ANTICANCER RESEARCH *38*: 4169-4178 (2018)
doi:10.21873/anticanres.12710

Antidiabetic Medication, Statins and the Risk and Prognosis of Non-endometrioid Endometrial Cancer in Women with Type 2 Diabetes

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Abstract. *Aim: To determine the incidence and prognosis of non-endometrioid endometrial cancer (EC) in relation to the use of metformin, other antidiabetic medication (ADM) and statins in patients with type 2 diabetes (T2D). Materials and Methods: In order to analyze the incidence and prognosis of non-endometrioid EC, two cohorts were obtained from a nationwide diabetes database (FinDM); 57 non-endometrioid ECs were observed in a cohort of 92,366 women with newly-diagnosed T2D during the follow-up (1996 to 2011) to assess the incidence, and a retrospective cohort of 105 women with T2D diagnosed with non-endometrioid EC (1998 to 2011) was used to estimate cumulative mortality from EC and other causes of death. Hazard ratios (HRs) with 95% confidence intervals (CIs) for EC incidence were estimated in the full-cohort analysis and in the nested case–control analysis, matched for age and duration of T2D. Cumulative mortality was estimated by using the Aalen–Johansen estimator. Cause-specific mortality rates were analyzed by using Cox models regarding the pre-diagnostic use of different forms of ADM and statins. Results: In the nested case–control analysis, the use of metformin was not associated with the risk of non-endometrioid EC (HR=1.09, 95% CI=0.59-2.00), whereas statin use was associated with a lower risk (HR=0.47, 95% CI=0.26-0.84). The results from the full-cohort analysis supported these findings. Mortality from non-endometrioid EC was not different between users of metformin and other types of oral ADM (HR=1.56, 95% CI=0.40-6.07) but was observed to be lower in statin users (HR=0.41, 95% CI=0.20-0.82). Conclusion: Our findings were inconclusive regarding the association of metformin with the risk and prognosis of non-endometrioid EC. However, statin use was associated with a lower incidence and mortality from this disease.*

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Key Words: Endometrial cancer, non-endometrioid, metformin, statins, cohort, case–control, prognosis.

Endometrial cancer (EC) is the fourth most common malignancy of women in developed countries, with an estimated overall cumulative risk of 1.8% by the age of 75 years (1). Based on histology, endometrial cancer has been classified into endometrioid (type I) and non-endometrioid (type II) subtypes. Endometrioid EC represents the majority of ECs and carries a relatively favorable prognosis. Non-endometrioid EC is typically poorly differentiated, has a high risk of metastasis and a poor prognosis (2). Recently this dualistic view was expanded by increased knowledge concerning a variety of molecular changes and prognostic factors in EC (3). Furthermore, the factors increasing (early menarche, nulliparity, late menopause, unopposed estrogen HRT use, diabetes and obesity) or reducing (oral contraceptive use and physical activity) the risk of EC which

have traditionally been associated specifically with endometrioid EC are now also considered to be involved in the development of the non-endometrioid subtype (2, 4).

Metformin is used as a first-line oral medication in the treatment of type 2 diabetes (T2D) (5). Metformin use has been linked to lower cardiovascular mortality (6) as well as to a smaller risk and more favorable prognosis in certain types of cancer (7) among patients with diabetes. In addition, metformin has been demonstrated to inhibit proliferation (8) and invasion (9) of EC cells in preclinical studies.

A few retrospective cohort studies have been carried out to explore the association between metformin use and the incidence of EC. In most of them, sufficient evidence for an association has not been found (10-12). However, recently a lower incidence of EC in metformin users was reported (13). In an Italian study, the incidence of EC in women with diabetes using metformin was observed to be slightly elevated, but this could have resulted from the higher average body mass index (BMI) in metformin users compared with other diabetics (14). In none of these studies endometrioid and non-endometrioid EC were assessed separately.

Some investigators have associated metformin with better prognosis in EC (15, 16). In an article by Nevadunsky *et al*., the apparent benefit was reported to be limited to non-endometrioid EC only (17). However, after controlling for several confounders, Al Hilli *et al*. found no evidence that metformin affects overall (OS) or progression-free (PFS) survival in patients with EC (18).

