Mendelian randomization analyses suggest a role for cholesterol in the development of endometrial cancer

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Short title

The effects of genetically predicted blood lipid levels on endometrial cancer risk

Keywords

Mendelian randomization, endometrial cancer risk, LDL cholesterol, HDL cholesterol, triglycerides

Article Category

Cancer Epidemiology

Novelty and Impact Statement

This is the first study to use Mendelian randomization analysis to explore the relationship between blood lipid levels and risk of endometrial cancer and its subtypes. Genetically predicted lower LDL cholesterol levels or higher HDL cholesterol levels were associated with increased non-endometrioid endometrial cancer risk. Further work is required to elucidate the biology underlying these associations. These results indicate that cholesterol levels could be considered risk factors for endometrial cancer, and studies are required to assess the clinical significance of this association.

Abbreviations

BMI: body mass index

CI: confidence interval

GSMR: Generalised Summary-data based Mendelian Randomisation

GWAS: genome-wide association study

HDL: high-density lipoprotein

HEIDI: Heterogeneity in Dependent Instruments

LD: linkage disequilibrium

LDL: low-density lipoprotein

mtCOJO: multi-trait-based conditional and joint analysis

OR: odds ratio

Abstract

Blood lipids have been associated with the development of a range of cancers, including breast, lung and colorectal cancer. For endometrial cancer, observational studies have reported inconsistent associations between blood lipids and cancer risk. To reduce biases from unmeasured confounding, we performed a bidirectional, two-sample Mendelian randomization analysis to investigate the relationship between levels of three blood lipids (low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol, and triglycerides) and endometrial cancer risk. Genetic variants associated with each of these blood lipid levels ($P < 5\times10^{-8}$) were identified as instrumental variables, and assessed using genome-wide association study data from the Endometrial Cancer Association Consortium (12,906 cases and 108,979 controls) and the Global Lipids Genetic Consortium (n=188,578). Mendelian randomization analyses found genetically raised LDL cholesterol levels to be associated with lower risks of endometrial cancer of all histologies combined, and of endometrioid and non-endometrioid subtypes. Conversely, higher genetically predicted HDL

cholesterol levels were associated with increased risk of non-endometrioid endometrial cancer. After accounting for the potential confounding role of obesity (as measured by genetic variants associated with body mass index), the association between genetically predicted increased LDL cholesterol levels and lower endometrial cancer risk remained significant, especially for non-endometrioid endometrial cancer. There was no evidence to support a role for triglycerides in endometrial cancer development. Our study supports a role for LDL and HDL cholesterol in the development of non-endometrioid endometrial cancer. Further studies are required to understand the mechanisms underlying these findings.

Introduction

Endometrial cancer primarily affects postmenopausal women and approximately 382,000 cases were diagnosed in 2018[1]. Risk factors for endometrial cancer include: family history of endometrial cancer[2]; increasing age, obesity (e.g. high body mass index (BMI) and low physical activity), unopposed estrogen exposure (e.g. early age of menarche, late age of menopause, nulliparity, hormone replacement therapy without progesterone and tamoxifen use)[3,4]; and fasting insulin levels[5]. Despite the advances that have been made in identifying endometrial cancer risk factors, endometrial cancer incidence is still rising[6].

Obesity is the strongest risk factor for endometrial cancer, with up to ~60% increased risk per 5 kg/m^2 higher BMI[7]. However, the mechanism(s) by which higher BMI predisposes to endometrial cancer are not well understood. Adipose tissue is an important site for the synthesis of estrogen (another endometrial cancer risk factor), especially after menopause, via the conversion of androgens to estrogens by aromatase[8]. BMI also has a complex relationship with blood lipid levels, with Mendelian randomization analyses finding bidirectional associations between levels of low-density lipoprotein (LDL) and high-density lipoprotein

(HDL) cholesterol, triglycerides and BMI[9]. Moreover, cholesterol has been suggested to play a role in cancer development by inducing chronic inflammation[10-12].

