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The role of metformin and statins in the incidence of epithelial ovarian cancer in type 2 diabetes: a cohort and nested case–control study

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Objective To obtain evidence of the effects of metformin and statins on the incidence of ovarian cancer in women with type 2 diabetes (T2D).

Design A retrospective cohort study and nested case–control study.

Setting The data were obtained from a diabetes database (FinDM) combining information from several nationwide registers.

Population A cohort of 137 643 women over 40 years old and diagnosed with T2D during 1996–2011 in Finland.

Methods In full cohort analysis Poisson regression was used to estimate the hazard ratios (HR) in relation to ever use of metformin, insulin other oral anti-diabetic medication or statins. In the nested case–control analysis 20 controls were matched to each case of ovarian cancer. Conditional logistic regression was used to estimate HRs in relation to medication use and cumulative use of different medications. The estimates were adjusted for age and duration of T2D.

Main outcome measure Incidence of ovarian cancer.

Results In all, 303 women were diagnosed with ovarian cancer during the follow up. Compared with other forms of oral anti-diabetic medication, metformin (HR 1.02, 95% CI: 0.72–1.45) was not found to be associated with the incidence of ovarian cancer. Neither was there evidence for statins to affect the incidence (HR 0.99, 95% CI: 0.78–1.25). In nested case–control analysis the results were essentially similar.

Conclusions No evidence of an association between the use of metformin or statins and the incidence of ovarian cancer in women with T2D was found.

Keywords Cancer incidence, case–control study, cohort study, metformin, ovarian cancer, statins.

Tweetable abstract No evidence found for metformin or statins reducing the incidence of ovarian cancer.

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Introduction

Ovarian cancer accounts for 3.7% of all cancers in women worldwide but it is one of the most lethal cancers, causing 140 000 deaths annually.[1] The risk factors of ovarian cancer include genetic factors (*BRCA1*, *BRCA2*, *HNPCC*), nulliparity, endometriosis, pelvic inflammatory disease, postmenopausal hormone therapy and polycystic ovary syndrome.[2,3] A recent meta-analysis also showed that increasing body weight in premenopausal women is associated with an increased incidence of ovarian cancer.[4] Protective factors include multiparity, lactation, oral contraceptives, hysterectomy, salpingectomy and sterilisation.[2,3]

People with type 2 diabetes (T2D) have been reported to have an increased incidence of various cancers, including ovarian cancer, compared with those without diabetes, the

risk being highest in insulin-treated patients.[5] However, Weiderpass et al.[6] did not find any association between diabetes and ovarian cancer. Metformin is an oral anti-diabetic medication that is recommended as the first-line treatment in T2D.[7] Metformin has anti-mitotic, anti-angiogenic and anti-inflammatory properties.[8] The main signalling route of metformin is via AMP-activated protein kinase (AMPK).[9,10] In some epidemiological studies the use of metformin has been linked to lower incidence of several cancer types.[11,12] Evans et al.[13] reported a 23% decrease in the incidence of any type of cancer in those using metformin compared with those on other anti-diabetic medication. In another study a reduction of ovarian cancer incidence in women with diabetes on metformin treatment was reported.[14] However, there are also publications where no association has been found between the incidence of ovarian cancer and the use of metformin.[15,16]

Individuals with T2D have an increased risk of cardiovascular diseases and hypercholesterolaemia, which are widely treated with statins. For example, in Finland, 79% of newly diagnosed people with T2D use statins for secondary prevention and 40% for primary prevention of coronary heart disease.[17] Statins (3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA)) reductase inhibitors) block formation of cholesterol by inhibiting 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) conversion to mevalonate.[18] The possible cancer-preventing effect of statins is thought to be mediated partly by this mechanism.[18]

In the present register-based retrospective cohort study and case–control analysis we assessed the role of anti-diabetic medication and statin use in the incidence of epithelial ovarian cancer in women with T2D.