Statins (inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme A reductase) are oral cholesterol-lowering drugs which are widely used in primary and secondary prevention of coronary heart disease, for which diabetes is a known risk factor. Statins reduce the level of mevalonate, inhibit the synthesis of isoprenoids, and were found to induce apoptosis of cancer cells in preclinical study (19). A possible association between statin use and EC risk has not been widely investigated. No connection between statin use and EC incidence was found in a recent Danish register-based study: the results were similar as regards endometrioid and non-endometrioid subtypes of EC (20). Liu *et al*. conducted a meta-analysis in which no correlation between the use of statins and the risk of EC was seen. However, among studies with Asian populations, a reduction in the incidence of EC has been observed in statin users (21). Previous observational studies have found some evidence of both neutral (22) and positive (23-25) effects of statin use on survival in cases of endometrial cancer.

The associations between the use of metformin, other forms of oral antidiabetic medication (ADM), insulin and statins, and the incidence and prognosis of non-endometrioid EC in a nationwide register-based cohort and case–control study were examined in women with T2D.

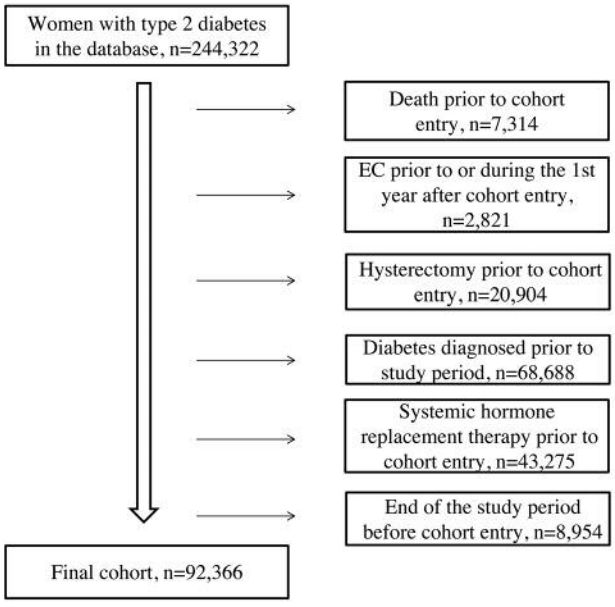

Figure 1. *Flow chart for formation of the non-endometrioid endometrial cancer incidence cohort.*

Materials and Methods

Data sources. This article was written following STROBE guidelines for the reporting of observational studies (26). The data were extracted from the Finnish diabetes database FinDM, which contains combined information from several nationwide registers from 1964 to 2011 (27). The patients with diabetes are enrolled in the database at the time of the first reimbursement for ADM or when diabetes diagnosis is encoded in hospital records. They are then further categorized into type 1 (insulin-dependent) and type 2 on the basis of the predominantly used form of first-line ADM. FinDM contains reliable information on all forms of ADM and other types of medication reimbursed since 1994. Information on cancer from the Finnish Cancer Registry (the date of diagnosis, histology and stage of cancer) as well as information on dates and causes of deaths and emigration from the Cause of Death Register of Statistics Finland was individually linked. Deaths were defined as cancer-specific or not by the specialists of the Cancer Registry.

Ethics approval. Approval from the Ethics Committee of the National Public Health Institute was received by FinDM (30th of January 2014, reference number 609).

Incidence

Identification of the study cohort. A detailed description of the formation of the study cohort is shown in Figure 1. Women who were 40 years of age or older and diagnosed with T2D between the 1st of January 1996 and the 31st of December 2011 were included. Women with a diagnosis of EC preceding cohort entry were omitted from the analysis. Women diagnosed with EC in the first year after being diagnosed with T2D were also excluded, as it is possible that enhanced medical monitoring after newly diagnosed diabetes might increase the detection rate of occult

Table I. *Distribution of person-years at risk in the cohort, numbers of cases and their matched controls, and the unadjusted incidence rates (*cases/100,000 person-years) of non-endometrioid endometrial cancer by age, duration of diabetes and ever-use of medications under study. Controls (up to 20 per case) were individually matched on age and duration of diabetes for each case.*