Blood lipid levels have been suggested to contribute to pathogenesis of endometrial cancer. As hypertriglyceridemia and hyper-LDL cholesterolemia are common in endometrial cancer survivors[13], case-control studies assessing changes in blood lipid levels at/after endometrial cancer diagnosis are susceptible to reverse causation bias[14-16]. Observational studies conducted to examine the association between pre-diagnostic blood lipid levels and endometrial cancer risk[17-23] reported significant positive associations from only three studies assessing blood triglycerides level and endometrial cancer risk[18,19,23]. Inconsistent findings from observational studies could be due to small study populations[17,20] and a lack of adjustment for obesity[18,22]. Further, the use of non-fasting blood lipid levels in observational studies could also contribute to the variation in published findings[17-19,21-23]. Several studies have assessed the association of blood lipids with endometrial cancer by subtype[15,19,21,23], but only one has assessed the pre-diagnostic blood lipid levels. This study reported increased triglycerides levels to be associated with the risk of both type 1 and 2 endometrial cancers[23]. However, this study did not adjust for obesity, and used non-fasting blood lipid levels. As obesity and blood lipid levels are interrelated[9], it has been difficult for observational studies to disentangle the effects of blood lipid levels on endometrial cancer risk. Thus, the relationship between blood lipids and endometrial cancer remains unclear from the existing evidence.

Mendelian randomization is an instrumental variable analysis that assesses the effects of exposures using genetic predictors as instrumental variables[24]. Mendelian randomization uses the principle that the alleles of genetic variants which predict higher levels of an exposure of interest are naturally randomized to individuals at meiosis, a process somewhat comparable

to the random assignment of participants to an exposure in a randomized controlled trial. Thus, associations between genetic variants and the outcome (and hence between the exposure and the outcome) will not be vulnerable to reverse causation because disease develops after meiosis. Provided that the selected genetic variants are associated with the outcome only via their effects on the exposure of interest (i.e. not via pleiotropic effects on other traits which could independently alter disease risk), effect estimates generated by Mendelian randomization analyses should also be less vulnerable to the influence of confounders[24].

In the current study, we employed a two-sample Mendelian randomization framework to assess the relationships between levels of three blood lipids (LDL and HDL cholesterol, and triglycerides) and the risk of endometrial cancer using genome-wide association study (GWAS) data from the Endometrial Cancer Association Consortium (ECAC) and Global Lipids Genetic Consortium (GLGC).

Materials and Methods

GWAS datasets

In this study, we assessed three major blood lipids: LDL and HDL cholesterol, and triglycerides. Summary statistics from GWAS for the three blood lipids in 188,577 individuals of predominantly European ancestry were obtained from the Global Lipid Genetics Consortium[25] (http://csg.sph.umich.edu/willer/public/lipids2013/). A detailed description of the GLGC study has been previously published[25]. Briefly, blood lipid levels were measured more than eight hours after fasting in most GLGC studies. For each genetic variant association with blood lipid levels, association estimates were expressed in standard deviation (SD) per copy of the effect allele.

Endometrial cancer risk estimates were obtained from the largest published meta-GWAS to date, conducted by ECAC in 12,906 endometrial cancer cases and 108,979 controls, all of European ancestry[26]. In a secondary analysis, we investigated relationships between the three blood lipids and endometrial cancer subtypes using ECAC meta-GWAS results restricted to cases with either endometrioid histology (8,758 cases), or non-endometrioid histology (1,230 cases)[26]. Histological subtypes of endometrial cancer were confirmed based on pathology reports, and detailed study descriptions have previously been reported[26,27]. The association estimates were expressed in log(OR) per copy of the effect allele.

Instrumental variable selection

Independent, genome-wide significant genetic variants ($r^2 < 0.05$, $P < 5 \times 10^{-8}$) that were associated with each type of blood lipid were chosen as instrumental variables. Genetic variants with ambiguous strand codification (A/T or C/G) and minor allele frequency more than 0.42 were removed. We compared the allele frequencies between the GLGC and ECAC datasets, and a UKB10K reference panel (a random subset of 10,000 unrelated participants from UK Biobank cohort; https://www.ukbiobank.ac.uk/), and genetic variants with a large allele frequency difference (> 0.2) were also excluded.

