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Oophorectomy and risk of non-alcoholic fatty liver disease and primary liver cancer in the Clinical Practice Research Datalink

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Abstract

Incidence of non-alcoholic fatty liver disease (NAFLD) and liver cancer are 2–3 times higher in males than females. Hormonal mechanisms are hypothesized, with studies suggesting that

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oophorectomy may increase risk, but population-based evidence is limited. Thus, we conducted a study within the Clinical Practice Research Datalink, with controls matched to cases of NAFLD (n=10,082 cases/40,344 controls) and liver cancer (n=767 cases/3,068 controls). Odds ratios and 95% confidence intervals were estimated using conditional logistic regression. Effect measure modification by menopausal hormone therapy (MHT) was examined, using likelihood ratio tests and relative excess risk due to interaction (RERI). Oophorectomy was associated with a 29% elevated NAFLD risk (OR=1.29,95% CI:1.18–1.43), which was more pronounced in women without diabetes (OR=1.41,95% CI:1.27–1.57) and in women who had oophorectomy prior to age 50 (OR=1.37,95% CI:1.22–1.52). Compared to women without oophorectomy or MHT use, oophorectomy and MHT were each associated with over 50% elevated risk of NAFLD. However, the combination of oophorectomy and MHT showed evidence of a negative interaction on the multiplicative ($p=0.003$) and additive scales (RERI=-0.28,95% CI:-0.60–0.03, $P=0.08$). Oophorectomy, overall, was not associated with elevated liver cancer risk (OR=1.16,95% CI:0.79–1.69). These findings suggest that oophorectomy may increase the risk of NAFLD, but not liver cancer.

Keywords

Hormones; Liver cancer; Menopausal hormone therapy; Non-alcoholic fatty liver disease; Oophorectomy

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is characterized by fat deposition in the liver which is not attributable to alcohol consumption; this encompasses simple steatosis (e.g., non-alcoholic fatty liver) to more progressive steatosis (e.g., non-alcoholic steatohepatitis) (1, 2). NAFLD prevalence is estimated to range from 10–30% in Western populations (3, 4). Rates of NAFLD have been increasing with the growing prevalence of the known primary risk factors, including obesity, diabetes, and metabolic syndrome (3, 5), and the prevalence of NAFLD is forecast to increase by over 20% between 2015 and 2030 (6). NAFLD can cause inflammation, oxidative stress, insulin resistance, and fibrosis, which may lead to cirrhosis and/or liver cancer (3, 5, 7).

Primary liver cancer accounts for approximately 5.6% of new cancer diagnoses worldwide (8), and incidence has been rising rapidly in a number of Western countries, including the United Kingdom (UK) (9). Liver cancer is usually predated by oxidative stress and inflammation (10, 11). While hepatitis B virus (HBV), hepatitis C virus (HCV), and aflatoxin consumption are well accepted risk factors for liver cancer, obesity, type 2 diabetes, and NAFLD have also recently become recognized as important risk factors (6, 11, 12).

Rates of NAFLD and liver cancer are 2–3 times higher in men than in women (3, 11, 13, 14). These differential rates have not been fully explained by known risk factors that vary by sex (15, 16). Thus, it has been suggested that hormones may account for the observed disparity. This hypothesis is supported by several epidemiologic studies have reported that oophorectomy is associated with increased risk of NAFLD (17) and liver cancer (18, 19).

Similarly, ovariectomy of female rodents increases the occurrence of liver disease and tumors (20–22). It has also been reported that ovariectomy increases oxidative stress and inflammation in the livers of female mice (23). Conversely, use of exogenous hormonal preparations, such as menopausal hormone therapy (MHT), has been associated with a lower risk of NAFLD (24) and liver cancer (18, 25002D27). This evidence suggests that oophorectomy may increase, and MHT may reduce, risk of NAFLD and liver cancer.

The few prior population-based studies that have examined oophorectomy have been limited by small sample size (17, 18) and/or self-reported oophorectomy (18, 19). Additionally, the association between age at oophorectomy and NAFLD or liver cancer risk has not been thoroughly examined, and no studies to date have examined if MHT modifies the association between oophorectomy and NAFLD or liver cancer. Thus, the current study examined oophorectomy ascertained from medical records in association with the risk of NAFLD and primary liver cancer, and whether MHT modifies risk, in a large cohort of UK women.

MATERIALS AND METHODS

Data source

We conducted a nested case-control study within the Clinical Practice Research Datalink (CPRD), a UK database of anonymized, population-based electronic medical records of the National Health Services (28). The age and gender distributions in the CPRD are representative of the general UK population (29). The CPRD contains medical data on approximately 6.9% of the UK population (28). Data, including demographic information, medical diagnoses, hospital referrals, and prescriptions, are collected on a monthly basis from general practitioners (30). Clinical information is recorded using Read codes rather than International Classification of Diseases (ICD) codes. Additionally, all prescribing information for medications is captured in an anonymous format for research purposes. Validation studies have shown the CPRD to be highly complete and accurate regarding clinical illness diagnoses and prescription information (30). Supporting medical documents routinely show that diagnoses in the CPRD are present in more than 90% of clinical records (31) and approximately 95% of primary cancers recorded in CPRD are confirmed as incident by another source (e.g., cancer registry) (32). This study was approved by the National Institutes of Health Office of Human Subjects Research.