Variable		Subgroup	Person-years	Cases, n (%)	Controls, n (%)	Incidence*
Age (years)		40-69	187,524	9 (15.8)	188 (16.5)	4.8
		70-74	77,105	12 (21.1)	236 (20.8)	15.6
		75-79	91,366	10 (17.5)	196 (17.3)	10.9
		80-84	81,070	13 (22.8)	251 (22.1)	16.0
		85-102	66,868	13 (22.8)	265 (23.3)	19.4
Duration of diabetes (years)		1-<3	160,742	13 (22.8)	254 (22.4)	8.1
		3-<5	118,797	11 (19.3)	220 (19.4)	9.3
		5-<8	120,018	13 (22.8)	278 (24.5)	10.8
		≥8	104,377	20 (35.1)	384 (33.8)	19.2
Medication	Metformin	Ever	321,346	38 (66.7)	754 (66.4)	11.8
		Never	182,588	19 (33.3)	382 (33.6)	10.4
	Other oral ADM	Ever	266,791	32 (56.1)	686 (60.4)	12.0
		Never	237,143	25 (43.9)	450 (39.6)	10.5
	Insulin	Ever	58,963	9 (15.8)	167 (14.7)	15.3
		Never	444,971	48 (84.2)	969 (85.3)	10.8
	Any ADM	Ever	417,726	49 (86.0)	973 (85.7)	11.7
		Never	86,208	8 (14.0)	163 (14.3)	9.3
	Statin	Ever	235,758	20 (35.1)	580 (51.1)	8.5
		Never	268,176	37 (64.9)	556 (48.9)	13.8
		Total	503,934	57 (100)	1136 (100)	11.3

ADM: Antidiabetic medication.

cancer (28). Next, women with a history of hysterectomy were removed from the cohort. However, as information about hysterectomies was recorded from 1987 onwards, it is possible that some women with a history of an unrecorded hysterectomy, especially in the older age groups, might have been included in the cohort. Women with a history of use of systemic hormone replacement therapy (HRT) were also omitted from the cohort and those commencing HRT during the follow-up period were censored from that moment onwards to exclude the impact of HRT on EC risk. An additional reason for excluding women with a history systemic HRT use was to remove from the cohort some of the women who had had hysterectomy before 1987. Information on HRT use was available from 1994. The size of the final cohort was 92,366 women.

Follow-up. Follow-up started at the time of diagnosis of T2D and ended at diagnosis of non-endometrioid EC (ICD-O-3 codes can be found at http://reetta.arima.fi/endometrial-cancer/appendix1_icd-o-3_codes.xlsx), hysterectomy due to other causes, onset of HRT, death, or the 31st of December 2011, whichever occurred first. The duration of T2D and medication use was recorded from the diagnosis of diabetes, but follow-up for EC diagnosis started no earlier than at 40 years of age. In addition to a full-cohort analysis, a nested case–control study was carried out, in which up to 20 controls (n=1,136) were randomly sampled for each of the 57 women diagnosed with non-endometrioid EC during the follow-up period. The sampling was matched for age and duration of diabetes (±182 days), and for each case, the matched controls were drawn from amongst the cohort members at risk of EC at the date of EC diagnosis of the case.

Classification of medication used. Use of ADM was evaluated in three groups: metformin, other types of oral ADM, and insulin. Furthermore, a separate group using statins was assessed (classification by ATC codes as presented at http://reetta.arima.fi/endometrial-cancer/appendix2_atc-codes.xlsx). In order to reduce possible bias due to reverse causality, exposure to all forms of medication studied was defined as starting 365 days after its first purchase date. Both in the full-cohort analysis and in the nested case–control analysis, the cohort members were considered to be exposed to a given medication beginning from that moment until the end of the individual follow-up period (ever/never exposed). Medication use was analyzed as a time-varying covariate.

Statistical analysis. In the full-cohort analysis, a multiple Poisson regression model (29) was fitted to estimate hazard ratios (HRs) with 95% CIs for non-endometrioid EC in relation to ever-use of metformin, other forms of ADM and statins. In this model, the effects of current age and duration of T2D were assumed to obey the piecewise constant hazards pattern over chosen intervals (see Table I) of these two timescales. In the nested case–control analysis, the corresponding HRs with 95% CIs were estimated by means of conditional logistic regression (30) in relation to ever-use of different forms of ADM and statins. Results of the full-cohort analysis and the nested case–control analysis were adjusted for the age, duration of T2D and use at any time of other forms of medication. The register data were pre-processed using data SAS/STAT® software version 9.4 of the SAS System for Windows (SAS Institute Inc., Cary, NC, USA), with consecutive data transformations and the statistical analysis was performed in R environment version 3.3.2 (31).

Prognosis

Identification of the study cohort. The cohort-selection process is illustrated in Figure 2. The final patient cohort included 105 women with T2D diagnosed with non-endometrioid EC (for ICD-O-3 codes, see http://reetta.arima.fi/endometrial-cancer/appendix1_icd-o-3_codes.xlsx) between the 1st of January 1998 and the 31st of December 2011 in whom the estimated duration of T2D was at least 180 days before the diagnosis of EC. Information on the cancer cases, their histology and stage of cancer was extracted from the Finnish Cancer Registry, which covers 99% of all cancers diagnosed in the country (32). Cancer stage at presentation was categorized as local, advanced (including growth to adjacent tissues, metastasis to regional lymph nodes, and distant metastasis) or unknown.

