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Statin use and mortality among ovarian cancer patients: A population-based cohort study

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Statin use has been suggested to improve prognosis in cancer patients, however, for ovarian cancer, the evidence is sparse. From the Danish Cancer Registry, we identified patients aged 30–84 years with a histologically verified first diagnosis of epithelial ovarian cancer between 2000 and 2013. Data on filled prescriptions, death, and potential confounding factors were obtained from nationwide registers. Cox proportional hazard regression models were used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between post-diagnostic statin use and all-cause or ovarian cancer-specific mortality. Among 4,419 patients with epithelial ovarian cancer, post-diagnostic statin use was not statistically significantly associated with all-cause (HR: 0.90, 95% CI: 0.78–1.04) or ovarian cancer-specific mortality (HR: 0.90, 95% CI: 0.76–1.08). There was little evidence of a dose-response relationship and the neutral associations persisted in sensitivity analyses. In women with endometrioid or clear cell tumour histology, cancer-specific mortality was reduced by 30–40% among statin users compared to non-users, however the analyses were limited by small numbers. Significantly reduced mortality with statin use was observed in subcohorts of new users of statins and of patients not using low-dose aspirin. In conclusion, we found no strong evidence of an association between post-diagnostic statin use and reduced mortality in ovarian cancer patients. However, our finding of potential differential susceptibility to statins among patients with different histologic types of ovarian cancer warrants further evaluation.

Ovarian cancer has a poor prognosis, as the early stages of the disease are typically associated with no or only vague symptoms. Approximately 60–70% of ovarian cancer cases are thus detected in an advanced stage, and the overall 5-year survival is only around 35–40%.[1,2] This emphasises the need for measures that could improve the prognosis of ovarian cancer.

Statins block the rate-limiting step in cholesterol biosynthesis. Besides lowering cholesterol, statins have been suggested to possess anticancer properties. Several *in vivo* and *in vitro* studies of animal tumour models and cancer cell lines have suggested that statins may exert antineoplastic effects through induction of apoptosis,[3,4] and suppression of tumour growth, angiogenesis and metastasis.[5,6] Although the laboratory findings appear promising, their clinical relevance remains largely unresolved, as results from both observational studies and clinical trials have been heterogeneous and inconclusive as to the anticancer effect of statins.[7–11] A number of observational studies have examined the association between statin use and mortality among ovarian cancer patients, with equivocal results.[10,12–15] These studies did not comprehensively evaluate potential risk variation according to different patterns of statin use, or to tumour or patient characteristics. This prompted us to examine the association between post-diagnostic statin use and mortality among patients in Denmark with epithelial ovarian cancer, using high-quality Danish nationwide health and demographic registries.

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Methods

Study population and data sources

We identified all women with a first diagnosis of histologically verified epithelial ovarian cancer between 2000 and 2013 from the nationwide Danish Cancer registry.[16,17] Patients were eligible if they were between 30 and 84 years and had no prior history of cancer, except non-melanoma skin cancer. The personal identification number[18,19] assigned to all residents of Denmark, was used to link the cancer registry data to other nationwide

What's new?

Statins don't boost overall survival in ovarian cancer patients, according to new results. Looking at previous evidence that statins spur apoptosis in cultured cells, these authors investigated whether statins, used after an ovarian cancer diagnosis, could impact ovarian cancer mortality. They looked at data from over 4,400 patients in the Danish Cancer Registry. Although they found no association between statin use and mortality among the whole group, they did note improved survival among patients with certain tumor types. Though the sample size in these subgroups was too small to draw a strong conclusion, it's an intriguing result, worthy of further study.

health and demographic registries. A detailed description of the included registries with codes for ovarian cancer characteristics, drug exposure, and a selection of covariates are provided in the online Supporting Information (Box S1, Box S2 and Table S1).