Study population

The study population was drawn from all females in the CPRD from January 1, 1988 through July 31, 2017, from practices with up to standard (UTS) time. UTS time does not ensure data quality, but it is recommended for use as a proxy of quality data recording by the practices (28). Cases included NAFLD (Read code: J61y100) and primary liver cancer (Read codes: B150300, B150z00, B152.00, BB5D500, BB5D700, BB5D800, B15z.00, B15.00, B150.00, B151.00, B151z00, B151200, B151400, B150000, B150200, B151000, BB5D513, BB5D512, Byu1100). For liver cancer, cases were not eligible if they had a liver metastasis or a diagnosis of any of the five cancers most likely to metastasize to the liver in the 5 years prior to liver cancer diagnosis (i.e., lung, stomach, breast, colon, or pancreatic cancer).

Controls were matched to cases at a four-to-one ratio by age (year of birth), general practice, and length of time in the CPRD. Controls met the following criteria: 1) no previous NAFLD or liver cancer diagnosis; 2) the same number of years as the matched case in the CPRD; and 3) alive with activity in the CPRD at the time of the matched case's date of diagnosis. The index date for each control was recorded as the diagnosis date of the matched case. Our study population consisted of 10,082 NAFLD cases and 40,344 matched controls and 767 liver cancer cases and 3,068 matched controls.

Three separate case-control matches were conducted for this study. In addition to the primary match, we conducted matches based on the presence or absence of diabetes at index date (for both the NAFLD and liver cancer analyses) and the presence or absence of chronic liver disease at index date (for the liver cancer analysis only). Both used the same matching factors as the primary match, but additionally allowed for stratification by diabetes and by chronic liver disease.

Oophorectomy

We identified all oophorectomies prior to diagnosis among the cases or index date among the controls. Oophorectomy was further classified by laterality of oophorectomy (bilateral, unilateral, or unknown), length of time between oophorectomy and diagnosis or index date (<20 or ≥20 years), and age at oophorectomy (<50 or ≥50 years of age). The referent group were women who had not had an oophorectomy prior to diagnosis date or index date. The ratio of the odds ratios (ROR) was calculated to determine heterogeneity between oophorectomy laterality, length of time between oophorectomy and diagnosis, and age at oophorectomy procedure.

Statistical Analysis

We calculated odds ratios (ORs) and 95% confidence intervals (95% CI) using conditional logistic regression analysis, adjusting for smoking status prior to diagnosis (never, former, current smoker), history of alcohol-related disorders, diagnosis of HBV or HCV, body mass index (BMI, <18.5, 18.5–<25, 25–<30, ≥30 kg/m²), and MHT use (ever, never). Covariates were recorded prior to diagnosis among the cases or index date among the controls. Missing values for BMI (24.1% of NAFLD population and 29.6% of the liver cancer population) and smoking status (2.2% and 6.9%, respectively) were imputed using the PROC MI procedure (SAS Institute Inc., Cary, NC). Effect measure modification was evaluated by testing for deviation from 1) a multiplicative interaction model, using the likelihood ratio test to compare the fit of models with and without an interaction term, and 2) an additive interaction model, using the relative excess risk due to interaction (RERI) (33). We further examined stratification of the oophorectomy-liver outcome relationship by type of MHT use (any MHT use, estrogen only, estrogen-progesterone combination only), diabetes, and, for the liver cancer cases, the presence of chronic liver disease. Finally, to ensure maximum recording of medical history, we conducted a sensitivity analysis whereby we required all patients to have at least three years of history in the CPRD prior to diagnosis or index date. All tests were 2-sided. All statistical analyses were performed using SAS Software 9.4 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Characteristics of the NAFLD and liver cancer cases and matched controls are represented in Table 1. Both case groups were more likely than the matched controls to have a history of diabetes and smoking. NAFLD cases were more likely to be classified as overweight or obese and to have used MHT. Liver cancer cases were more likely to have alcohol-related disorders, chronic HBV or HCV infection, and a history of chronic liver disease.

Women who had undergone an oophorectomy had a 29% increased risk of NAFLD (OR=1.29, 95% CI: 1.18, 1.43), compared to women with both ovaries (Table 2). The increased risk of NAFLD associated with oophorectomy was consistent for bilateral and unilateral oophorectomy (OR_{bilateral}=1.30, 95% CI: 1.16, 1.44 and OR_{unilateral}=1.37, 95% CI: 1.11, 1.68) and length of time between surgery and NAFLD diagnosis (OR_{<20 years}=1.34, 95% CI: 1.20, 1.49 and OR_{≥20 years}=1.20, 95% CI: 1.01, 1.43). There was evidence of heterogeneity by age at oophorectomy, with women receiving an oophorectomy prior to age 50 at a higher risk of NAFLD (OR_{<50 years}=1.37, 95% CI: 1.22, 1.52 and OR_{≥50 years}=1.15, 95% CI: 0.98, 1.36; ROR=1.18, 95% CI: 0.98, 1.43, *p*=0.09). Further stratification by age at oophorectomy (<40, 40–<45, 45–<50, and ≥50 years) produced similar results. Oophorectomy was not associated with an increased risk of liver cancer (OR=1.16, 95% CI: 0.79, 1.69). However, oophorectomy prior to age 45 was associated with a 71–75% increased risk, though estimates included the null (OR_{<40 years}=1.75, 95% CI: 0.80, 3.79, OR_{40–<45 years}=1.71, 95% CI: 0.80, 3.65). In the sensitivity analysis where we required all women to have at least a three-year history in the CPRD prior to diagnosis or index date, results were consistent (data not shown).