Classification of medication used. ADM use was assessed in the following patient groups: I) metformin only, II) other oral ADM only, III) metformin plus other oral ADM, IV) insulin at any time, V) none. Use of statins was considered in two groups: users and non-users (for ATC codes, see http://reetta.arima.fi/endometrial-cancer/appendix2_atc-codes.xlsx). The duration of medication use had to be at least 180 days in the first three groups and among statin users. Therefore, data on two patients with metformin/other oral ADM use for 1-179 days were omitted from the results. Patients with at least one purchase of insulin were categorized into group IV. The duration of exposure to different forms of ADM and statins was defined during the 3 years preceding EC diagnosis, from the first purchase to 90 days after the last purchase, or the date of EC diagnosis if it occurred earlier.

Follow-up. Follow-up for each individual patient began at the date of diagnosis of non-endometrioid EC and ended with emigration, death or the 31st of December 2013, whichever occurred first. The follow-up data were acquired from The Finnish Cancer Registry, the records of which are annually linked (based on personal identity codes) with the Cause of Death Register maintained by Statistics Finland, which includes individual-level information about dates and causes of death (cancer-related and other causes, based on ICD-10 codes). In addition, data from the Finnish Cancer Registry are matched at regular intervals with the Central Population Register of Finland, containing individual-level information based on personal identity codes about the vital status, possible date of death, or emigration, and the official place of residence of Finnish citizens (33).

Statistical analysis. Mortality rates from EC and other causes were examined in the different ADM and statin groups using the Aalen–Johansen estimator of cumulative incidence function for competing risks (34). Cox proportional hazards models were used to control for the effects of year, age and stage at diagnosis of EC and the duration of T2D, and adjusted HRs with 95% CIs were estimated from these models. Statistical analyses were carried out with SPSS (version 24) and R environment (version 3.3.0) software (31).

Results

Incidence. The final cohort included 92,366 women diagnosed with T2D in 1996 through 2011. The total follow-up covered 503,934 person-years at risk, with a median follow-up time of 4.6 years. The patients' ages at the time of cohort entry ranged from 40 to 102 years. Fifty-seven women were diagnosed with non-endometrioid EC over the

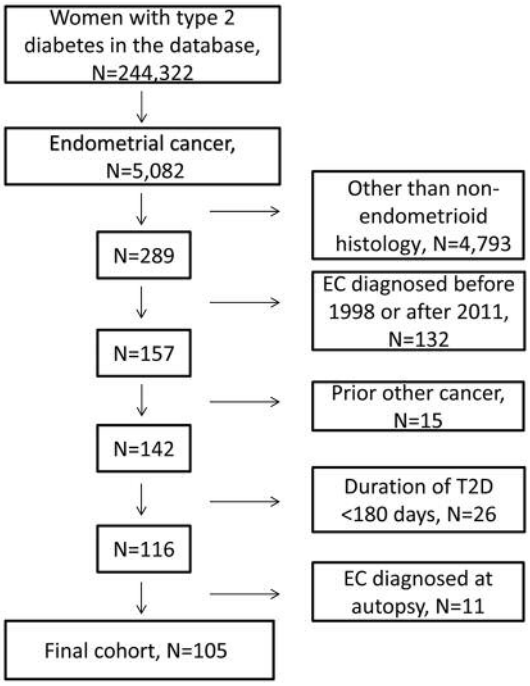

Figure 2. *Flow chart for formation of the non-endometrioid endometrial cancer prognosis cohort.*

follow-up period. Histology of EC was serous in 27 (47%) and clear cell in nine (16%) cases. The incidence of non-endometrioid EC was highest in patients who were 85 years of age or older. The incidence was also elevated in women in whom the duration of T2D was 8 years or more, compared to those with a shorter duration of the disease. Among the 57 women diagnosed with non-endometrioid EC, the number of ever-users was 38 (66.7%) for metformin, 32 (56.1%) for other forms of oral ADM, 9 (15.8%) for insulin and 20 (35.1%) for statins (Table I). The most frequent types of oral ADM other than metformin in the nested case–control analysis (by number of ever-users) were sulfonylureas (n=6301, 94%) and thiazolidinediones (n=579, 9%). The most common types of statins included hydrophobic simvastatin (n=4296, 69%) and atorvastatin (n=2159, 35%).