Follow-up and outcome assessment

The ovarian cancer patients were followed from one year after the diagnosis (referred to as the 1 y-baseline) until death, migration or end of study (December 31, 2014). The primary outcomes were all-cause and ovarian cancer-specific deaths, as recorded in the Danish Civil Registration System[18] and the Register of Causes of Death.[20] Patients who died within the first year after the ovarian cancer diagnosis were excluded because post-diagnostic statin exposure was unlikely to influence mortality within such a short period.

Assessment of statin use

Information on statin use was retrieved from the Danish National Prescription Registry.[21] We defined post-diagnostic statin use as two or more statin prescriptions filled on separate dates after the ovarian cancer diagnosis, and "non-use" as less than two prescriptions. Pre-diagnostic statin use was defined as two or more statin prescriptions filled within three years prior to diagnosis. Post-diagnostic use was the primary exposure in all analyses. New users of statins were defined as ovarian cancers patients who (according to our exposure definitions) started statin treatment after the ovarian cancer diagnosis, while continued users comprised patients who used statins both before and after the diagnosis. We calculated the cumulative amount of statins by adding the total number of daily defined doses (DDDs)[22] filled after the ovarian cancer diagnosis. Intensity of post-diagnostic statin use was evaluated by continuously estimating average dose of statin as the cumulated number of DDDs divided by the number of days between the first and the latest statin prescription during follow-up. The cumulative amount and the intensity of use were updated at each statin prescription.

In the main analysis, post-diagnostic statin use was assessed continuously and included as a time-varying covariate, allowing patients to move from a period of "non-use" to a period of use throughout follow-up. For use in three sensitivity analyses, post-diagnostic statin use was assessed between the date of diagnosis and baseline for follow-up at one (1 y-baseline) and three years (3 y-baseline), respectively, after the ovarian cancer diagnosis.

Statistical analysis

Cox proportional-hazard regression models were used to estimate hazard ratios (HRs) and 95% Wald confidence intervals (CIs) for all-cause and ovarian cancer-specific mortality among post-diagnostic statin users compared with post-diagnostic non-users. All analyses were performed with basic adjustment for age at diagnosis, clinical stage, and year of diagnosis. Fully adjusted analyses additionally included tumour histology, chemotherapy, highest achieved education, disposable income, marital status, non-statin drug use, and several comorbidities (Supporting Information Table S1). The proportional hazards assumption was assessed by testing for trends in the scaled Schoenfeld residuals.[23]

In the main analysis, statin use was modelled as a time-varying covariate and exposed person-time was lagged by one year following the second statin prescription. This was done to allow a biological meaningful latency time and to minimize the influence of changes in prescribing habits close to death.[24,25] Further, we evaluated associations according to patterns of use as categorical (intensity, cumulative amount, timing of use) or continuous variables (intensity, cumulative amount). In the latter case, we performed a test for a non-linear association using restricted cubic splines,[26] followed by estimation of a linear effect in case of statistical non-significance. To evaluate effect measure modification, we stratified analyses according to clinical stage, tumour histology, age at diagnosis, post-diagnostic use of low-dose aspirin, and ischaemic heart disease.

Subsequently, three pre-specified sensitivity analyses were performed to test the robustness of results (Fig. 1). First, statin exposure was modelled as a dichotomous variable based on statin use up to the 1 y-baseline, following a post-diagnostic "intention to treat" principle. Second, we repeated the 1 y-baseline analysis separating survival time for individual patients at 3 y after diagnosis. Thereby, we aimed to evaluate the timing of a potential effect of post-diagnostic statin use, differentiating between the early (1–3 y following diagnosis) versus late (>3 y following diagnosis) deaths among ovarian cancer patients. Finally, we performed a conditional survival analysis by moving the baseline to three years after the ovarian cancer diagnosis (3 y-baseline), in order to evaluate the effect of statin use in longer-term survivors.

