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

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153

154 **Short title**

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

156

157 **Keywords**

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

159 triglycerides

160

161 **Article Category**

162 Cancer Epidemiology

163

164 **Novelty and Impact Statement**

165 This is the first study to use Mendelian randomization analysis to explore the relationship

166 between blood lipid levels and risk of endometrial cancer and its subtypes. Genetically

167 predicted lower LDL cholesterol levels or higher HDL cholesterol levels were associated

168 with increased non-endometrioid endometrial cancer risk. Further work is required to

169 elucidate the biology underlying these associations. These results indicate that cholesterol

170 levels could be considered risk factors for endometrial cancer, and studies are required to

171 assess the clinical significance of this association.

172

173 **Abbreviations**

174 BMI: body mass index

175 CI: confidence interval

176 GSMR: Generalised Summary-data based Mendelian Randomisation

177 GWAS: genome-wide association study

178 HDL: high-density lipoprotein

179 HEIDI: Heterogeneity in Dependent Instruments

180 LD: linkage disequilibrium

181 LDL: low-density lipoprotein

182 mtCOJO: multi-trait-based conditional and joint analysis

183 OR: odds ratio

184

185 **Abstract**

186 Blood lipids have been associated with the development of a range of cancers, including

187 breast, lung and colorectal cancer. For endometrial cancer, observational studies have

188 reported inconsistent associations between blood lipids and cancer risk. To reduce biases

189 from unmeasured confounding, we performed a bidirectional, two-sample Mendelian

190 randomization analysis to investigate the relationship between levels of three blood lipids

191 (low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol, and

192 triglycerides) and endometrial cancer risk. Genetic variants associated with each of these

193 blood lipid levels ($P < 5 \times 10^{-8}$) were identified as instrumental variables, and assessed using

194 genome-wide association study data from the Endometrial Cancer Association Consortium

195 (12,906 cases and 108,979 controls) and the Global Lipids Genetic Consortium (n=188,578).

196 Mendelian randomization analyses found genetically raised LDL cholesterol levels to be

197 associated with lower risks of endometrial cancer of all histologies combined, and of

198 endometrioid and non-endometrioid subtypes. Conversely, higher genetically predicted HDL

199 cholesterol levels were associated with increased risk of non-endometrioid endometrial

200 cancer. After accounting for the potential confounding role of obesity (as measured by

201 genetic variants associated with body mass index), the association between genetically

202 predicted increased LDL cholesterol levels and lower endometrial cancer risk remained

203 significant, especially for non-endometrioid endometrial cancer. There was no evidence to

204 support a role for triglycerides in endometrial cancer development. Our study supports a role

205 for LDL and HDL cholesterol in the development of non-endometrioid endometrial cancer.

206 Further studies are required to understand the mechanisms underlying these findings.

207

Introduction

209 Endometrial cancer primarily affects postmenopausal women and approximately 382,000

210 cases were diagnosed in 2018[1]. Risk factors for endometrial cancer include: family history of

211 endometrial cancer[2]; increasing age, obesity (e.g. high body mass index (BMI) and low

212 physical activity), unopposed estrogen exposure (e.g. early age of menarche, late age of

213 menopause, nulliparity, hormone replacement therapy without progesterone and tamoxifen

214 use)[3,4]; and fasting insulin levels[5]. Despite the advances that have been made in identifying

215 endometrial cancer risk factors, endometrial cancer incidence is still rising[6].

216 Obesity is the strongest risk factor for endometrial cancer, with up to ~60% increased risk per

217 5 kg/m^2 higher BMI[7]. However, the mechanism(s) by which higher BMI predisposes to

218 endometrial cancer are not well understood. Adipose tissue is an important site for the

219 synthesis of estrogen (another endometrial cancer risk factor), especially after menopause, via

220 the conversion of androgens to estrogens by aromatase[8]. BMI also has a complex relationship

221 with blood lipid levels, with Mendelian randomization analyses finding bidirectional

222 associations between levels of low-density lipoprotein (LDL) and high-density lipoprotein

223   (HDL) cholesterol, triglycerides and BMI[9]. Moreover, cholesterol has been suggested to play

224   a role in cancer development by inducing chronic inflammation[10-12].