In the full-cohort analysis the incidence of non-endometrioid EC in the chosen reference category (age 70-74 years, duration of T2D less than 3 years, no ADM use) was 14 per 100,000 person-years. The use of metformin (HR=1.25, 95% CI=0.71-2.21), other forms of oral ADM (HR=0.82, 95% CI=0.47-1.44) or insulin (HR=1.24, 95% CI=0.57-2.68) was not linked to the risk of developing non-endometrioid EC in the multiple Poisson regression model. In an additional analysis, the risk of developing the disease was not observed to be different when metformin ever-users and ever-users of other types of oral ADM were compared

Table II. *Baseline characteristics in different antidiabetic medication groups. The entries are numbers of patients if not otherwise stated.*

	Other oral ADM*	Metformin*	Metformin and other oral ADM*	Insulin ever	No ADM	Total
Patients, n (%)	12 (11.4)	21 (20.0)	26 (24.8)	26 (24.8)	18 (17.1)	105 (100)
Median age at diagnosis (IQR), years	78 (70-84)	73 (66-80)	73 (69-85)	77 (70-81)	77 (72-82)	75 (69-82)
Age, n (%)						
<60 Years	1 (8.3)	1 (4.8)	1 (3.8)	0 (0.0)	0 (0.0)	4 (3.8)
60-69 Years	2 (16.7)	7 (33.3)	6 (23.1)	6 (23.1)	2 (11.1)	23 (21.9)
70-79 Years	4 (33.3)	7 (33.3)	9 (34.6)	9 (34.6)	11 (61.1)	41 (39.0)
≥80 Years	5 (41.7)	6 (28.6)	10 (38.5)	11 (42.3)	5 (27.8)	37 (35.2)
Median duration of T2D (IQR), years	3.5 (1.4-7.8)	3.2 (1.4-4.6)	8.1 (5.4-13.4)	15.4 (13.1-17.7)	12.2 (8.2-27.4)	8.4 (3.7-15.4)
Stage, n (%)						
Local	6 (50.0)	8 (38.1)	8 (30.8)	10 (38.5)	5 (27.8)	37 (35.2)
Advanced	3 (25.0)	10 (47.6)	15 (57.7)	10 (38.5)	8 (44.4)	47 (44.8)
Unknown	3 (25.0)	3 (14.3)	3 (11.5)	6 (23.1)	5 (27.8)	21 (20.0)

*Duration of medication ≥180 days.

(HR=1.23, 95% Cl=0.82-1.85). However, history of statin use was observed to be associated with a lower incidence of non-endometrioid EC (HR=0.53, 95% CI=0.30-0.93).

The results of the nested case–control analysis were consistent with those of the full-cohort analysis. Ever-use of metformin (HR=1.09, 95% CI=0.59-2.00), other types of oral ADM (HR=0.76, 95% CI=0.41-1.39), or insulin (HR=1.20, 95% CI=0.53-2.70) was not observed to be related to the risk of non-endometrioid EC. The incidence was not found to be different between metformin ever-users and ever-users of other forms of oral ADM (HR=1.20, 95% Cl=0.76-1.89). Statin use was again found to be inversely related to the incidence of non-endometrioid EC (HR=0.47, 95% CI=0.26-0.84). In an additional analysis, sufficient evidence was not found for an interaction between metformin and statin use (interaction HR=2.42, 95% Cl=0.58-10.17).

Prognosis. After applying the chosen inclusion criteria, the final patient cohort included 105 women with T2D who subsequently were diagnosed with non-endometrioid EC. The histology of EC was serous in 53 (50%) and clear-cell in 18 (17%) patients and the rest had high-grade mixed epithelial tumors. The age range of the patients in the cohort was from 53 to 94 years. Users of metformin, and metformin plus other forms of oral ADM were slightly younger than patients in the other ADM groups. The duration of T2D was shorter in patients on metformin only and in those on other types of oral ADM only (Table II). Statin users were on average younger (median age 73 *vs*. 78 years) but had longer duration of diabetes (median 11.3 *versus* 8.1 years) than non-users. The most frequently used types of other oral ADM (by number of ever-users in the other oral ADM group) were sulphonylureas (n=11, 92%). The most common statins included simvastatin (n=32, 74%) and atorvastatin (n=10, 23%).

A total of 83 patients died during the follow-up period, 55 deaths resulting from EC. The overall cumulative mortality from EC rose to 55% and that from other causes to over 25% during 8 years after diagnosis. Some variability in these curves across the different medication groups is apparent (Figure 3), but this can largely be attributable to chance variation given the smallness of group sizes and observed numbers of deaths.