All analyses were performed using R statistical software version 3.2.3[27] and the survival package.[28]

Results

The study population comprised 4,419 women with primary epithelial ovarian cancer. A total of 2,444 patients (55%) died

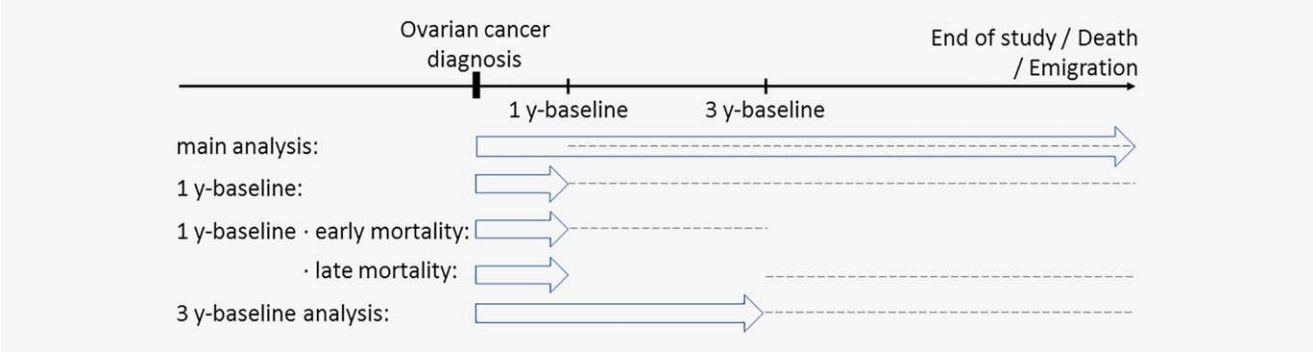

Figure 1. Explanatory scheme of the main and sensitivity analyses, depicting the timeline for assessment of post-diagnostic statin prescriptions (hollow arrow) and for follow-up (dashed line). [Color figure can be viewed at wileyonlinelibrary.com]

Table 1. Characteristics of ovarian cancer patients surviving at least one year after the ovarian cancer diagnosis, according to post-diagnostic use of statins within the first year after the diagnosis

		Non-users *n* = 3,943 (89%)	Post-diagnostic statin users *n* = 476 (11%)
Pre-diagnostic statin use	Use	144 (4%)	433 (91%)
	Non-use	3,799 (96%)	43 (9%)
Year of diagnosis	2000–2003	1,276 (32%)	51 (11%)
	2004–2006	875 (22%)	73 (15%)
	2007–2010	1,030 (26%)	191 (40%)
	2011–2013	762 (19%)	161 (34%)
Age	Median (IQR)	61 (53–69)	68 (61–73)
Age groups	30–55	1,289 (33%)	54 (11%)
	56–64	1,120 (28%)	114 (24%)
	65–72	876 (22%)	174 (37%)
	73–84	658 (17%)	134 (28%)
Clinical stage	Localised	1,607 (41%)	218 (46%)
	Non-localised	2,073 (53%)	210 (44%)
	Unknown	263 (7%)	48 (10%)
Tumour histology	Serous	2,339 (59%)	295 (62%)
	Endometrioid	528 (13%)	72 (15%)
	Mucinous	384 (10%)	31 (7%)
	Clear cell	212 (5%)	27 (6%)
	Epithelial, other	480 (12%)	51 (11%)
Chemotherapy	Yes	2,908 (74%)	371 (78%)
Highest achieved education	Basic	112 (3%)	9 (2%)
	Vocational/short	2,765 (70%)	380 (80%)
	Medium/long	964 (24%)	78 (16%)
	Unknown	102 (3%)	9 (2%)
Disposable income	Low	1,142 (29%)	196 (41%)
	Medium	1,335 (34%)	174 (37%)
	High	1,466 (37%)	106 (22%)
Marital status	Married	2,407 (61%)	286 (60%)
	Unmarried	435 (11%)	39 (8%)
	Divorced/widow	1,090 (28%)	151 (32%)
	Unknown	11 (0%)	0 (0%)