Bidirectional Mendelian randomization analysis

We employed bidirectional Generalised Summary-data based Mendelian Randomisation (GSMR) analysis[28] to explore the relationship between the three blood lipids and endometrial cancer. As Mendelian randomization estimates may be confounded by including pleiotropic variants, we implemented the built-in Heterogeneity in Dependent Instruments (HEIDI) outlier test[28] with a P-value threshold of 0.01 to detect and filter heterogeneous variants that are likely pleiotropic. Remaining variants not excluded by HEIDI outlier test were used as non-pleiotropic instrumental variables.

Results with a Bonferroni-adjusted $P < 0.05/3 = 0.017$, correcting for the three blood lipid traits tested, were considered statistically significant. When blood lipid levels were treated as the exposure trait, the resulting effect estimates were expressed as odds ratios (OR) and 95% confidence intervals (CI) for endometrial cancer risk per SD increment in genetically predicted blood lipid level. When endometrial cancer risk was treated as the exposure trait, the resulting estimates represent the SD change for blood lipid level per SD increase in the genetic liability to endometrial cancer. Analyses were performed using default settings in the GSMR extension in GCTA (version 1.92)[28], using the UKB10K reference panel to estimate linkage disequilibrium (LD) between variants. For comparison, we also performed inverse variance weighted (IVW) and MR-Egger regression Mendelian randomization analyses using MR-Base[29].

Conditional Mendelian randomization Analysis

Since obesity could affect associations between blood lipid levels and endometrial cancer[9], we additionally performed conditional Mendelian randomization analysis. GWAS summary statistics for the lipid of interest were conditioned for the effect of genetically predicted BMI using results from the largest GWAS of BMI to date[30]. Conditional analyses were performed using multi-trait-based conditional and joint analysis (mtCOJO) in the GCTA software package (version 1.92)[28] and adjusted estimates were then reanalysed by GSMR.

Results

After removal of potential pleiotropic variants, 140 LDL cholesterol, 163 HDL cholesterol and 104 triglyceride independent genome-wide significant variants were considered as instrumental variables (**Supplementary Tables 1-3**). These instrumental variables were used by GSMR to estimate the effect of blood lipids on endometrial cancer risk of all histologies

combined (results presented in **Table 1** and **Figure 1**). GSMR analysis indicated that genetically raised LDL cholesterol levels were associated with reduced risk of all endometrial cancer histologies combined (OR per SD increase in LDL cholesterol level = 0.88; 95% CI = 0.83-0.93; $P = 7.26 \times 10^{-6}$). Consistent with the divergent roles of LDL and HDL cholesterol[31], GSMR analysis provided evidence that increased HDL cholesterol levels may be associated with increased risk of all endometrial cancer histologies combined (OR 1.07; 95% CI = 1.00-1.14; P = 0.037). Secondary analysis assessing the relationships between blood lipid levels and endometrial cancer subtypes found genetically predicted higher LDL cholesterol levels were associated with lower risk of both endometrioid and non-endometrioid endometrial cancer (**Table 1**). Conversely, genetically predicted higher HDL cholesterol levels showed suggestive evidence of association with higher risk of non-endometrioid endometrial cancer only (**Table 1**). No significant effects were observed for triglycerides on endometrial cancer overall, or its subtypes (**Table 1**). Bidirectional GSMR analysis provided evidence for a unidirectional association e.g. genetically elevated LDL cholesterol level may affect endometrial cancer risk, while genetic liability to endometrial cancer does not appear to affect LDL cholesterol levels (**Table 2**).

To reduce the influence of obesity on the associations between blood lipid levels and endometrial cancer risk, we performed Mendelian randomization analysis conditioning on genetically predicted BMI. Results are presented in **Table 3** and **Supplementary Figure 1**. After controlling for the influence of genetically predicted BMI, the association between genetically predicted LDL cholesterol levels and risk of all histologies combined and non-endometrioid endometrial cancer remained; whereas, the effect of LDL cholesterol level on endometrioid endometrial cancer risk was attenuated and no longer significant (OR 0.93, 95% CI 0.87-1.01; P = 0.07). Conditioning on genetically predicted BMI had minimal impact

on the risk estimates for HDL and endometrial cancer, but associations did not pass the Bonferroni-correction threshold, reflecting the decreased power for these analyses.