In the Cox proportional hazards model, more advanced age and stage were associated with higher mortality from non-endometrioid EC, but no differences were observed between the different ADM groups. Mortality from other causes was not found to be different between the users of metformin and users of other types of oral ADM. Statin use was observed to be associated with a decrease in mortality from EC (HR=0.41, 95% CI=0.20-0.82) (Table III).

Discussion

In our nationwide register-based study, we were not able to find evidence of an association between the use of metformin or other types of ADM and the incidence or prognosis of non-endometrioid EC in women with type 2 diabetes. In contrast, statin use was observed to be inversely correlated both to the risk of developing and the mortality from non-endometrioid EC. These results must be viewed with caution given the small number of cases in our cohorts, with the consequence that the error margins of the estimated HRs were quite wide.

The strengths of our study include the use of a reliable, high-quality nationwide database containing precise information about the types, timing (in relation to the diagnosis of non-endometrioid EC) and amounts of ADM and statins used during a 15-year period. All patients with T2D in Finland are diagnosed by WHO criteria (35), and in FinDM

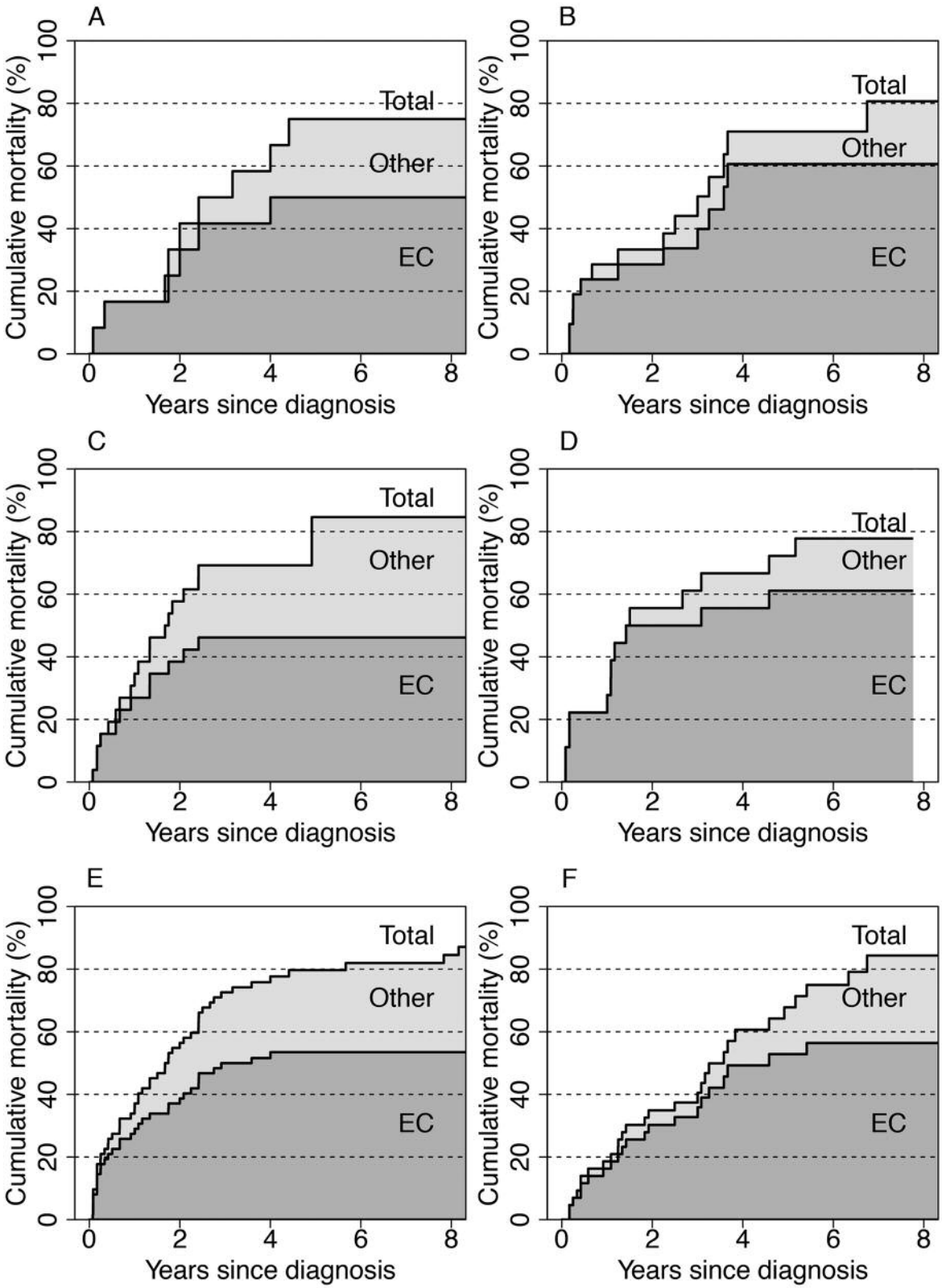

Figure 3. *Cumulative mortality (%) from endometrial cancer (EC) and from other causes of death (Other) after diagnosis of non-endometrioid EC in different medication groups. The curves are based on unadjusted Aalen–Johansen estimates. A: Other oral antidiabetic medication (ADM), B: metformin, C: insulin ever, D: no ADM, E: no statin use, F: statin.*

Table III. *Results from Cox proportional hazards models of mortality from endometrial cancer (EC) and other causes. The entries are estimated hazard ratios (HRs), their 95% confidence intervals (CIs), and p-values associated with the chosen covariates. Numbers of patients as well as numbers of deaths from non-endometrioid EC and from other causes are presented. Patients on any form of oral antidiabetic medication (ADM) or statin for less than 180 days were excluded from the analysis.*

		Endometrial cancer				Other causes			
Factor	Number of patients	Number of deaths	HR	95% CI	*p*-Value	Number of deaths	HR	95% CI	*p*-Value
Age at EC diagnosis (years)									
<60	4	1	0.57	0.06-5.98	0.64	0	0	0-∞	0.98
60-69	23	6	1			7	1		
70-79	41	23	2.28	0.87-5.95	0.092	12	0.83	0.27-2.61	0.75
≥80	37	25	4.18	1.57-11.17	0.004	9	2.36	0.61-9.19	0.21