225   Blood lipid levels have been suggested to contribute to pathogenesis of endometrial cancer.

226   As hypertriglyceridemia and hyper-LDL cholesterolemia are common in endometrial cancer

227   survivors[13], case-control studies assessing changes in blood lipid levels at/after endometrial

228   cancer diagnosis are susceptible to reverse causation bias[14-16]. Observational studies

229   conducted to examine the association between pre-diagnostic blood lipid levels and

230   endometrial cancer risk[17-23] reported significant positive associations from only three studies

231   assessing blood triglycerides level and endometrial cancer risk[18,19,23]. Inconsistent findings

232   from observational studies could be due to small study populations[17,20] and a lack of

233   adjustment for obesity[18,22]. Further, the use of non-fasting blood lipid levels in observational

234   studies could also contribute to the variation in published findings[17-19,21-23]. Several studies

235   have assessed the association of blood lipids with endometrial cancer by subtype[15,19,21,23], but

236   only one has assessed the pre-diagnostic blood lipid levels. This study reported increased

237   triglycerides levels to be associated with the risk of both type 1 and 2 endometrial cancers[23].

238   However, this study did not adjust for obesity, and used non-fasting blood lipid levels. As

239   obesity and blood lipid levels are interrelated[9], it has been difficult for observational studies

240   to disentangle the effects of blood lipid levels on endometrial cancer risk. Thus, the

241   relationship between blood lipids and endometrial cancer remains unclear from the existing

242   evidence.

243   Mendelian randomization is an instrumental variable analysis that assesses the effects of

244   exposures using genetic predictors as instrumental variables[24]. Mendelian randomization uses

245   the principle that the alleles of genetic variants which predict higher levels of an exposure of

246   interest are naturally randomized to individuals at meiosis, a process somewhat comparable

247 to the random assignment of participants to an exposure in a randomized controlled trial.

248 Thus, associations between genetic variants and the outcome (and hence between the

249 exposure and the outcome) will not be vulnerable to reverse causation because disease

250 develops after meiosis. Provided that the selected genetic variants are associated with the

251 outcome only via their effects on the exposure of interest (i.e. not via pleiotropic effects on

252 other traits which could independently alter disease risk), effect estimates generated by

253 Mendelian randomization analyses should also be less vulnerable to the influence of

254 confounders[24].

255 In the current study, we employed a two-sample Mendelian randomization framework to

256 assess the relationships between levels of three blood lipids (LDL and HDL cholesterol, and

257 triglycerides) and the risk of endometrial cancer using genome-wide association study

258 (GWAS) data from the Endometrial Cancer Association Consortium (ECAC) and Global

259 Lipids Genetic Consortium (GLGC).

260

261 **Materials and Methods**

262 *GWAS datasets*

263 In this study, we assessed three major blood lipids: LDL and HDL cholesterol, and

264 triglycerides. Summary statistics from GWAS for the three blood lipids in 188,577

265 individuals of predominantly European ancestry were obtained from the Global Lipid

266 Genetics Consortium[25] (http://csg.sph.umich.edu/willer/public/lipids2013/). A detailed

267 description of the GLGC study has been previously published[25]. Briefly, blood lipid levels

268 were measured more than eight hours after fasting in most GLGC studies. For each genetic

269 variant association with blood lipid levels, association estimates were expressed in standard

270 deviation (SD) per copy of the effect allele.

271 Endometrial cancer risk estimates were obtained from the largest published meta-GWAS to

272 date, conducted by ECAC in 12,906 endometrial cancer cases and 108,979 controls, all of

273 European ancestry[26]. In a secondary analysis, we investigated relationships between the three

274 blood lipids and endometrial cancer subtypes using ECAC meta-GWAS results restricted to

275 cases with either endometrioid histology (8,758 cases), or non-endometrioid histology (1,230

276 cases)[26]. Histological subtypes of endometrial cancer were confirmed based on pathology

277 reports, and detailed study descriptions have previously been reported[26,27]. The association

278 estimates were expressed in log(OR) per copy of the effect allele.

