.0)	†
80–89	78 (23.0)	290 (22.0)	†
Mean ± SD	68.1 ± 13.8	67.9 ± 13.8	†
BMI			
<18.5	14 (4.1)	27 (2.1)	2.04 (1.01, 4.13)
18.5–25	102 (30.1)	402 (30.5)	1.00 (Ref)
25–30	93 (27.4)	394 (29.9)	0.94 (0.69, 1.29)
30+	77 (22.7)	239 (18.1)	1.29 (0.92, 1.81)
Unknown	53 (15.6)	256 (19.4)	0.77 (0.52, 1.15)
Mean ± SD	26.7 ± 5.4	26.7 ± 5.4	
Smoking status			
Non smoker	163 (48.1)	711 (54.0)	1.00 (Ref)
Smoker	64 (18.9)	170 (12.9)	1.67 (1.18, 2.35)
Ex-smoker	85 (25.1)	286 (21.7)	1.33 (0.98, 1.79)
Unknown	27 (8.0)	151 (11.5)	0.69 (0.41, 1.14)
Diabetes	58 (17.1)	104 (7.9)	2.52 (1.76, 3.61)
Type-I	9 (2.7)	8 (0.6)	4.53 (1.74, 11.8)
Type-II	42 (12.4)	89 (6.8)	2.13 (1.41, 3.22)
Type unknown	7 (2.1)	7 (0.5)	3.93 (1.38, 11.21)
Alcohol-related conditions	15 (4.4)	18 (1.4)	3.46 (1.67, 7.16)
HBV and/or HCV infection	7 (2.1)	1 (0.1)	28.00 (3.45, 227.58)
Chronic Liver Disease	40 (11.8)	4 (0.3)	52.21 (16.14, 169.84)
Rare Metabolic Disorders	4 (1.2)	2 (0.2)	8.00 (1.47, 43.7)
Bilateral Oophorectomy	13 (3.8)	74 (5.6)	0.68 (0.37, 1.25)
Hysterectomy	59 (20.7)	280 (20.4)	1.02 (0.74, 1.40)
Paracetamol use[c]	239 (70.5)	841 (63.8)	1.43 (1.08, 1.91)

	Cases N=339 (%)	Controls N=1318 (%)	Univariable OR[a] (95% CI)
Diabetic medication use	31 (9.1)	70 (5.3)	1.83 (1.16, 2.89)
Statin use[c]	67 (19.8)	286 (21.7)	0.87 (0.62, 1.20)
Aspirin use[c]	96 (28.3)	318 (24.1)	1.27 (0.95, 1.71)

[†] Matching factors

[a] Adjusted for matching factors

[b] Rare metabolic disorders=hemochromatosis, Wilson Disease, alpha-1 antitrypsin deficiency, porphyrias

[c] Defined as having at least one prescription before index date

Table 2

Odds ratios for the association between menopausal hormone therapy (MHT) use and risk of liver cancer

	Cases N=339 (%)	Controls N=1318 (%)	Crude OR[a] (95% CI)	Univariable OR[b] (95% CI)
Any MHT Use				
0–1 Prescription	297 (87.6)	1092 (82.9)	1.00 (Ref)	1.00 (Ref)
2+ Prescriptions	42 (12.4)	226 (17.2)	0.62 (0.42, 0.94)	0.58 (0.37, 0.90)
Number of MHT Prescriptions				
Non use (0–1 Prescription)	297 (87.6)	1092 (82.9)	1.00 (Ref)	1.00 (Ref)
2–9	13 (3.8)	86 (6.5)	0.51 (0.27, 0.96)	0.46 (0.24, 0.89)
10+	29 (8.6)	140 (10.6)	0.70 (0.44, 1.12)	0.66 (0.40, 1.10)
Type of MHT				
Non use (0–1 Prescription)	297 (87.6)	1092 (82.9)	1.00 (Ref)	1.00 (Ref)
Estrogen	14 (4.1)	91 (6.9)	0.52 (0.28, 0.96)	0.44 (0.22, 0.88)
Estrogen/Progesterone	23 (6.8)	113 (8.6)	0.69 (0.41, 1.14)	0.63 (0.37, 1.09)
Both E/P and Estrogen	5 (1.5)	22 (1.7)	0.74 (0.27, 2.03)	0.73 (0.26, 2.06)
Recency of MHT Use[c]				
Non use (0–1 Prescription)	297 (87.6)	1092 (82.9)	1.00 (Ref)	1.00 (Ref)
Current MHT Use	12 (3.5)	63 (4.8)	0.64 (0.32, 1.26)	0.72 (0.36, 1.40)
2–9 Prescriptions	3 (0.9)	18 (1.4)	0.57 (0.16, 2.03)	0.63 (0.17, 2.29)
10+ Prescriptions	9 (2.7)	45 (3.4)	0.67 (0.30, 1.46)	0.76 (0.34, 1.71)
Past MHT Use	30 (8.9)	163 (12.4)	0.62 (0.39, 0.98)	0.53 (0.32, 0.88)
2–9 Prescriptions	10 (3.0)	68 (5.2)	0.50 (0.25, 1.01)	0.42 (0.20, 0.89)
10+ Prescriptions	20 (5.9)	95 (7.2)	0.71 (0.41, 1.24)	0.61 (0.34, 1.11)

[a] Conditional on matching factors

[b] Adjusted for BMI, smoking, alcohol-re I a ted di orders, HBV, HCV, diabetes, paracetamol use, rare metabolic disorders, aspirin, diabetes medications, bilateral oophorectomy, hysterectomy, and statins, conditional on