Table 1. Characteristics of ovarian cancer patients surviving at least one year after the ovarian cancer diagnosis, according to post-diagnostic use of statins within the first year after the diagnosis (Continued)

		Non-users $n = 3,943$ (89%)	Post-diagnostic statin users $n = 476$ (11%)
Comorbidities[1]	Ischaemic heart disease	149 (4%)	118 (25%)
	Congestive heart disease	55 (1%)	27 (6%)
	Cerebrovascular disease	142 (4%)	69 (14%)
	Diabetes mellitus[2]	149 (4%)	108 (23%)
	Chronic lower respiratory disease	260 (7%)	52 (11%)
	Obesity[2]	309 (8%)	78 (16%)
Non-statin drug use[3]	Low-dose aspirin	258 (7%)	180 (38%)
	Non-aspirin NSAIDs	557 (14%)	65 (14%)
	Paracetamol	625 (16%)	127 (27%)
	Beta-blockers	304 (8%)	149 (31%)
	Metformin	37 (1%)	49 (10%)
	Cardiovascular drugs (other)[4]	1,533 (39%)	342 (72%)
	"Renin-angiotensin system" drugs[5]	632 (16%)	271 (57%)
	Drugs against CLRD	682 (17%)	105 (22%)
	Antihistamines	607 (15%)	111 (23%)
	Proton pump inhibitors	1,087 (28%)	205 (43%)
	Bisphosphonates	142 (4%)	37 (8%)

Abbreviations: CLRD: chronic lower respiratory disease; IQR: interquartile range.
[1]Up to 1 year after diagnosis.
[2]Diagnosis and/or ≥2 prescriptions for disease-specific drugs.
[3]≥2 prescriptions, up to 1 year after diagnosis.
[4]Includes calcium channel blockers, anti-adrenergic drugs, diuretics, anti-thrombotic drugs, and drugs for cardiac therapy.
[5]Includes angiotensin-converting-enzyme (ACE) inhibitors and angiotensin-receptor blockers (ARB).

during the follow-up period and of these 1,903 (78%) died due to ovarian cancer. Overall, the median follow-up time was 2.4 years. Table 1 shows descriptive characteristics of the ovarian cancer patients according to statin use within the first year after diagnosis (characteristics of ovarian cancer patients by tumour histology are listed in Supporting Information Table S2). Eleven percent ($n = 476$) of the patients filled ≥2 statin prescriptions, of whom the majority (91%) was also pre-diagnostic users. Compared to patients with <2 statin prescriptions, statin users were older (median ages 68 *vs.* 61 y) and had a higher comorbidity burden with substantially higher prevalence of ischaemic and congestive heart disease, cerebrovascular disease, diabetes mellitus, and obesity. Furthermore, statin users were more likely to use non-statin drugs (included as covariates) and had slightly lower income and educational level. No major differences according to statin use were seen for clinical stage or tumour histology, and similar proportions of statin users and non-users received chemotherapy.

Table 2 shows associations between post-diagnostic statin use (≥2 prescriptions) and mortality among ovarian cancer patients. In the main time-varying analysis, statin use was associated with fully adjusted HRs of 0.90 (95% CI: 0.78–1.04) for all-cause mortality and 0.90 (95% CI: 0.76–1.08) for ovarian cancer-specific mortality. In analyses defining statin use according to patterns of use, no clear trends were apparent for intensity of statin use or cumulative amount used. For new statin users compared to non-users, we found a statistically significant reduction in all-cause mortality (HR: 0.76, 95% CI: 0.60–0.98), whereas a neutral association was observed with continued statin use.