In Table 3, we examined the interaction between oophorectomy and MHT use. There is evidence of a negative interaction of MHT use on the association between oophorectomy and NAFLD on both the multiplicative (*P*-interaction=0.003) and additive scale (RERI=−0.28, 95% CI: −0.60, 0.03, *p*=0.08). Oophorectomy was associated with a 54% increased risk of NAFLD (OR=1.54, 95% CI: 1.33, 1.77) among women with no MHT use, but only a 15% increased risk of NAFLD (OR=1.15, 95% CI: 1.02, 1.30) among women with MHT use. Compared to women with no oophorectomy and no MHT use, the combination of oophorectomy and MHT use was associated with a less-than-additive 89% increased risk of NAFLD (OR=1.89, 95% CI: 1.68, 2.13). This relationship was similar for estrogen only use and estrogen-progesterone use. There was no evidence for effect modification by age, BMI, or smoking status (*P* 0.05) on the association between oophorectomy and NAFLD or liver cancer. Additionally, there was no evidence for effect modification by MHT use (*P*-interaction 0.05) on the association between oophorectomy and liver cancer, with women that had an oophorectomy and used MHT at no increased risk (OR=1.01, 95% CI: 0.55, 1.87).

When stratified by diabetes, oophorectomy was associated with a slightly higher risk of NAFLD among individuals without a history of diabetes (OR=1.41, 95% CI: 1.27, 1.57) versus those with a history of diabetes (OR=1.10, 95% CI: 0.85, 1.42, *P*-interaction=0.07, Supplemental Table 1). The lack of an association between oophorectomy and liver cancer

was consistent when stratified by history of diabetes or chronic liver disease (Supplemental Table 2).

DISCUSSION

Oophorectomy was associated with a 29% increased risk of NAFLD, which was stronger for women that had the procedure prior to age 50 or women without a history of diabetes. There was a less-than-additive interaction between MHT use and oophorectomy, resulting in an 89% increased risk of NAFLD among women with a history of both MHT use and oophorectomy, compared to women with neither. Overall, oophorectomy was not associated with liver cancer risk.

In this study, we comprehensively evaluated the association between oophorectomy and NAFLD and liver cancer, utilizing data recorded by general practitioners. We report that any oophorectomy is associated with a 29% increased risk of NAFLD, and a bilateral oophorectomy is associated with a 30% increased risk. Similarly, in a study of women with a prior diagnosis of endometrial cancer, medically recorded bilateral oophorectomy increased risk of NAFLD by 70% (17). Premenopausal bilateral oophorectomy at the time of hysterectomy has also been found to increase risk of death by cardiovascular disease and all-cause mortality compared to women with ovarian preservation in UK (34) and US populations (35–37). As cardiovascular disease is the main cause of death among persons with NAFLD (38), the association observed between oophorectomy and cardiovascular disease further supports the findings of the current study.

Experimentally, ovariectomized rats fed a high-fat diet have disrupted lipid metabolism, which results in hepatic fat and cholesterol accumulation (39). Similarly, ovariectomized mice fed a high-fat diet have accelerated NAFLD progression (22). Mechanisms underlying liver fat accumulation may be in part due to improper activation of lipid oxidation and attenuated lipid exportation in ovariectomized rodents fed a high-fat diet (39).

We found no association between oophorectomy, overall, and liver cancer. However, unilateral oophorectomy, <20 years since oophorectomy, and oophorectomy prior to age 50 were associated with possible increased risk of liver cancer. These findings differ from prior experimental and population-based studies. Several experimental animal studies have reported that ovariectomy increases liver cancer development (20, 21) and accelerates tumor growth in rodents (40). Two population-based studies of the oophorectomy-liver cancer association have previously been conducted (18, 19). In a Taiwanese study, women who had a premenopausal oophorectomy were at 2.6-fold increased risk factor of hepatocellular carcinoma (the dominant histology of liver cancer) (18), while a US study conducted by our group reported bilateral oophorectomy to be associated with twice the risk of hepatocellular carcinoma (19). The previous two reports included only diagnostically confirmed hepatocellular carcinoma cases and relied on self-reported oophorectomy (18, 19), which may have lower accuracy than oophorectomy recorded in medical records (41). In contrast, the current study includes all primary liver cancer cases and utilized oophorectomy recorded in the medical records. Thus, the somewhat discrepant findings might be partially explained by differences in case definition and exposure assessment.