Year of EC diagnosis									
1998-2002	21	8	1			10	1		
2003-2007	32	16	1.04	0.38-2.84	0.94	11	0.91	0.27-3.02	0.87
2008-2011	52	31	1.29	0.48-3.47	0.62	7	0.42	0.11-1.62	0.21
Stage of EC									
Local	37	8	1			14	1		
Advanced	47	35	8.73	3.65-20.89	<0.001	9	2.61	0.84-8.09	0.097
Unknown	21	12	3.89	1.47-10.30	0.006	5	1.16	0.35-3.85	0.81
Duration of DM (years)									
0.5-3	20	10	1			3	1		
3-6	19	7	0.39	0.13-1.15	0.088	8	1.77	0.43-7.30	0.43
6-12	28	16	0.77	0.23-2.53	0.66	9	1.75	0.38-8.12	0.47
12-36	38	22	0.90	0.24-3.45	0.88	8	0.74	0.10-5.66	0.77
Medication									
ADM									
Other oral ADM*	12	6	1			4	1		
Metformin*	21	11	1.56	0.40-6.07	0.52	3	2.09	0.25-17.59	0.50
Metformin and other oral ADM*	26	13	1.03	0.34-3.11	0.96	10	3.66	0.92-14.52	0.065
Insulin ever	26	13	0.84	0.22-3.26	0.80	7	5.98	0.94-37.98	0.058
None	18	11	1.44	0.42-4.95	0.57	4	2.43	0.40-14.81	0.34
Statins*									
No	62	34	1			20	1		
Yes	43	21	0.41	0.20-0.82	0.012	8	0.41	0.12-1.36	0.14

*Duration of medication ≥180 days.

data on the duration of T2D are also quite reliable. All patients with diabetes are included in FinDM when they receive their first reimbursement for ADM, or when diabetes diagnosis is marked in hospital records. Moreover, the Finnish Cancer Registry contains reliable information about the date of diagnosis and histology of cancer as well as on causes of death (both cancer-related and other causes of death).

The relatively small number of EC cases represents a major limitation of our study. Another weakness is missing information on the BMI of the patients. Results from earlier research indicate that metformin users may be heavier than other diabetics (11, 14), which might be a confounder when comparing the incidence of EC between different medication groups. However, the effect of BMI may be smaller in non-endometrioid EC compared with endometrioid EC (4). Higher BMI in metformin users might also bias our results towards worse EC-related survival in metformin users, as obesity (BMI ≥30 kg/m^2) has been associated with increased overall mortality in patients with non-endometrioid EC (36). Information on laboratory tests related to the severity of diabetes (HbA1c, blood glucose/insulin levels) is not included in FinDM, but the history of insulin use and duration of T2D can be seen as surrogate markers of the severity of the disease. Furthermore, FinDM does not contain information about many other factors connected with the risk of mortality from other causes such as smoking, common age-related comorbidities, and the severity and complications of T2D.