279 ***Instrumental variable selection***

280 Independent, genome-wide significant genetic variants ($r^2 < 0.05$, $P < 5 \times 10^{-8}$) that were

281 associated with each type of blood lipid were chosen as instrumental variables. Genetic

282 variants with ambiguous strand codification (A/T or C/G) and minor allele frequency more

283 than 0.42 were removed. We compared the allele frequencies between the GLGC and ECAC

284 datasets, and a UKB10K reference panel (a random subset of 10,000 unrelated participants

285 from UK Biobank cohort; https://www.ukbiobank.ac.uk/), and genetic variants with a large

286 allele frequency difference (> 0.2) were also excluded.

287 ***Bidirectional Mendelian randomization analysis***

288 We employed bidirectional Generalised Summary-data based Mendelian Randomisation

289 (GSMR) analysis[28] to explore the relationship between the three blood lipids and endometrial

290 cancer. As Mendelian randomization estimates may be confounded by including pleiotropic

291 variants, we implemented the built-in Heterogeneity in Dependent Instruments (HEIDI)

292 outlier test[28] with a P-value threshold of 0.01 to detect and filter heterogeneous variants that

293 are likely pleiotropic. Remaining variants not excluded by HEIDI outlier test were used as

294 non-pleiotropic instrumental variables.

295   Results with a Bonferroni-adjusted $P < 0.05/3 = 0.017$, correcting for the three blood lipid

296   traits tested, were considered statistically significant. When blood lipid levels were treated as

297   the exposure trait, the resulting effect estimates were expressed as odds ratios (OR) and 95%

298   confidence intervals (CI) for endometrial cancer risk per SD increment in genetically

299   predicted blood lipid level. When endometrial cancer risk was treated as the exposure trait,

300   the resulting estimates represent the SD change for blood lipid level per SD increase in the

301   genetic liability to endometrial cancer. Analyses were performed using default settings in the

302   GSMR extension in GCTA (version 1.92)[28], using the UKB10K reference panel to estimate

303   linkage disequilibrium (LD) between variants. For comparison, we also performed inverse

304   variance weighted (IVW) and MR-Egger regression Mendelian randomization analyses using

305   MR-Base[29].

306   *Conditional Mendelian randomization Analysis*

307   Since obesity could affect associations between blood lipid levels and endometrial cancer[9],

308   we additionally performed conditional Mendelian randomization analysis. GWAS summary

309   statistics for the lipid of interest were conditioned for the effect of genetically predicted BMI

310   using results from the largest GWAS of BMI to date[30]. Conditional analyses were performed

311   using multi-trait-based conditional and joint analysis (mtCOJO) in the GCTA software

312   package (version 1.92)[28] and adjusted estimates were then reanalysed by GSMR.

313

314   **Results**

315   After removal of potential pleiotropic variants, 140 LDL cholesterol, 163 HDL cholesterol

316   and 104 triglyceride independent genome-wide significant variants were considered as

317   instrumental variables (**Supplementary Tables 1-3**). These instrumental variables were used

318   by GSMR to estimate the effect of blood lipids on endometrial cancer risk of all histologies

319 combined (results presented in **Table 1** and **Figure 1**). GSMR analysis indicated that

320 genetically raised LDL cholesterol levels were associated with reduced risk of all endometrial

321 cancer histologies combined (OR per SD increase in LDL cholesterol level = 0.88;

322 95% CI = 0.83-0.93; P = 7.26×10^{-6}). Consistent with the divergent roles of LDL and HDL

323 cholesterol[31], GSMR analysis provided evidence that increased HDL cholesterol levels may

324 be associated with increased risk of all endometrial cancer histologies combined (OR 1.07;

325 95% CI = 1.00-1.14; P = 0.037). Secondary analysis assessing the relationships between

326 blood lipid levels and endometrial cancer subtypes found genetically predicted higher LDL

327 cholesterol levels were associated with lower risk of both endometrioid and non-

328 endometrioid endometrial cancer (**Table 1**). Conversely, genetically predicted higher HDL

329 cholesterol levels showed suggestive evidence of association with higher risk of non-

330 endometrioid endometrial cancer only (**Table 1**). No significant effects were observed for

331 triglycerides on endometrial cancer overall, or its subtypes (**Table 1**). Bidirectional GSMR

332 analysis provided evidence for a unidirectional association e.g. genetically elevated LDL

333 cholesterol level may affect endometrial cancer risk, while genetic liability to endometrial

334 cancer does not appear to affect LDL cholesterol levels (**Table 2**).