MHT use has also been associated with lower risk of NAFLD and lower liver enzyme levels (24, 42, 43). However, in the current study, MHT use among women without an oophorectomy was associated with a 64% increased risk of NAFLD. MHT has been shown to improve insulin sensitivity without affecting body composition, and this improved insulin sensitivity typically reverses within one year after discontinuation of MHT (44). Thus, the current study may have included some women after they have discontinued MHT use. Prior studies also have suggested that prolonged exposure to estrogen reduces the risk of liver cancer (45). MHT use has been found to be associated with a 30–80% decreased risk of liver cancer in studies conducted within the UK (14), Italy (26, 46), Sweden (27), and Taiwan (18). However, these findings are contradicted by several studies reporting null associations of MHT and liver cancer (19, 47). Similar to a prior study conducted by our team using data from CPRD (25), we report that MHT use among women without an oophorectomy was associated with a 17% decreased liver cancer risk. The prior study, however, did not have information on oophorectomy status. In our current study, we report that women that had an oophorectomy and used MHT had no increased risk of liver cancer.

The mammalian liver is a sexually dimorphic organ, where many metabolic processes are regulated by androgens and estrogens. For example, the liver exhibits major sex differences in the profiles of steroid and drug metabolism (48, 49). Recent evidence suggests that estrogens could have both a protective and deleterious effect on hepatocarcinogenesis (50). In the current study, we found that MHT and oophorectomy were both associated with an elevated risk of NAFLD. This suggests that any imbalance in the hormonal milieu may have consequences for early liver tumorigenesis.

Our study has several limitations. First, as this study was not linked to a cancer registry, it is possible that some secondary liver cancer cases were misclassified as primary liver cancer cases. However, we attempted to control for this by excluding patients with diagnoses of cancers most likely to metastasize to the liver (i.e., lung, stomach, breast, colon, pancreatic cancer) in the past five years. Additionally, NAFLD may not have been completely ascertained as it can be asymptomatic at early stages (51). However, nondifferential sensitivity of disease detection will likely result in our reported OR being biased towards the null (52). Second, because we did not have data on age at menopause, we stratified the analysis on age 50. Third, we cannot be certain that all HBV and HCV diagnoses were captured in the medical record data, as infected individuals can be asymptomatic and persons are only tested when there is a reason to do so. Additionally, CPRD captures limited information on alcohol use; thus, we utilized medical disorders known to be associated with alcohol use (e.g., cirrhosis) (53). While these conditions likely serve as a proxy only for individuals with extreme alcohol use, heavy, not light-to-moderate, alcohol consumption is associated with an increased risk of liver cancer (54). Finally, CPRD does not consistently record race and ethnicity of individuals, thus these variables were not included as covariates. Nonetheless, the UK population is predominantly white, therefore racial/ethnic differences are unlikely to attenuate our results. Generalizing our findings to other populations and racial/ethnic groups, however, should be done with caution.

Despite these limitations, our study had several strengths including its large sample size. Additionally, the CPRD has demonstrated completeness of cancer diagnoses and

pharmaceutical information (30, 31). Our study pulled from medical records that are routinely collected from the population without the intention of being included in a study, minimizing recall and self-report biases. Since the UK utilizes a universal healthcare system, potential systematic exclusion of specific socioeconomic groups was minimized. Finally, our analysis accounted for many potential confounders, including BMI, diabetes, history of alcohol abuse, smoking, and HBV/HCV infection.

In conclusion, oophorectomy increased the risk of NAFLD, particularly among women with oophorectomy at a younger age or without diabetes. The highest NAFLD risk was among women who had an oophorectomy and used MHT, suggesting that a perturbation in the hormonal milieu may be involved in NAFLD development, but the interaction was less-than-additive. There was no overall association between oophorectomy and liver cancer risk. Future studies are needed to determine hormonal mechanisms underlying the oophorectomy-NAFLD association and to further clarify the sex disparity found in NAFLD and liver cancer.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

BMI	body mass index
CI	confidence interval
CPRD	Clinical Practice Research Datalink
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
MHT	menopausal hormone therapy
NAFLD	non-alcoholic fatty liver disease
OR	odds ratio
UK	United Kingdom