In our study, the classification of exposure to different forms of ADM and statins was based on registered purchases of those medications. We were unable to confirm if the patients actually used the purchased medication, thereby raising the possibility of misclassification. Among patients with newly-diagnosed diabetes in Finland, statin use has been observed to be more common among persons of higher

socioeconomic status, which could present a possible bias in our study (healthy-user effect) (37). Patients with diabetes treated in institutional wards do not receive reimbursement for their medication and can be categorized as no-ADM/no-statin users in FinDM, but this would have had a minor impact on the final results.

Diabetes has been associated with an increased incidence of several other cancer types in addition to EC (38). Elevated blood glucose, insulin and insulin-like growth factor 1 can promote tumor growth in patients with diabetes. Different forms of ADM may have different effects on cancer risk. In a meta-analysis carried out by Wu *et al*., the use of metformin or thiazolidinediones was related to a lower incidence of cancer, while insulin, sulfonylureas and alpha glucosidase inhibitors were associated with a higher incidence (39). The potential anticancer properties of metformin are thought to be mediated both directly *via* the 5' adenosine monophosphate-activated protein kinase (AMPK)/mammalian target of rapamycin (mTOR) pathway and indirectly by reducing circulating glucose and insulin levels (7). Recently there has been much interest in the idea of repurposing metformin as a preventive agent and co-treatment for cancer (40), and several clinical studies on metformin and EC are ongoing despite limited scientific data available.

In most of the previous studies, use of metformin was not linked to the risk of EC (10-12, 14). Only one study reported a lower incidence of EC in metformin users (13). Non-endometrioid EC was not analyzed separately in any of these studies, and some of them may have been affected by time-related biases (41). Only a few studies have concerned the association between metformin and the prognosis of EC. Two retrospective cohort studies in which metformin users were compared with other persons with diabetes yielded improved OS and PFS but not time to recurrence in patients with EC using metformin (16), and better OS in metformin-treated women with advanced EC (stage III-IV/recurrent) receiving chemotherapy (15). In another retrospective cohort study, the favorable impact of metformin on OS in patients with diabetes diagnosed with EC was reported to be limited to non-endometrioid EC only (17). In a retrospective cohort study carried out by Al Hilli *et al*., OS and PFS were not observed to differ between patients with diabetes on metformin when propensity score matching was used to account for confounding factors (18). Limitations of these studies include a lack of data about the duration of T2D and the dose and duration of treatment with metformin and other types of ADM. The primary endpoint in the studies (15-18) was OS, and cause-specific mortality from EC was not assessed.

Statins have been shown to inhibit the cell cycle, destabilize the cell membrane and induce apoptosis of cancer cells. Hydrophobic statins may have stronger anticancer properties than hydrophilic statins as a result of inhibition of the compensatory increase in extra-hepatic mevalonate synthesis. Studies carried out *in vitro* and *in vivo* have demonstrated that statins potentiate the effects of cytotoxic therapy on cancer cells (19, 42-44).

Epidemiological data on the relation between statin use and the risk of EC is sparse, but in general no evidence for an association has been shown so far (20, 21). Statin users in our full-cohort and case–control analysis were observed to have a lower risk of non-endometrioid EC. Statin use might have a different impact on the risk of non-endometrioid EC in women with diabetes compared with the general female population, which could explain why our results are not in line with those of the previous studies. In previous studies, associations observed between statin use and the prognosis of EC were variable: either no association was found (22), or a better prognosis in all types of EC (25) or in the non-endometrioid subtype alone (23, 24) was reported.

In conclusion, our findings are inconclusive as to whether the use of metformin is related to the risk or prognosis of non-endometrioid EC. However, statin use was observed to be associated with a lower incidence and mortality from this disease, but these findings require corroboration from new studies. It would also be interesting to study the possible combination effect of metformin and statins in a larger cohort.

Acknowledgements

This work was supported by grants from the Jane and Aatos Erkko Foundation (grant number T59127), the Finnish Cancer Foundation (grant number T59129) and Finnish Government Research Funds allocated to the University Hospital of Oulu (grant number K77729). These funders had no role in study design, in the collection, analysis and interpretation of data, in the writing of the report or in the decision to submit the article for publication.

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Received May 12, 2018
Revised June 4, 2018
Accepted June 15, 2018