Methods

The STROBE guidelines for reporting of observational studies were followed in this article.[19]

Data sources

The data were obtained from the FinDM database, in which information from several Finnish nationwide registers and register-holders (National Institute for Health and Welfare, Statistics Finland, the Care Register for Health Care and the Social Insurance Institution) has been combined from 1964 to 2011.[20]

The FinDM database includes accurate information about the quantity and the date of purchase of all medication prescribed by doctors and reimbursed by the Social Insurance Institution, including anti-diabetic and statin medication, starting from 1994. Data on diagnoses from hospital records were obtainable from 1969 for inpatients and from 1998 for outpatients. Information on surgical procedures performed in hospitals is available from 1987. Identification of persons with diabetes is entered in the register on the basis of diagnoses documented in hospital records or by reimbursement for anti-diabetic medication. Comparison of data from FinDM against a regional diabetes register covering the Helsinki district has shown good agreement.[21] In certain cases, the duration of T2D is likely to have been longer than indicated from the register, as FinDM does not carry information on former treatment of diet-controlled diabetes, which occurred only in an outpatient primary-care setting. The categorisation of patients in the register into type 1 (primary insulin-dependent diabetes mellitus) and type 2 diabetes was based primarily on the anti-diabetic medication used as first-line treatment.

The records in FinDM are linked to information from the Finnish Cancer Registry, which has outstanding coverage of over 99% of all cancer cases in Finland since 1953.[22] The date of diagnosis, histology and morphology of cancer are recorded in the Finnish Cancer Registry. Information about the date of the death was available from Statistics Finland. Data linkage between various registers was carried out on the basis of personal identification codes unique to each resident of Finland.

Identification of the study cohort

Details of the cohort selection process are presented in a flow chart (Figure 1). From our source population contained in the FinDM database we first identified 172 070 women with incident T2D diagnosed between 1 January 1996 and 31 December 2011. With this inclusion criterion the data covering the whole purchase history of the drugs under study from the diagnosis of T2D onwards up to the end of 2011 was available for all women of our intended study cohort.

The entry to the follow up for the incidence of ovarian cancer was set either at the date of 40th birthday, or at the date when 1 year had passed after the diagnosis of T2D, whichever date occurred later. The first year of follow up was excluded to reduce the risk of detection bias and reverse causality bias associated with the increased surveillance for cancer immediately after diagnosis of diabetes.[5] Women with a diagnosis of ovarian cancer before cohort entry were excluded. In addition, women with certain previous gynaecological operations, including oophorectomy, salpingo-oophorectomy or hysterectomy with bilateral salpingo-oophorectomy, before entry were excluded from the cohort. Data on surgical operations were available only from 1987 onwards, leaving the possibility of some women with previous operations remaining in the cohort. This concerned mainly women in the older age categories. The final cohort consisted of 137 643 women diagnosed with T2D between 1996 and 2011.

In addition, a nested case–control study within the cohort was conducted, mainly to evaluate the association

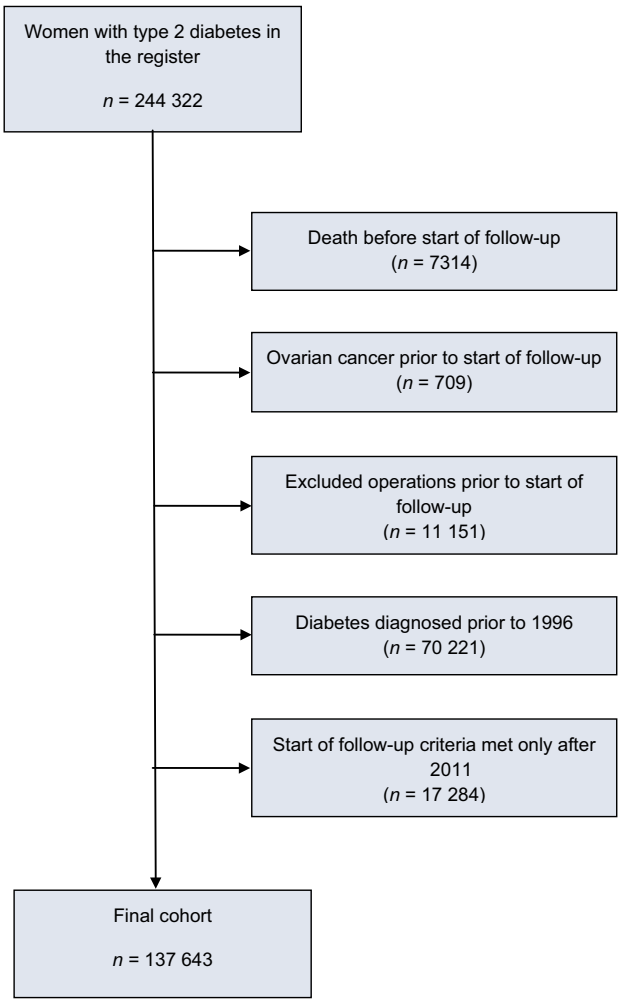

Figure 1. Flowchart. Forming the cohort.

of ovarian cancer with the cumulative use of the medications under study. This design, compared with a full cohort design, enables more straightforward calculation of the number of defined daily doses (DDD) of medication used by each patient before their respective index date for analysing the effect of the accumulated DDD. For each case, up to 20 controls were selected without replacement from among those women in the cohort who were alive and at risk of ovarian cancer at the date of ovarian cancer diagnosis of the case, and who were also matched for both age (date of birth) and duration of diabetes (±182 days).