References

1. Sayiner M, Koenig A, Henry L, et al. Epidemiology of Nonalcoholic Fatty Liver Disease and Nonalcoholic Steatohepatitis in the United States and the Rest of the World. *Clin Liver Dis* 2016;20(2):205–14. [PubMed: 27063264]
2. Chalasani N, Younossi Z, Lavine JE, et al. The diagnosis and management of non-alcoholic fatty liver disease: practice guideline by the American Gastroenterological Association, American Association for the Study of Liver Diseases, and American College of Gastroenterology. *Gastroenterology* 2012;142(7):1592–609. [PubMed: 22656328]
3. Vernon G, Baranova A, Younossi ZM. Systematic review: the epidemiology and natural history of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in adults. *Alimentary pharmacology & therapeutics* 2011;34(3):274–85. [PubMed: 21623852]
4. Lazo M, Hernaez R, Eberhardt MS, et al. Prevalence of nonalcoholic fatty liver disease in the United States: the Third National Health and Nutrition Examination Survey, 1988–1994. *Am J Epidemiol* 2013;178(1):38–45. [PubMed: 23703888]
5. Engin A Non-Alcoholic Fatty Liver Disease. *Adv Exp Med Biol* 2017;960:443–67. [PubMed: 28585211]
6. Estes C, Razavi H, Loomba R, et al. Modeling the epidemic of nonalcoholic fatty liver disease demonstrates an exponential increase in burden of disease. *Hepatology* 2018;67(1):123–33. [PubMed: 28802062]
7. Shen M, Shi H. Sex Hormones and Their Receptors Regulate Liver Energy Homeostasis. *Int J Endocrinol* 2015;2015:294278. [PubMed: 26491440]
8. Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012. *International Journal of Cancer* 2015;136(5):E359–E86. [PubMed: 25220842]
9. Ladeb NG, Khan SA, Crossey MM, et al. Incidence and mortality of primary liver cancer in England and Wales: changing patterns and ethnic variations. *World J Gastroenterol* 2014;20(6):1544–53. [PubMed: 24587630]
10. Ambade A, Mandrekar P. Oxidative stress and inflammation: essential partners in alcoholic liver disease. *International journal of hepatology* 2012;2012:853175. [PubMed: 22500241]
11. McGlynn KA, Petrick JL, London WT. Global epidemiology of hepatocellular carcinoma: an emphasis on demographic and regional variability. *Clinics in liver disease* 2015;19(2):223–38. [PubMed: 25921660]
12. Makarova-Rusher OV, Altekruse SF, McNeel TS, et al. Population attributable fractions of risk factors for hepatocellular carcinoma in the United States. *Cancer* 2016;122(11):1757–65. [PubMed: 26998818]
13. Guy J, Peters MG. Liver Disease in Women: The Influence of Gender on Epidemiology, Natural History, and Patient Outcomes. *Gastroenterology & Hepatology* 2013;9(10):633–9. [PubMed: 24764777]
14. Petrick JL, Braunlin M, Laverson M, et al. International trends in liver cancer incidence, overall and by histologic subtype, 1978–2007. *Int J Cancer* 2016;139(7):1534–45. [PubMed: 27244487]
15. Bakiri L, Wagner EF. Mouse models for liver cancer. *Mol Oncol* 2013;7(2):206–23. [PubMed: 23428636]
16. London WT, Petrick JL, McGlynn KA. Liver Cancer In: Thun MJ, Linet MS, Cerhan JR, et al., eds. *Schottenfeld and Fraumeni Cancer Epidemiology and Prevention*. New York, NY: Oxford University Press, 2018:p. 635–60.
17. Matsuo K, Gualtieri MR, Cahoon SS, et al. Surgical menopause and increased risk of nonalcoholic fatty liver disease in endometrial cancer. *Menopause* 2016;23(2):189–96. [PubMed: 26173075]
18. Yu MW, Chang HC, Chang SC, et al. Role of reproductive factors in hepatocellular carcinoma: Impact on hepatitis B- and C-related risk. *Hepatology* 2003;38(6):1393–400. [PubMed: 14647050]
19. McGlynn KA, Sahasrabudhe VV, Campbell PT, et al. Reproductive factors, exogenous hormone use and risk of liver cancer among U.S. women: Results from the Liver Cancer Pooling Project. *British journal of cancer* 2015;(In Press).