In analyses stratified according to tumour characteristics (Table 3), we observed more pronounced reductions in ovarian cancer-specific mortality with statin use among patients with endometrioid (HR: 0.72, 95% CI: 0.43–1.22) or clear cell (HR: 0.67, 95% CI: 0.27–1.69) ovarian tumours, although the statistical precision was low. Null associations of statin use and ovarian cancer-specific mortality were seen among patients with serous or mucinous tumours. A tendency towards a stronger reduction in ovarian cancer-specific mortality was observed with statin use among patients with localised compared to non-localised clinical stage (Table 3). Stratification according to post-diagnostic low-dose aspirin use (Table 3) yielded statistically significant reductions in all-cause mortality (HR: 0.79, 95% CI: 0.66–0.96) with statin use among patients who did not use low-dose aspirin, whereas a statistically non-significant increase (HR: 1.14, 95% CI: 0.89–1.45) was observed with statin use among low-dose aspirin users. Among patients with a history of ischaemic heart disease, statin use was associated with

Table 2. Association between post-diagnostic statin use and all-cause or ovarian cancer-specific mortality, using a time-varying analysis

	All-cause mortality				Ovarian cancer-specific mortality			
Post-diagnostic statin use	Deaths	Person- years	Adjusted HR (95% CI)[1]	Fully adjusted HR (95% CI)[2]	Deaths	Person-years	Adjusted HR (95% CI)[1]	Fully adjusted HR (95% CI)[2]
Non-use	2,187	14,424	1	1	1,733	12,935	1	1
Use	257	2,224	0.94 (0.82–1.07)	0.90 (0.78–1.04)	170	1,811	0.92 (0.78–1.08)	0.90 (0.76–1.08)
Intensity of use[3]								
<1 DDD	145	1,267	0.95 (0.80–1.13)	0.92 (0.77–1.11)	96	1,061	0.90 (0.73–1.11)	0.90 (0.72–1.12)
1–2 DDDs	103	875	0.95 (0.78–1.16)	0.90 (0.73–1.12)	67	689	0.96 (0.75–1.24)	0.94 (0.72–1.22)
>2 DDDs	9	82	0.68 (0.35–1.32)	0.60 (0.31–1.17)	7	61	0.80 (0.38–1.69)	0.71 (0.33–1.51)
/unit DDD[4]			0.92 (0.77–1.09)	0.89 (0.73–1.07)			0.93 (0.76–1.14)	0.89 (0.72–1.12)
Cumulative amount[5]								
Low	117	841	0.88 (0.73–1.06)	0.86 (0.70–1.04)	88	733	0.90 (0.72–1.12)	0.89 (0.71–1.11)
Medium	88	775	0.92 (0.74–1.15)	0.88 (0.70–1.10)	61	632	0.97 (0.75–1.26)	0.94 (0.72–1.23)
High	52	608	1.16 (0.87–1.54)	1.13 (0.84–1.52)	21	446	0.88 (0.57–1.36)	0.89 (0.57–1.40)
/100 DDD[4]			1.01 (1.00–1.03)	1.01 (1.00–1.03)			1.00 (0.98–1.03)	1.01 (0.98–1.03)
Timing[6]								
New use	73	1,170	0.76 (0.60–0.97)	0.76 (0.60–0.98)	41	960	0.67 (0.49–0.92)	0.70 (0.50–0.96)
Continued use	184	1,054	1.03 (0.88–1.21)	0.97 (0.82–1.15)	129	851	1.04 (0.87–1.25)	1.00 (0.82–1.23)

Abbreviations: CI: confidence interval; DDD: daily defined dose; HR: hazard rate ratio.
[1]Adjusted for age at diagnosis, year of diagnosis, and clinical stage.
[2]Adjusted for age at diagnosis, year of diagnosis, clinical stage, tumour histology, socio-economic variables (highest achieved education, disposable income, marital status), chemotherapy (yes/no), non-statin drug use (low-dose aspirin, non-aspirin NSAIDs, paracetamol, beta-blockers, metformin, drugs affecting the renin-angiotensin system, antihistamines, proton pump inhibitors, other cardiovascular drugs, bisphosphonates, drugs for chronic lower respiratory disease), comorbidity (ischaemic heart disease, congestive heart disease, cerebrovascular disease, chronic lower respiratory disease, diabetes mellitus diagnosis and/or antidiabetic drugs, obesity diagnosis and/or anti-obesity drugs).
[3]Defined as the cumulative number of DDDs, divided by the number of days between the first and latest post-diagnostic prescription.
[4]Estimated linear effect; treating intensity of use and cumulative amount as continuous variables. There was no evidence of a non-linear association (P-values >0.05).
[5]Based on tertiles.
[6]New use: post-diagnostic statin use, no pre-diagnostic use. Continued use: both post- and pre-diagnostic statin use.