Classification of medication

Exposure to anti-diabetic medication was evaluated in three separate categories: metformin, other oral anti-diabetic medication and insulin. The use of statins was assessed as one category. Exposure to any medication was considered to begin 365 days after its first purchase date to avoid reverse causality problems and to allow a minimum reasonable latency period for any medication effect. In both the full-cohort analysis and the nested case–control analysis patients were categorised as being exposed to a given medication from this moment onwards throughout the individual follow up time (ever-exposed versus never-exposed). In addition, the effects of cumulative use of metformin, insulin, other forms of oral anti-diabetic medication and statins were assessed in the nested case–control analysis using the total amount of DDDs purchased during the follow-up period.

Follow up

Follow up of each patient started 1 year after diagnosis of T2D or at the age of 40 years, whichever happened later, and it ended on the date of diagnosis of ovarian cancer, oophorectomy for reasons other than cancer, death or the end of the study period (31 December 2011), whichever occurred earliest.

Statistical analysis

In the full-cohort analysis, a multiple Poisson regression model[23] was used to estimate the hazard ratios (HRs) with 95% CIs of the incidence of ovarian cancer in relation to ever-use of metformin, other forms of anti-diabetic medication and statins. In this model, the effects of current age and duration of T2D were assumed to obey a piecewise constant hazards pattern over chosen intervals of these two time scales. Age was split into 5-year intervals from 40–44 years to 85–89 years plus one more interval covering 90–106 years, and duration of T2D was split into the intervals that are shown in Table 1. In the nested case–control analysis, the corresponding HRs with 95% CIs were estimated by means of conditional logistic regression[24] in relation to the ever use of different forms of anti-diabetic medication and statins. Cumulative doses were categorised according to tertiles of total amounts of DDDs used. The register data were pre-processed using SAS/STAT® software version 9.4 of the SAS System for Windows, with consecutive data transformations and the statistical analysis was performed in R environment version 3.3.2.[25] A person-period file was created using the Lexis tools in the Epi package of R, where individual follow-up time of each person was simultaneously split into the appropriate periods of age, duration of T2D and the time-dependent medication use status.[26,27] In the analysis of the full cohort data, the Poisson regression model was fitted using the glm function,[25] and in the analysis of the nested case–control data the conditional logistic regression model was fitted using the clogit function from the survival package of R.[28]

Results

The total follow up covered 748 282 person-years at risk (Table 1), the mean follow-up time being 5.4 years. During

Table 1. Incidence rates of ovarian cancer (per 100 000 person-years), distribution of person-years at risk, and numbers (%) of cases and matched controls by age, duration of diabetes and medication use

Variable	Value	Incidence (per 100 000 person-years)	Person-years in cohort	Cases (%)	Controls (%)
Age (years)	40–49	12.7	47 229	6 (2.0)	126 (2.1)
	50–59	28.9	127 996	37 (12.2)	730 (12.0)
	60–69	51.4	194 406	100 (33.0)	2000 (33.0)
	70–79	49.5	216 225	107 (35.3)	2140 (35.3)
	80–89	35.9	142 166	51 (16.8)	1023 (16.9)
	90–106	9.9	20 260	2 (0.7)	41 (0.7)
Duration of diabetes (years)	1 to <3	38.0	239 473	91 (30.0)	1903 (31.4)
	3 to <5	38.1	175 744	67 (22.1)	1289 (21.3)
	5 to <8	52.5	177 254	93 (30.7)	1771 (29.2)
	8 to <16	33.4	155 811	52 (17.2)	1097 (18.1)
Metformin use	Ever	41.1	486 197	200 (66.0)	4080 (67.3)
	Never	39.3	262 085	103 (34.0)	1980 (32.7)
Other oral anti-diabetic medication use	Ever	40.8	367 964	150 (49.5)	2978 (49.1)
	Never	40.2	380 319	153 (50.5)	3082 (50.9)
Insulin use	Ever	43.4	87 654	38 (12.5)	658 (10.9)
	Never	40.1	660 629	265 (87.5)	5402 (89.1)
Any anti-diabetic medication use	Ever	42.0	606 537	255 (84.2)	4979 (82.2)
	Never	33.9	141 745	48 (15.8)	1081 (17.8)
Statin use	Ever	42.8	371 806	159 (52.5)	3235 (53.4)
	Never	38.2	376 476	144 (47.5)	2825 (46.6)