20. Vesselinovitch SD, Itze L, Mihailovich N, et al. Modifying role of partial hepatectomy and gonadectomy in ethylnitrosourea-induced hepatocarcinogenesis. *Cancer Res* 1980;40(5):1538–42. [PubMed: 7370992]
21. Nakatani T, Roy G, Fujimoto N, et al. Sex hormone dependency of diethylnitrosamine-induced liver tumors in mice and chemoprevention by leuprorelin. *Jpn J Cancer Res* 2001;92(3):249–56. [PubMed: 11267934]
22. Kamada Y, Kiso S, Yoshida Y, et al. Estrogen deficiency worsens steatohepatitis in mice fed high-fat and high-cholesterol diet. *Am J Physiol Gastrointest Liver Physiol* 2011;301(6):G1031–43. [PubMed: 21885686]
23. Kireev RA, Tresguerres AC, Garcia C, et al. Hormonal regulation of pro-inflammatory and lipid peroxidation processes in liver of old ovariectomized female rats. *Biogerontology* 2010;11(2):229–43. [PubMed: 19633997]
24. Clark JM, Brancati FL, Diehl AM. Nonalcoholic fatty liver disease. *Gastroenterology* 2002;122(6):1649–57. [PubMed: 12016429]
25. McGlynn KA, Hagberg K, Chen J, et al. Menopausal hormone therapy use and risk of primary liver cancer in the clinical practice research datalink. *Int J Cancer* 2016;138(9):2146–53. [PubMed: 26662112]
26. Fernandez E, Gallus S, Bosetti C, et al. Hormone replacement therapy and cancer risk: a systematic analysis from a network of case-control studies. *Int J Cancer* 2003;105(3):408–12. [PubMed: 12704678]
27. Persson I, Yuen J, Bergkvist L, et al. Cancer incidence and mortality in women receiving estrogen and estrogen-progestin replacement therapy--long-term follow-up of a Swedish cohort. *Int J Cancer* 1996;67(3):327–32. [PubMed: 8707404]
28. Herrett E, Gallagher AM, Bhaskaran K, et al. Data Resource Profile: Clinical Practice Research Datalink (CPRD). *Int J Epidemiol* 2015;44(3):827–36. [PubMed: 26050254]
29. Lawson DH, Sherman V, Hollowell J. The General Practice Research Database. Scientific and Ethical Advisory Group. *QJM : monthly journal of the Association of Physicians* 1998;91(6):445–52. [PubMed: 9709463]
30. Jick H, Jick SS, Derby LE. Validation of information recorded on general practitioner based computerised data resource in the United Kingdom. *BMJ* 1991;302(6779):766–8. [PubMed: 2021768]
31. Jick SS, Kaye JA, Vasilakis-Scaramozza C, et al. Validity of the general practice research database. *Pharmacotherapy* 2003;23(5):686–9. [PubMed: 12741446]
32. Margulis AV, Fortuny J, Kaye JA, et al. Validation of Cancer Cases Using Primary Care, Cancer Registry, and Hospitalization Data in the UK. *Epidemiology* 2017.
33. Hosmer DW, Lemeshow S. Confidence interval estimation of interaction. *Epidemiology* 1992;3(5):452–6. [PubMed: 1391139]
34. Mytton J, Evison F, Chilton PJ, et al. Removal of all ovarian tissue versus conserving ovarian tissue at time of hysterectomy in premenopausal patients with benign disease: study using routine data and data linkage. *BMJ* 2017;356:j372. [PubMed: 28167486]
35. Parker WH. Ovarian conservation versus bilateral oophorectomy at the time of hysterectomy for benign disease. *Menopause* 2014;21(2):192–4. [PubMed: 23880797]
36. Parker WH, Feskanich D, Broder MS, et al. Long-Term Mortality Associated With Oophorectomy Compared With Ovarian Conservation in the Nurses' Health Study. *Obstetrics & Gynecology* 2013;121(4):709–16. [PubMed: 23635669]
37. Rivera CM, Grossardt BR, Rhodes DJ, et al. Increased cardiovascular mortality after early bilateral oophorectomy. *Menopause* 2009;16(1):15–23. [PubMed: 19034050]
38. Francque SM, van der Graaff D, Kwanten WJ. Non-alcoholic fatty liver disease and cardiovascular risk: Pathophysiological mechanisms and implications. *Journal of hepatology* 2016;65(2):425–43. [PubMed: 27091791]
39. Ngo Sock ET, Cote I, Mentor JS, et al. Ovariectomy stimulates hepatic fat and cholesterol accumulation in high-fat diet-fed rats. *Horm Metab Res* 2013;45(4):283–90. [PubMed: 23225241]

40. Goldfarb S, Pugh TD. Ovariectomy accelerates the growth of microscopic hepatocellular neoplasms in the mouse: possible association with whole body growth and fat deposition. *Cancer Res* 1990;50(21):6779–82. [PubMed: 2208142]
41. Phipps AI, Buist DS. Validation of self-reported history of hysterectomy and oophorectomy among women in an integrated group practice setting. *Menopause* 2009;16(3):576–81. [PubMed: 19169161]
42. Kanaya AM, Herrington D, Vittinghoff E, et al. Glycemic effects of postmenopausal hormone therapy: The heart and estrogen/progestin replacement study: a randomized, double-blind, placebo-controlled trial. *Annals of Internal Medicine* 2003;138(1):1–9.
43. McKenzie J, Fisher BM, Jaap AJ, et al. Effects of HRT on liver enzyme levels in women with type 2 diabetes: a randomized placebo-controlled trial. *Clinical Endocrinology* 2006;65(1):40–4. [PubMed: 16817817]
44. Sites CK, L'Hommedieu GD, Toth MJ, et al. The effect of hormone replacement therapy on body composition, body fat distribution, and insulin sensitivity in menopausal women: a randomized, double-blind, placebo-controlled trial. *J Clin Endocrinol Metab* 2005;90(5):2701–7. [PubMed: 15687338]
45. Zhong GC, Liu Y, Chen N, et al. Reproductive factors, menopausal hormone therapies and primary liver cancer risk: a systematic review and dose-response meta-analysis of observational studies. *Hum Reprod Update* 2016;23(1):126–38. [PubMed: 27655589]
46. Tavani A, Negri E, Parazzini F, et al. Female hormone utilisation and risk of hepatocellular carcinoma. *Br J Cancer* 1993;67(3):635–7. [PubMed: 8382515]
47. Yu MC, Tong MJ, Govindarajan S, et al. Nonviral risk factors for hepatocellular carcinoma in a low-risk population, the non-Asians of Los Angeles County, California. *Journal of the National Cancer Institute* 1991;83(24):1820–6. [PubMed: 1660542]
48. Makrilia N, Syrigou E, Kaklamanos I, et al. Hypersensitivity reactions associated with platinum antineoplastic agents: a systematic review. *Met Based Drugs* 2010;2010.
49. Yates FE, Herbst AL, Urquhart J. Sex difference in rate of ring A reduction of delta 4–3-keto-steroids in vitro by rat liver. *Endocrinology* 1958;63(6):887–902. [PubMed: 13609563]
50. Li Z, Tuteja G, Schug J, et al. Foxa1 and Foxa2 are essential for sexual dimorphism in liver cancer. *Cell* 2012;148(1–2):72–83. [PubMed: 22265403]
51. Simeone JC, Bae JP, Hoogwerf BJ, et al. Clinical course of nonalcoholic fatty liver disease: an assessment of severity, progression, and outcomes. *Clin Epidemiol* 2017;9:679–88. [PubMed: 29276410]
52. Rothman KJ, Greenland S, Lash TL. *Modern epidemiology*. 3rd ed Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2008.
53. Efrid LM, Miller DR, Ash AS, et al. Identifying the risks of anticoagulation in patients with substance abuse. *J Gen Intern Med* 2013;28(10):1333–9. [PubMed: 23620189]
54. Petrick JL, Campbell PT, Koshiol J, et al. Tobacco, alcohol use and risk of hepatocellular carcinoma and intrahepatic cholangiocarcinoma: The Liver Cancer Pooling Project. *Br J Cancer* 2018;118(7):1005–12. [PubMed: 29520041]