335 To reduce the influence of obesity on the associations between blood lipid levels and

336 endometrial cancer risk, we performed Mendelian randomization analysis conditioning on

337 genetically predicted BMI. Results are presented in **Table 3** and **Supplementary Figure 1**.

338 After controlling for the influence of genetically predicted BMI, the association between

339 genetically predicted LDL cholesterol levels and risk of all histologies combined and non-

340 endometrioid endometrial cancer remained; whereas, the effect of LDL cholesterol level on

341 endometrioid endometrial cancer risk was attenuated and no longer significant (OR 0.93,

342 95% CI 0.87-1.01; P = 0.07). Conditioning on genetically predicted BMI had minimal impact

343   on the risk estimates for HDL and endometrial cancer, but associations did not pass the

344   Bonferroni-correction threshold, reflecting the decreased power for these analyses.

345   Results from IVW and MR-Egger analyses were consistent with our GSMR results

346   (**Supplementary Tables 4 and 5**). None of the MR-Egger intercepts were significantly

347   different from zero (P>0.05), except for the relationship between genetically predicted HDL

348   cholesterol and non-endometrioid endometrial cancer, suggesting pleiotropy may have biased

349   IVW results of HDL cholesterol and non-endometrioid endometrial cancer. However, the

350   MR-Egger regression slope of HDL cholesterol and non-endometrioid endometrial cancer

351   remained statistically significant after accounting for potential pleiotropy, supporting a

352   relationship between HDL cholesterol and endometrial cancer risk (**Supplementary Tables 4**

353   **and 5**).

354

355   **Discussion**

356   To our knowledge, this is the first Mendelian randomization study to assess the effects of

357   genetically predicted blood lipid levels on endometrial cancer risk. While genetically

358   increased LDL cholesterol had a protective effect on endometrial cancer, especially non-

359   endometrioid endometrial cancer, results suggest that genetically increased HDL cholesterol

360   may have an adverse effect on non-endometrioid endometrial cancer risk. The opposing

361   findings for LDL and HDL cholesterol are consistent with their opposing roles. For example,

362   LDL delivers cholesterol to peripheral tissues, whereas HDL removes cholesterol from these

363   tissues and transports it to the liver[31]. We found no evidence of a causal link between

364   triglycerides and endometrial cancer, in contrast to three observational studies that have

365   reported positive associations[18,19,23]. However, as previously noted, none of these studies

366   assessed fasting blood triglycerides and one did not control for the effect of obesity[18].

367   Mendelian randomization analysis has previously illustrated the complex interrelationship

368   between BMI and blood lipid levels[9]. We therefore performed conditional Mendelian

369   randomization analysis to investigate the influence of genetically predicted BMI on

370   associations between LDL/HDL cholesterol and endometrial cancer risk. Comparison of the

371   LDL/HDL cholesterol association estimates, before and after adjusting for genetically

372   predicted BMI, did not support a role for BMI in the associations with endometrial cancer of

373   non-endometrioid and combined histologies. In contrast, the LDL cholesterol association

374   with endometrioid endometrial cancer was weaker with wider confidence intervals after

375   including genetically predicted BMI as covariate. While a modest protective effect of LDL

376   cholesterol for the endometrioid subtype of endometrial cancer cannot be excluded, this

377   finding indicated that LDL cholesterol is likely to lie in the same causal pathway as obesity, a

378   hypothesis consistent with results from previous genetic studies. Indeed, somewhat

379   surprisingly, previous Mendelian randomization analyses have demonstrated a bidirectional

380   relationship between LDL cholesterol and BMI with one study reporting that increased LDL

381   cholesterol levels were associated with reduced BMI[9] and, another reporting that increased

382   BMI was associated with reduced LDL cholesterol levels[32]. Using Mendelian randomization

383   analyses, we have previously found increased BMI to be associated with increased

384   endometrioid endometrial cancer risk[26,33]. Measured LDL cholesterol levels have also been

385   found to diminish with increasing BMI in overweight individuals[34]; whereas, in the same

386   study, LDL cholesterol levels were only positively correlated with BMI in lean individuals.