Table 3. Association between post-diagnostic statin use and all-cause or ovarian cancer-specific mortality, using a time-varying analysis and stratified by clinical stage, tumour histology, age, low-dose aspirin use, and diagnosis of Ischaemic heart disease

		All-cause mortality				Ovarian cancer-specific mortality			
	Post-diagnostic statin use	Deaths	Person-years	Adjusted HR (95% CI)[1]	Fully adjusted HR (95% CI)[2]	Deaths	Person-years	Adjusted HR (95% CI)[1]	Fully adjusted HR (95% CI)[2]
Clinical stage									
Localised	Non-use	535	7,373	1	1	369	6,472	1	1
	Statin use	90	1,327	0.98 (0.78–1.23)	0.95 (0.75–1.20)	48	1,075	0.90 (0.66–1.22)	0.89 (0.65–1.22)
Non-localised	Non-use	1,488	6,253	1	1	1,232	5,751	1	1
	Statin use	143	727	0.95 (0.80–1.13)	0.92 (0.76–1.11)	108	597	0.99 (0.81–1.21)	0.99 (0.80–1.23)
Tumour histology									
Serous	Non-use	1,436	7,482	1	1	1,160	6,702	1	1
	Statin use	174	1,067	1.00 (0.85–1.17)	0.94 (0.79–1.11)	125	858	1.02 (0.85–1.24)	0.99 (0.80–1.21)
Endometrioid	Non-use	222	2,443	1	1	170	2,184	1	1
	Statin use	29	461	0.79 (0.53–1.16)	0.80 (0.54–1.19)	16	380	0.69 (0.41–1.16)	0.72 (0.43–1.22)
Mucinous	Non-use	113	1,967	1	1	66	1,753	1	1
	Statin use	19	295	1.40 (0.85–2.31)	1.30 (0.78–2.16)	6	242	1.08 (0.46–2.53)	1.00 (0.43–2.35)
Clear cell	Non-use	93	903	1	1	76	807	1	1
	Statin use	8	182	0.60 (0.29–1.25)	0.63 (0.30–1.33)	5	146	0.63 (0.25–1.59)	0.67 (0.27–1.69)
Age									
<median age	Non-use	1,119	9,599	1	1	907	8,623	1	1
	Statin use	96	1,145	1.07 (0.87–1.33)	0.99 (0.79–1.23)	70	937	1.09 (0.85–1.40)	1.03 (0.79–1.33)
≥median age	Non-use	1,068	4,824	1	1	826	4,312	1	1
	Statin use	161	1,079	0.89 (0.75–1.05)	0.87 (0.72–1.04)	100	874	0.85 (0.68–1.05)	0.84 (0.67–1.06)
Low-dose aspirin use									
No	Non-use	2,031	13,448	1	1	1,630	12,070	1	1
	Statin use	131	1,354	0.82 (0.69–0.98)	0.79 (0.66–0.96)	86	1,104	0.78 (0.63–0.98)	0.76 (0.60–0.95)
Yes	Non-use	156	975	1	1	103	865	1	1
	Statin use	126	870	1.10 (0.87–1.39)	1.14 (0.89–1.45)	84	707	1.25 (0.93–1.67)	1.28 (0.95–1.73)
Ischaemic heart disease									
No	Non-use	2,085	13995	1	1	1,652	12,547	1	1
	Statin use	188	1,892	0.88 (0.76–1.03)	0.86 (0.73–1.01)	121	1,532	0.86 (0.71–1.04)	0.86 (0.70–1.05)
Yes	Non use	102	429	1	1	81	388	1	1
	Statin use	69	332	0.98 (0.71–1.37)	1.09 (0.78–1.52)	49	279	0.96 (0.66–1.42)	1.09 (0.73–1.16)