Table 1.

Characteristics of Non-Alcoholic Fatty Liver Disease and Liver Cancer Cases and Matched Controls in the Clinical Practice Research Datalink (CPRD), 1988–2017.

Characteristics	Non-alcoholic Fatty Liver Disease		Liver Cancer	
	Cases (N=10,082)	Controls (N=40,344)	Cases (N=767)	Controls (N=3,068)
Age (years), mean (SD)	56.1 (12.8)	56.0 (12.8)	70.3 (13.8)	70.3 (13.8)
Body Mass Index (kg/m ²), n (%)				
<18.5	27 (0.3)	794 (2.0)	37 (4.8)	110 (3.6)
18.5–<25.0	779 (7.7)	14323 (35.5)	289 (37.7)	1,181 (38.5)
25.0–<30.0	2,716 (26.9)	13248 (32.8)	248 (32.3)	1,045 (34.1)
>30	6,560 (65.1)	11979 (29.7)	193 (25.2)	732 (23.9)
Alcohol-related disorders, n (%)				
Yes	262 (2.6)	1026 (2.5)	43 (5.6)	42 (1.4)
No	9,820 (97.4)	39318 (97.5)	724 (94.4)	3026 (98.6)
Smoking status, n (%)				
Never	2,972 (29.5)	12,786 (31.7)	167 (21.8)	860 (28.0)
Former	5,221 (51.8)	18,640 (46.2)	409 (53.3)	1717 (56.0)
Current	1,889 (18.7)	8,918 (22.1)	191 (24.9)	491 (16.0)
Chronic HBV/HCV infection, n (%)				
Yes	31 (0.3)	71 (0.2)	23 (3.0)	2 (0.1)
No	10,051 (99.7)	40,273 (99.8)	744 (97.0)	3,066 (99.9)
Chronic Liver Disease, n (%)				
Yes			123 (16.0)	8 (0.3)
No			644 (84.0)	3,060 (99.7)
Diabetes, n (%)				
Yes	2,261 (22.4)	2,443 (6.1)	176 (23.0)	328 (10.7)
No	7,821 (77.6)	37,901 (93.9)	591 (77.0)	2,740 (89.3)
Menopausal Hormone Therapy(MHT), n (%)				
Any MHT use	3,290 (32.6)	10,331 (25.6)	144 (18.8)	660 (21.5)
Estrogen Only	1,248 (12.4)	3,288 (8.2)	55 (8.1)	238 (9.0)
Estrogen+progesterone Only	1,103 (10.9)	4,250 (10.5)	59 (9.3)	248 (8.7)

Table 2.

Adjusted* Odds Ratios (ORs) and 95% Confidence Intervals (CIs) for the Association Between Oophorectomy and Risk of Non-Alcoholic Fatty Liver Disease and Liver Cancer, Clinical Practice Research Datalink (CPRD), 1988–2017.

	Non-alcoholic Fatty Liver Disease			Liver Cancer		
	Cases	Controls	OR(95%CI)	Cases	Controls	OR(95%CI)
Oophorectomy						
No	9,190	38,118	Referent	717	2,902	Referent
Yes	892	2,226	1.29 (1.18, 1.43)	50	166	1.16 (0.79, 1.69)
Laterality						
Bilateral	670	1,630	1.30 (1.16, 1.44)	34	125	1.01 (0.65, 1.59)
Unilateral	165	421	1.37 (1.11, 1.68)	12	31	2.00 (0.93, 4.32)
Unknown	57	175	1.17 (0.84, 1.63)	4	10	0.87 (0.19, 3.92)
Years since oophorectomy						
<20	663	1,583	1.34 (1.20, 1.49)	22	65	1.28 (0.71, 2.32)
20	228	639	1.20 (1.01, 1.43)	28	101	1.09 (0.67, 1.76)
Oophorectomy prior to age 50						
No	245	712	1.15 (0.98, 1.36)	15	66	0.92 (0.48, 1.76)
Yes	647	1,514	1.37 (1.22, 1.52)	35	100	1.30 (0.83, 2.05)
Age at oophorectomy						
<40	250	525	1.50 (1.26, 1.79)	13	28	1.75 (0.80, 3.79)
40–<45	164	425	1.23 (1.00, 1.52)	12	30	1.71 (0.80, 3.65)
45–<50	233	564	1.34 (1.23, 1.59)	10	42	0.78 (0.34, 1.75)
50	245	712	1.15 (0.98, 1.36)	15	66	0.92 (0.48, 1.77)
p-trend			<0.0001			0.4