387   These findings indicate that the inverse relationship between LDL cholesterol and

388   endometrioid endometrial cancer, a disease primarily affecting overweight individuals[33], may

389   be related to high BMI. Thus, we hypothesise that obesity is likely to be the mediator of the

390   effect of LDL cholesterol on endometrioid endometrial cancer risk (i.e. ↑LDL → ↓BMI →

391   ↓Endometrioid Endometrial Cancer risk) (**Figure 2**). Moreover, as obesity is a stronger risk

392 factor for endometrioid than for non-endometrioid endometrial cancer[26], it is perhaps not

393 surprising that after adjusting for genetically predicted BMI we only observed an attenuation

394 of the effect of LDL cholesterol on endometrioid endometrial cancer risk.

395 It is intriguing that our results indicated that, independent of obesity, decreased LDL

396 cholesterol level is inversely associated with risk of non-endometrioid endometrial cancer.

397 While both endometrioid and non-endometrioid endometrial cancer share many other risk

398 factors[35], recent Mendelian randomization analyses have found that obesity and age at

399 menarche are risk factors of endometrioid endometrial cancer only[26].Given the rare nature of

400 non-endometrioid histologies (~10% of all endometrial cancer cases), the tumorigenic

401 mechanisms for these histological subtypes remain largely unknown[35,36]. Thus, further studies

402 are required to explore how higher LDL cholesterol levels could protect against non-

403 endometrioid endometrial cancer development.

404 As shown in **Table 1**, the association between HDL cholesterol and endometrial cancer

405 appears to be largely driven by the non-endometrioid histological subtype. Despite not

406 passing a Bonferroni statistical significance threshold, there was no substantial change in the

407 association estimate before and after conditioning on BMI, suggesting HDL cholesterol may

408 also affect non-endometrioid endometrial cancer risk independently of obesity. The wide

409 confidence intervals suggest that future studies with more non-endometrioid endometrial

410 cancer cases are required to further dissect any effect.

411 The conflicting findings regarding the relationships between blood lipids and endometrial

412 cancer risk in observational studies may be due to small sample sizes, varying timing of

413 blood collection (e.g. fasting or non-fasting, and pre- or post- endometrial cancer diagnosis),

414 and varying control for confounding factors. Findings presented in the current study, through

415 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

440 analyses, and this suggests that residual confounding may have negligible impact on our

441 results. The two-sample Mendelian randomization framework allowed us to incorporate data

442 from two very large independent GWAS datasets to bolster power and yield more precise

443 association estimates. However, we were restricted to summary-level GWAS data, and thus,

444 could not perform more refined analyses (e.g. stratification analysis by BMI).

445 This Mendelian randomization study provides evidence that increased LDL cholesterol and

446 decreased HDL cholesterol, independent of obesity, may reduce the risk of endometrial

447 cancer. This effect was particularly apparent for the non-endometrioid endometrial cancer

448 subtype, which typically has a more aggressive phenotype and results in poorer prognosis.

449 Although further work is required to elucidate the biological rationale underlying this

450 association, these results suggest low LDL cholesterol levels and high HDL cholesterol levels

451 should be considered as potential risk factors for endometrial cancer.

452

558 **Conflict of Interest Statement**

559 P.A.F. reports personal fees from Novartis, grants from Biontech, personal fees from Roche,

560 personal fees from Pfizer, personal fees from Daiichi-Sankyo, personal fees from Astra

561 Zeneca, personal fees from Eisai, personal fees from Merck Sharp & Dohme, grants from

562 Cepheid, personal fees from Lilly, personal fees from Pierre Fabre, personal fees from Seattle

563 Genetics, during the conduct of the study. D.J.T. is an employee of Genomics plc. The

564 research described in this article was completed before her employment at Genomics plc. All

565 other authors declare no potential conflicts of interest.

566

567 **Data accessibility**

568 Only publicly available data were used in this study, and data sources and handling of these

569 data are described in the Materials and Methods. Further details are available from the

570 corresponding author upon request.

571

572 **Ethics approval**

573 This work used published summary-level GWAS meta-analysis results, and thus ethical

574 approval was not required.

575

582

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