Cases and controls were matched for age (±182 days) and duration of diabetes (±182 days).

the study period, 303 women were diagnosed with epithelial ovarian cancer. The incidence of ovarian cancer was highest in the age-group of 60–69 years (51.4 per 100 000 person-years) and in the group where the duration of diabetes was 5–8 years (52.5 per 100 000 person-years).

In the nested case–control analysis, we selected 6060 matched (on age and T2D duration) controls for the 303 women diagnosed with epithelial ovarian cancer. Two-thirds of the cases and controls were ever-users of metformin, and over 50% were ever-users of statins (Table 1). The most used other oral anti-diabetic medications were sulphonylureas and the most used statin was simvastatin. Details on ATC (Anatomical Therapeutic Chemical) codes and percentages of other oral anti-diabetic medication used, and statins, are listed in the (Table S1).

In the full cohort analysis, neither ever-use of metformin, nor ever-use of insulin was found to be associated with a different incidence of ovarian cancer, when compared with ever-use of other oral anti-diabetic medication (Table 2); the adjusted HR with ever-use of metformin was 1.02 (95% CI: 0.72–1.45) and that for ever-use of insulin was 1.19 (95% CI: 0.73–1.93). The incidence of ovarian cancer was not found to be different with ever-use of statins either with an HR of 0.99 (95% CI: 0.78–1.25). No consistent trend was observed for the incidence of ovarian cancer by time since onset of T2D (see Figure S1), nor was there sufficient evidence for any interaction between duration of T2D and any of the medications concerned (data not shown).

Table 2. Adjusted estimates of hazard ratios (HR, with 95% CI) for the association between ovarian cancer incidence and 'ever-use' of metformin and insulin compared with the use of other forms of oral anti-diabetic medication, and the use (at any time) of statins compared with no use of statins at any time

Ever use	Full cohort, HR (95% CI)	Case–control, HR (95% CI)
Metformin	1.02 (0.72–1.45)	0.91 (0.61–1.34)
Insulin	1.19 (0.73–1.93)	1.19 (0.72–1.97)
Statin	0.99 (0.78–1.25)	0.96 (0.75–1.23)

The estimates are based on Poisson regression using the full-cohort data, and conditional logistic regression using the nested case–control data, both adjusted for age and duration of diabetes.

In the case–control analysis, the main findings were similar. Ever-use of metformin had an adjusted HR of 0.91 (95% CI: 0.61–1.34) and ever-use of insulin had an adjusted HR of 1.19 (95% CI: 0.72–1.97) when compared with ever-use of other oral anti-diabetic medication. The

incidence of ovarian cancer was not found to be associated with ever-use of statins either, the adjusted HR being 0.96 (95% CI: 0.75–1.23). There was no evidence of any interaction effect of ever-use of statins and metformin, the interaction HR being 0.88 (95% CI: 0.54–1.45). Neither was any consistent trend observed in the incidence of ovarian cancer with respect to rising cumulative use of metformin, other oral anti-diabetic medication, insulin or statins in terms of defined daily doses (Figure 2).

Discussion

Main findings

We found no evidence of an association between metformin or other forms of oral anti-diabetic medication and the incidence of epithelial ovarian cancer in women aged 40 years or older with T2D. Neither did we observe any trend in the incidence of ovarian cancer with increasing DDDs of metformin. We could not find any association between statin use and the risk of epithelial ovarian cancer either.

Strengths and limitations

As far as we know, our study is the first in which the effect of statin use in women with T2D and their risk of ovarian cancer has been explored. Many of the previous studies on the risk of ovarian cancer in association with medication have suffered from methodological issues and their sizes have been relatively small.