Results from IVW and MR-Egger analyses were consistent with our GSMR results (**Supplementary Tables 4 and 5**). None of the MR-Egger intercepts were significantly different from zero (P>0.05), except for the relationship between genetically predicted HDL cholesterol and non-endometrioid endometrial cancer, suggesting pleiotropy may have biased IVW results of HDL cholesterol and non-endometrioid endometrial cancer. However, the MR-Egger regression slope of HDL cholesterol and non-endometrioid endometrial cancer remained statistically significant after accounting for potential pleiotropy, supporting a relationship between HDL cholesterol and endometrial cancer risk (**Supplementary Tables 4 and 5**).

Discussion

To our knowledge, this is the first Mendelian randomization study to assess the effects of genetically predicted blood lipid levels on endometrial cancer risk. While genetically increased LDL cholesterol had a protective effect on endometrial cancer, especially non-endometrioid endometrial cancer, results suggest that genetically increased HDL cholesterol may have an adverse effect on non-endometrioid endometrial cancer risk. The opposing findings for LDL and HDL cholesterol are consistent with their opposing roles. For example, LDL delivers cholesterol to peripheral tissues, whereas HDL removes cholesterol from these tissues and transports it to the liver[31]. We found no evidence of a causal link between triglycerides and endometrial cancer, in contrast to three observational studies that have reported positive associations[18,19,23]. However, as previously noted, none of these studies assessed fasting blood triglycerides and one did not control for the effect of obesity[18].

Mendelian randomization analysis has previously illustrated the complex interrelationship between BMI and blood lipid levels[9]. We therefore performed conditional Mendelian randomization analysis to investigate the influence of genetically predicted BMI on associations between LDL/HDL cholesterol and endometrial cancer risk. Comparison of the LDL/HDL cholesterol association estimates, before and after adjusting for genetically predicted BMI, did not support a role for BMI in the associations with endometrial cancer of non-endometrioid and combined histologies. In contrast, the LDL cholesterol association with endometrioid endometrial cancer was weaker with wider confidence intervals after including genetically predicted BMI as covariate. While a modest protective effect of LDL cholesterol for the endometrioid subtype of endometrial cancer cannot be excluded, this finding indicated that LDL cholesterol is likely to lie in the same causal pathway as obesity, a hypothesis consistent with results from previous genetic studies. Indeed, somewhat surprisingly, previous Mendelian randomization analyses have demonstrated a bidirectional relationship between LDL cholesterol and BMI with one study reporting that increased LDL cholesterol levels were associated with reduced BMI[9] and, another reporting that increased BMI was associated with reduced LDL cholesterol levels[32]. Using Mendelian randomization analyses, we have previously found increased BMI to be associated with increased endometrioid endometrial cancer risk[26,33]. Measured LDL cholesterol levels have also been found to diminish with increasing BMI in overweight individuals[34]; whereas, in the same study, LDL cholesterol levels were only positively correlated with BMI in lean individuals. These findings indicate that the inverse relationship between LDL cholesterol and endometrioid endometrial cancer, a disease primarily affecting overweight individuals[33], may be related to high BMI. Thus, we hypothesise that obesity is likely to be the mediator of the effect of LDL cholesterol on endometrioid endometrial cancer risk (i.e. ↑LDL → ↓BMI → ↓Endometrioid Endometrial Cancer risk) (**Figure 2**). Moreover, as obesity is a stronger risk

factor for endometrioid than for non-endometrioid endometrial cancer[26], it is perhaps not surprising that after adjusting for genetically predicted BMI we only observed an attenuation of the effect of LDL cholesterol on endometrioid endometrial cancer risk.

It is intriguing that our results indicated that, independent of obesity, decreased LDL cholesterol level is inversely associated with risk of non-endometrioid endometrial cancer. While both endometrioid and non-endometrioid endometrial cancer share many other risk factors[35], recent Mendelian randomization analyses have found that obesity and age at menarche are risk factors of endometrioid endometrial cancer only[26].Given the rare nature of non-endometrioid histologies (~10% of all endometrial cancer cases), the tumorigenic mechanisms for these histological subtypes remain largely unknown[35,36]. Thus, further studies are required to explore how higher LDL cholesterol levels could protect against non-endometrioid endometrial cancer development.