[c] Current use=last Rx with 1 year of index date

Table 3

Odds ratios for the association between menopausal hormone therapy (MHT) and risk of liver cancer among non-users of statins

	Cases N=272 (%)	Controls N=1032 (%)	Crude OR[a] (95% Cl)	Adjusted OR[b] (95% Cl)
Any MHT Use				
0–1 Prescription	238 (87.5)	862 (83.5)	1.00 (Ref)	1.00 (Ref)
2+ Prescriptions	34 (12.5)	170 (16.7)	0.64 (0.40, 1.03)	0.55 (0.32, 0.92)
Number of prescriptions				
Non use (0–1 Prescription)	238 (87.5)	862 (83.5)	1.00 (Ref)	1.00 (Ref)
2–9	11 (4.0)	68 (6.6)	0.56 (0.28, 1.14)	0.47 (0.22, 1.00)
10+	23 (8.5)	102 (9.9)	0.69 (0.39, 1.20)	0.60 (0.32, 1.11)
Type of MHT				
Non use (0–1 Prescription)	238 (87.5)	862 (83.5)	1.00 (Ref)	1.00 (Ref)
Estrogen	8 (2.9)	65 (6.3)	0.45 (0.21, 0.94)	0.39 (0.17, 0.89)
Estrogen/Progesterone	21 (7.7)	87 (8.4)	0.87 (0.51, 1.44)	0.78 (0.46, 1.33)
Both E/P and Estrogen	5 (1.8)	18 (1.74)	1.01 (0.37, 2.74)	1.00 (0.36, 2.83)

[a] Conditional on matching factors (index year, age at index, length of history before index date)

[b] Adjusted for BMI, smoking, alcohol-related disorders, HBV or HCV, diabetes, paracetamol use, rare metabolic disorders, aspirin, diabetes medications, bilateral oophorectomy, and hysterectomy, conditional on matching factors

Table 4

Odds ratios for the association between menopausal hormone therary (MHT) use amond risk of liver cancer among women with and without diabetes

	Cases and controls without diabetes (N= 1405)				Cases and controls with diabetes (N= 290)			
	Cases N=281 (%)	Controls N=1124 (%)	OR[a] (95% CI)	OR[b](95%CI)	Cases N=58 (%)	Controls N=232 (%)	OR[a] (95% CI)	OR[b](95%CI)
MHT Use								
0–1 Rx	245 (87.2)	936 (83.3)	1.00 (Ref)	1.00 (Ref)	52 (89.7)	205 (88.4)	1.00 (Ref)	1.00 (Ref)
2+Rx	36 (12.8)	188 (16.7)	0.67 (0.44, 1.03)	0.49 (0.30, 0.80)	6 (10.3)	27 (11.6)	0.84 (0.29, 2.45)	0.57 (0.09, 3.53)
Number of Prescriptions								
0–1	245 (87.2)	936 (83.3)	1.00 (Ref)	1.00 (Ref)	52 (89.7)	205 (88.4)	1.00 (Ref)	1.00 (Ref)
2–9	11 (3.9)	75 (6.7)	0.52 (0.26, 1.02)	0.41 (0.19, 0.90)	2 (3.5)	7 (3.0)	1.11 (0.22, 5.67)	0.51 (0.04, 6.53)
≥ 10	25 (8.9)	113 (10.1)	0.28 (0.47, 1.28)	0.54 (0.30, 0.95)	4 (6.9)	20 (8.6)	0.72 (0.19, 2.67)	0.61 (0.07, 5.77)
Recency of MHT Use								
No Use (0–1 Rx)	245 (87.2)	936 (83.3)	1.00 (Ref)	1.00 (Ref)	52 (89.7)	205 (88.4)	1.00 (Ref)	1.00 (Ref)
Current Use[c]	12 (4.3)	69 (6.1)	0.62 (0.32, 1.20)	0.52 (0.25, 1.08)	0 (0.0)	2 (0.9)	--	--
Past Use[d]	24 (8.5)	119 (10.6)	0.71 (0.42, 1.19)	0.47 (0.26, 0.86)	6 (10.3)	25 (10.8)	0.91 (0.31, 2.63)	0.59 (0.10, 3.66)
Type of MHT								
No Use (0–1 Rx)	245 (87.2)	936 (83.3)	1.00 (Ref)	1.00 (Ref)	52 (89.7)	205 (88.4)	1.00 (Ref)	1.00 (Ref)
Estrogen	13 (4.6)	79 (7.0)	0.58 (0.30, 1.10)	0.41 (0.20, 0.84)	1 (1.7)	12 (5.2)	0.23 (0.02, 2.29)	0.80 (0.04, 15.10)
Estrogen/Progesterone	18 (6.4)	92 (8.2)	0.70 (0.41, 1.22)	0.58 (0.32, 1.08)	5 (8.6)	13 (5.6)	1.56 (0.46, 5.34)	0.53 (0.07, 4.06)
Both E/P and Estrogen	5 (1.8)	17 (1.5)	0.98 (0.35, 2.79)	0.37 (0.08, 1.61)	0 (0.0)	2 (0.9)	--	--

[a] Conditional on matching variables

[b] Adjusted for BMI, smoking, alcohol-related disorders, HBV or HCV, chronic liver disease, rare metabolic disorders, aspirin, paracetamol, diabetes medications, and statins, conditional on matching factors

[c] Last rx within 1 year of index date

[d] Last rx more than 1 year before index date

[e] Oral use with or without any other route of administration