* Matched on age, general practice, and length of time in the CPRD and adjusted for body mass index (<18.5, 18.5–<25, 25–<30, ≥30 kg/m²), alcohol-related disorders, smoking status (never, former, current), chronic hepatitis B or C infection, chronic liver disease, diabetes, and menopausal hormone therapy use (ever, never).

Table 3.

Adjusted* Odds Ratios (ORs) and 95% Confidence Intervals (CIs) for Interaction Between Oophorectomy and Menopausal Hormone Therapy (MHT) Use and Risk of Non-Alcoholic Fatty Liver Disease and Liver Cancer, Clinical Practice Research Datalink (CPRD), 1988–2017.

Non-alcoholic Fatty Liver Disease		Cases	Controls	Multiplicative Scale		Additive Scale	
				Stratified OR (95% CI)	p-interaction	Single Referent OR (95% CI)	RERI [§] (95%CI)
MHT Use	Oophorectomy						
No	No	6,442	29,113	Referent		Referent	
	Yes	350	900	1.54 (1.33, 1.77)		1.54 (1.33, 1.77)	
Yes	No	2,748	9,005	Referent		1.64 (1.54, 1.75)	
	Yes	542	1,326	1.15 (1.02, 1.30)	0.003	1.89 (1.68, 2.13)	-0.28 (-0.60, 0.03)
Estrogen Use[†]	Oophorectomy						
No	No	6,442	29,113	Referent		Referent	
	Yes	350	900	1.56 (1.34, 1.81)		1.56 (1.34, 1.81)	
Yes	No	889	2,398	Referent		1.83 (1.65, 2.03)	
	Yes	359	890	1.01 (0.85, 1.21)	0.0003	1.85 (1.58, 2.16)	-0.54 (-0.94, -0.13)
Estrogen-Progesterone[‡]	Oophorectomy						
No	No	6,442	29,113	Referent		Referent	
	Yes	350	900	1.60 (1.37, 1.86)		1.60 (1.37, 1.86)	
Yes	No	1,072	4,142	Referent		1.49 (1.36, 1.64)	
	Yes	31	108	0.90 (0.55, 1.48)	0.03	1.34 (0.82, 2.20)	-0.75 (-1.46, -0.03)
Liver Cancer	Oophorectomy						
MHT Use	Oophorectomy						
No	No	593	2,310	Referent		Referent	
	Yes	30	98	1.12 (0.70, 1.81)		1.12 (0.70, 1.81)	
Yes	No	124	592	Referent		0.83 (0.64, 1.08)	
	Yes	20	68	1.22 (0.64, 2.32)	0.8	1.01 (0.55, 1.87)	0.06 (-0.77, 0.90)
Estrogen Use[†]	Oophorectomy						
No	No	593	2,310	Referent		Referent	
	Yes	30	98	1.11 (0.68, 1.82)		1.11 (0.68, 1.82)	
Yes	No	41	189	Referent		0.99 (0.65, 1.50)	
	Yes	14*	49	1.15 (0.51, 2.64)	0.9	1.14 (0.55, 2.36)	0.04 (-1.03, 1.11)
Estrogen-Progesterone[‡]	Oophorectomy						
No	No	593	2,310	Referent		Referent	
	Yes	30	98	1.09 (0.67, 1.78)		1.09 (0.67, 1.78)	

Non-alcoholic Fatty Liver Disease		Cases	Controls	Multiplicative Scale		Additive Scale	
				Stratified OR (95% CI)	p-interaction	Single Referent OR (95% CI)	RERI [§] (95%CI)
Yes	No	57	240	Referent		0.79 (0.53, 1.16)	
	Yes	2	8	0.73 (0.10, 5.53)	0.7	0.58 (0.08, 4.21)	-0.30 (-1.60, 0.99)

* Matched on age, general practice, and length of time in the CPRD and adjusted for body mass index (<18.5, 18.5–<25, 25–<30, 30 kg/m²), alcohol-related disorders, smoking status (never, former, current), chronic hepatitis B or C infection, chronic liver disease, and diabetes.

[†] Estrogen-only use was examined compared to the referent group of no MHT use.

[‡] Estrogen-progesterone combination-only use was examined compared to the referent group of no MHT use.

[§] Relative excess risk due to interaction (RERI). The null hypothesis is that RERI=0. RERI>0 indicates a positive or additive interaction and a RERI<0 indicates a negative or less than additive interaction.

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