A major strength of our study is the use of very reliable and comprehensive national registers. Patient's details are entered into the diabetes register at the time of the first purchase for any form of anti-diabetic medication. Data in the register concerning the diagnosis date of T2D are considered to be fairly accurate. The coverage of the prescription register of the Social Insurance Institution of Finland of reimbursed medications prescribed by physicians is virtually complete for the pertinent study period.[29] We also have a reliable history of previous operations among the patients in the cohort. The other major strength of our study lies in its time-dependent design. We are able to calculate the time-related use and to make good estimates of

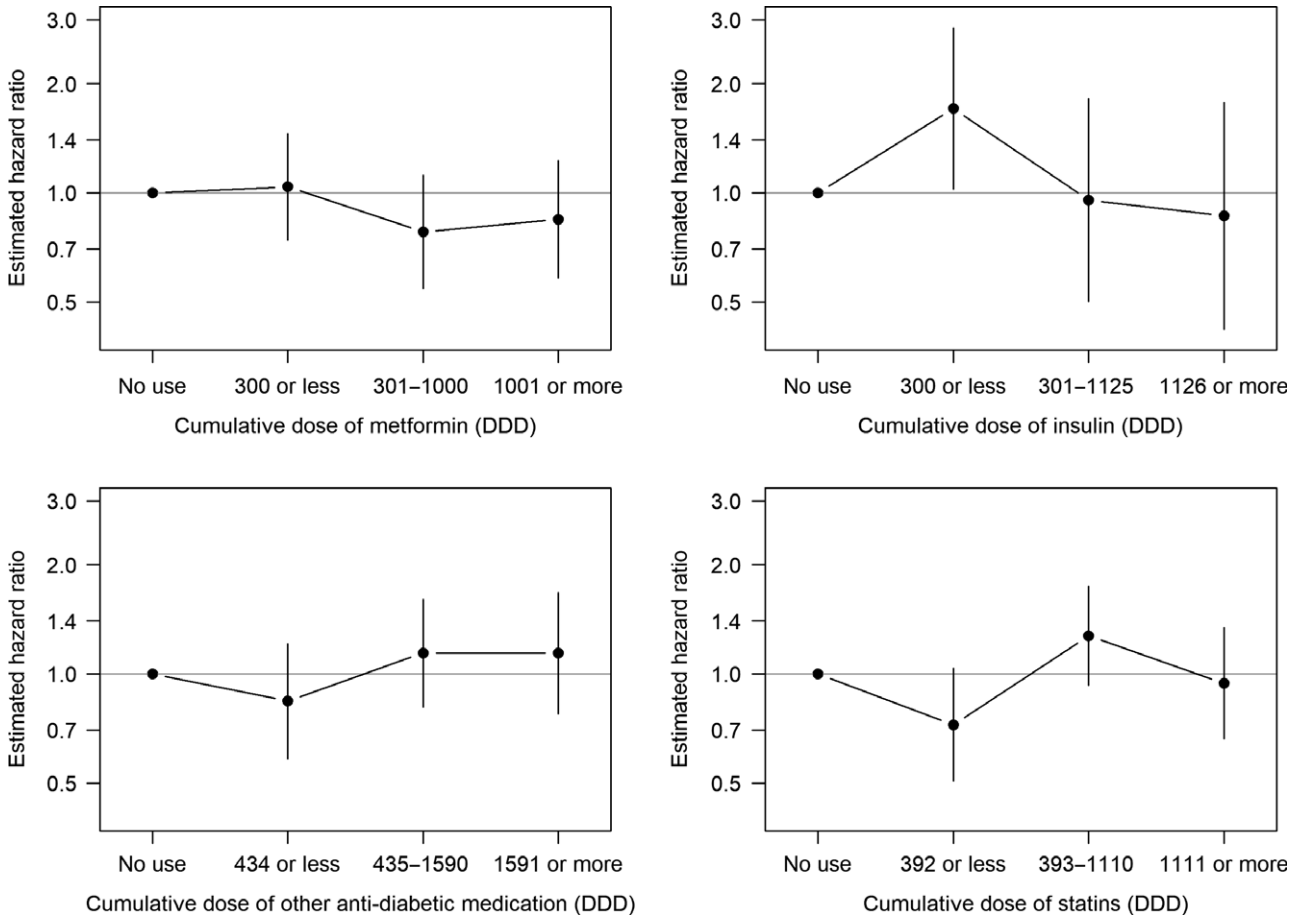

Figure 2. Estimated hazard ratios (with 95% CI) of ovarian cancer by cumulative doses of different forms of anti-diabetic medication and statins, adjusted for age and duration of diabetes medication, using case–control data.

cumulative amounts (DDDs) of metformin and other types of anti-diabetic medication and statins. However, DDDs of anti-diabetic medication also correlate with the duration and severity of T2D.