As shown in **Table 1**, the association between HDL cholesterol and endometrial cancer appears to be largely driven by the non-endometrioid histological subtype. Despite not passing a Bonferroni statistical significance threshold, there was no substantial change in the association estimate before and after conditioning on BMI, suggesting HDL cholesterol may also affect non-endometrioid endometrial cancer risk independently of obesity. The wide confidence intervals suggest that future studies with more non-endometrioid endometrial cancer cases are required to further dissect any effect.

The conflicting findings regarding the relationships between blood lipids and endometrial cancer risk in observational studies may be due to small sample sizes, varying timing of blood collection (e.g. fasting or non-fasting, and pre- or post- endometrial cancer diagnosis), and varying control for confounding factors. Findings presented in the current study, through the application of bidirectional Mendelian randomization which is less vulnerable to reverse

causation and confounding, have helped to clarify the effects of blood lipids on endometrial cancer risk. Consistent with our findings, other Mendelian randomization studies have observed a positive association between HDL cholesterol and breast cancer risk[37-39], and an inverse association between LDL cholesterol and lung cancer risk[40]. Similarly, a time-to-event Mendelian randomization using data from five longitudinal cohort studies reported increased LDL cholesterol level to be associated with reduced cancer risk (all reported cancer types combined)[41].

The potential mechanisms underlying the effects of decreased LDL and increased HDL cholesterol on cancer risk are unclear as reports of the effects of cholesterol in the literature are conflicting. However, oxidised LDL has been shown to be cytotoxic to cancer cells[42] and can inhibit angiogenesis[43,44], a key oncogenic process. Furthermore, given the prevalence of type 2 diabetes in endometrial cancer patients, it is noteworthy that HDL cholesterol from diabetic patients, which is often glycosylated or oxidised, promotes cancer cell proliferation, migration and invasion in vitro[45] and metastasis in vivo[46].

The validity of Mendelian randomization analysis lies upon the satisfaction of the assumption that the effect of the instrumental variables on the outcome is only mediated through their influence on the measured exposure (i.e. no horizontal pleiotropy). One caveat of our study is that we do not have complete information of all confounding factors, and thus we did not have the ability to evaluate or adjust for unmeasured confounders in the Mendelian randomization analysis. Despite the lack of information on confounding factors, we also performed several Mendelian randomization analyses that are more robust to unmeasured confounding (i.e. HEIDI test in GSMR analysis removes variants which show evidence of horizontal pleiotropy, and MR-Egger analysis allows instrumental variables to be pleiotropic). We observed consistent results across different Mendelian randomization

analyses, and this suggests that residual confounding may have negligible impact on our results. The two-sample Mendelian randomization framework allowed us to incorporate data from two very large independent GWAS datasets to bolster power and yield more precise association estimates. However, we were restricted to summary-level GWAS data, and thus, could not perform more refined analyses (e.g. stratification analysis by BMI).

This Mendelian randomization study provides evidence that increased LDL cholesterol and decreased HDL cholesterol, independent of obesity, may reduce the risk of endometrial cancer. This effect was particularly apparent for the non-endometrioid endometrial cancer subtype, which typically has a more aggressive phenotype and results in poorer prognosis. Although further work is required to elucidate the biological rationale underlying this association, these results suggest low LDL cholesterol levels and high HDL cholesterol levels should be considered as potential risk factors for endometrial cancer.

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Conflict of Interest Statement

P.A.F. reports personal fees from Novartis, grants from Biontech, personal fees from Roche, personal fees from Pfizer, personal fees from Daiichi-Sankyo, personal fees from Astra Zeneca, personal fees from Eisai, personal fees from Merck Sharp & Dohme, grants from Cepheid, personal fees from Lilly, personal fees from Pierre Fabre, personal fees from Seattle Genetics, during the conduct of the study. D.J.T. is an employee of Genomics plc. The

research described in this article was completed before her employment at Genomics plc. All other authors declare no potential conflicts of interest.

Data accessibility

Only publicly available data were used in this study, and data sources and handling of these data are described in the Materials and Methods. Further details are available from the corresponding author upon request.

Ethics approval

This work used published summary-level GWAS meta-analysis results, and thus ethical approval was not required.

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