Abbreviations: CI: confidence interval; HR: hazard rate ratio.
[1]Adjusted for age at diagnosis, year of diagnosis, and clinical stage.
[2]Adjusted for age at diagnosis, year of diagnosis, clinical stage, tumour histology, socio-economic variables (highest achieved education, disposable income, marital status), chemotherapy (yes/no), non-statin drug use (low-dose aspirin, non-aspirin NSAIDs, paracetamol, beta-blockers, metformin, drugs affecting the renin-angiotensin system, antihistamines, proton pump inhibitors, other cardiovascular drugs, bisphosphonates, drugs for chronic lower respiratory disease), comorbidity (ischaemic heart disease, congestive heart disease, cerebrovascular disease, chronic lower respiratory disease, diabetes mellitus diagnosis and/or antidiabetic drugs, obesity diagnosis and/or anti-obesity drugs).

slightly increased all-cause mortality (HR: 1.09, 95% CI: 0.78–1.52), whereas a slight decrease in all-cause mortality (HR: 0.86, 95% CI: 0.73–1.01) was seen among those without such history (Table 3).

The sensitivity analyses defining statin use up to the 1 y- and 3 y- baselines (Fig. 1) showed overall results comparable to those of the main analysis for all-cause and ovarian cancer-specific mortality (Supporting Information Table S3). Similarly, the sensitivity analysis evaluating a potential difference in timing of the effect of post-diagnostic statin use yielded null associations for both early (1–3 y) and late (>3 y) deaths following the ovarian cancer diagnosis.

Discussion

Our nationwide cohort study of 4,419 ovarian cancer patients is the largest so far to evaluate the association between post-diagnostic statin use and mortality. We did not find strong evidence of an overall protective effect of statin use on all-cause or ovarian cancer-specific mortality. These findings are in contrast to the results from two small studies, conducted in United States (US)[12] and Israel,[13] reporting reductions in mortality of 55–75% among ovarian cancer patients who used statins. Another US study reported a statistically non-significant 20% risk reduction in ovarian cancer-specific mortality among statin users compared to non-users with no hyperlipidaemia.[14] In a sub-analysis of a previous Danish registry-based study, pre-diagnostic statin use among ovarian cancer patients was associated with a statistically non-significant 13% risk reduction in ovarian cancer-specific mortality.[10] Reasons for the considerable heterogeneity among study results remain obscure, however differences in study population, definitions of statin use, or analytical strategy are likely involved. Importantly, in our study, we averted immortal time bias.[29] Additionally, we minimised or evaluated the influence of selection bias by using a nationwide registry-based approach,[30] and exposure misclassification by applying a 1-year exposure lag-time and excluding patients who died within one year after diagnosis.[24] Furthermore, 1 y- and 3 y-baseline analyses, performed to test the robustness of our findings, did not materially change our results. We also performed two *post hoc* sensitivity analyses delaying start of follow-up with six months (*i.e.*, 1.5 year after the ovarian cancer diagnosis), and redefining statin exposure to 0, 1 and ≥2 prescriptions (*i.e.*, to compare ≥2 prescriptions with 0 prescriptions), respectively. Both analyses also yielded similar results to those of the main analyses (data not shown). The consistency of the results of the main and sensitivity analyses support the overall finding of a null association.

Interestingly, we found that post-diagnostic statin use was associated with larger reductions in ovarian cancer-specific mortality among patients with endometrioid or clear cell ovarian cancer, whereas no associations were observed for mucinous and serous (the most common) histological subtypes of ovarian cancer. Although the statistical precision was limited, our finding is compatible with the results of a previous study by Habis *et al.*[14] reporting a substantial reduction in mortality with statin use among patients with non-serous ovarian cancer, whereas no association was observed for ovarian cancer overall. Further evaluation of the potential heterogeneity in the effect of statin use with histological subtypes of ovarian cancer is warranted, ideally with attention for molecular variation and predictive markers that might explain differential susceptibility to statin use.