Limitations of our study include the lack of information on the family history of ovarian cancer, and parity of the women in the diabetes cohort. In addition, we do not have data on the BMI or other markers of insulin resistance of the patients. However, the proportion of premenopausal women, in which obesity would affect the incidence of ovarian cancer,[4] is relatively small among women with T2D. Our study cohort was confined to women who were at least 40 years old. This restriction should not carry any essential implications to the overall picture conveyed by our results, considering that the contribution of younger women to the total caseload of ovarian cancer is very modest also in the population of women with T2D. In fact, no cases of ovarian cancer were found among women in the FinDM population, who fulfilled all the other inclusion criteria but who were <40 years old. Hence, the results of both the full cohort analysis and the nested case–control analysis would remain the same whether this age restriction was employed or not.

As to the measurement and classification of drug use we note that the national prescription register contains only prescribed medications (for example, anti-diabetic medications and statins) reimbursed by the national health insurance system. Over-the-counter drugs and drugs dispensed in hospitals and outpatient clinics are not covered by this register,[29] but only a small proportion of persons with T2D are treated in healthcare facilities. Moreover, no direct data exist on whether the purchased drug was actually taken or not. However, the concordance between self-reported medication use and information contained in the prescription register has been shown to be quite good.[30] In addition, exposure classification based on registered purchases of diabetes drugs and statins before diagnosis of ovarian cancer is in no way dependent on whether a study subject develops cancer or not. Therefore, any misclassification is most likely nondifferential, which implies that the direction of a possible bias associated with it would be 'towards zero', i.e. the estimated HRs would have a tendency to be closer to 1 than the true HR.

Interpretation

The possible cancer-preventing effect of metformin has led to a considerable number of observational studies in this field, although, many studies have had methodological challenges, for example time-related biases, as a result of their observational nature.[31] However, only a few studies have been published on metformin and the incidence of ovarian cancer. In a systematic review by Dilokthornsakul et al.,[16] little evidence was found concerning the association between metformin use and the incidence of ovarian cancer. In a retrospective cohort study, Tseng reported that women with T2D who used metformin had a decreased risk of ovarian cancer compared with those who did not use it.[14] However, the relatively large epidemiological case–control study carried out by Bodmer et al.[15] could not find any association between metformin use and a reduction in the incidence of ovarian cancer. On the other hand, long-term use of insulin was associated with an increased incidence of ovarian cancer.[15] BMI seemed not to have any effect on the incidence of ovarian cancer in their study.

In our study, the most used statin was simvastatin, which is categorised as a lipophilic statin. Hydrophilic and lipophilic statins might have different impacts on cancer risk. In one study, lipophilic statins reduced the risk of breast cancer.[32] Both *in vitro* and *in vivo* studies have shown that lipophilic statins, at least, have anti-proliferative, pro-apoptotic, anti-invasive and radio-sensitising effects.[33] In 2014, Liu et al.[34] published a review on statins and gynaecological cancers in which ovarian cancer incidence seemed to be lower among statin users, and the protective effect was dose-dependent. There was no significant benefit of statin use as regards other gynaecological cancers.[34] However, in line with our findings, in some other studies no association between statin use and the risk of ovarian cancer has been found.[35–37]

Conclusion

We found no evidence for an association between the use of metformin or other forms of oral anti-diabetic medication and the incidence of epithelial ovarian cancer in women with T2D. Neither did we find any evidence for an association between statin use and the risk of epithelial ovarian cancer.

Disclosure of interests

Full disclosure of interests form available to view online as supporting information.

Contribution to authorship

EU, UP and MH drafted the article. MM, AH and EL had access to the databases and MM undertook the analyses. EU, UP, MH, MM, AH, EL, MA, RS, PI-P, RA and JK reviewed the drafts.

Details of ethics approval

FinDM has received approval from the Ethics Committee of National Institute for Health and Welfare (30 January 2014, proceeding \$609). Data on individual persons in FinDM are stored according to Finnish data-protection legislation. The data received by the research group were anonymised such that the personal identity codes were converted into unidentified codes.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Estimated hazard ratios (bullets) with 95% CIs (segments about the bullets) for ovarian cancer associated with different intervals of duration of type 2 diabetes based on Poisson regression fitted on full cohort data.

Table S1. ATC codes and percentages of other forms of oral anti-diabetic medication and statins.■

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