New users of statins (*i.e.*, patients who started statin use following the ovarian cancer diagnosis) had a statistically significant reduction in all-cause mortality, whereas those who used statins both prior and after the diagnosis did not experience reduced mortality. Caution should be exercised when interpreting these results. One explanation could be that women developing ovarian cancer despite statin use may be resistant to an anticancer effect of statins and therefore experience no survival benefit of post-diagnostic statin use, as suggested by Lavie *et al.*[13] However, it is highly debatable whether this argument holds in our study population since we found no apparent association between long-term statin use and risk of ovarian cancer in a previous study.[31] An alternative explanation would be that new users of statins represent a selected patient population who were more likely to be offered prophylactic statin treatment which requires lengthy use to provide clinical benefit.[32] Although we adjusted the mortality risk estimates for important prognostic determinants, including clinical stage, we cannot rule out residual confounding by prognostic predictors. Still, in an additional *post hoc* analysis of new users versus non-users according to clinical stage, we found inverse associations of similar magnitude among patients with localised and non-localised disease (data not shown), indicating that the reduced mortality in new users was not explained by differential prescribing according to clinical stage alone. New users of statins comprised only 9% of all post-diagnostic users, and thus for most statin users in our study the decision for initiating statin treatment was taken prior to the cancer diagnosis and was therefore not influenced by prognostic determinants of the ovarian cancer diagnosis.

We observed a statistically significant inverse association between post-diagnostic statin use and mortality among non-users of low-dose aspirin, whereas statin use was associated with a statistically non-significant increase in mortality among users of low-dose aspirin. Although caution should be exercised for these findings, one potential explanation could be that a potential prognostic effect of statins is attenuated when used in combination with low-dose aspirin.[33,34] Alternatively, the different effect of post-diagnostic statin use by use of low-dose aspirin may reflect differences in population characteristics as the majority of users of low-dose aspirin have cardiovascular disease or risk.[35] On the other hand, statin use among non-users of low-dose aspirin is predominantly prescribed for indications other than cardiovascular prophylaxis, and mainly hyperlipidaemia. The latter assumption is supported by the analysis stratified by ischaemic heart disease that similarly revealed a slight inverse association between statin use and ovarian cancer-specific mortality among women without such heart disease.

Our study had a number of limitations. We had no information on over-the-counter (OTC) purchase of drugs. However, statins and the majority of non-statin drugs included in our study were only available by prescription during the entire study period. Still, we cannot entirely exclude some residual confounding by aspirin and non-aspirin NSAID use, although the majority of these agents are prescribed in Denmark.[35] We had no information on the compliance to statin and other drug use among the ovarian cancer patients, however, in order to minimize the influence of non-compliance, we required at least two prescriptions for all included drugs in the analyses in order to be classified as a user. Furthermore, the general compliance to statin therapy in Denmark has been reported high (>80%),[36,37] although no evaluation has been performed specifically for ovarian cancer patients. Finally, residual confounding from unmeasured or incomplete variables cannot be ruled out, although we were able to adjust for a wide range of potential confounders using data from several nationwide registries.

In conclusion, our study did not indicate an overall beneficial effect of post-diagnostic statin use on all-cause or ovarian cancer-specific mortality among ovarian cancer patients, and these results were consistent in sensitivity analyses and by patterns of statin use. However, we observed reductions in mortality with post-diagnostic statin use in specific patient subpopulations, including patients with an endometrioid or clear cell ovarian tumour, and patients not using low-dose aspirin. Given the clinical importance of identifying patient or disease characteristics that may modify the prognostic effect of statins, these results merit further investigation.

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