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# Statin use and risk for ovarian cancer: a Danish nationwide case–control study

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**Background:** Limited data suggest that statin use reduces the risk for ovarian cancer.

**Methods:** Using Danish nationwide registries, we identified 4103 cases of epithelial ovarian cancer during 2000–2011 and age-matched them to 58 706 risk-set sampled controls. Conditional logistic regression was used to estimate adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for epithelial ovarian cancer overall, and for histological types, associated with statin use.

**Results:** We observed a neutral association between ever use of statins and epithelial ovarian cancer risk (OR=0.98, 95% CI=0.87–1.10), and no apparent risk variation according to duration, intensity or type of statin use. Decreased ORs associated with statin use were seen for mucinous ovarian cancer (ever statin use: OR=0.63, 95% CI=0.39–1.00).

**Conclusions:** Statin use was not associated with overall risk for epithelial ovarian cancer. The inverse association between statin use and mucinous tumours merits further investigation.

Identification of protective factors against ovarian cancer has huge public health implications, as this gynaecological cancer continues to have a sinister prognosis (Klint *et al*, 2010).

It has been suggested that statins protect against the development of cancer, including ovarian cancer (Boudreau *et al*, 2010). Experimental studies of human cancer cell lines and animal tumour models have demonstrated that statins induce apoptosis (Liu *et al*, 2009; Matsuura *et al*, 2011), inhibit angiogenesis (Chen *et al*, 2012) and suppress tumour growth and metastases (Alonso *et al*, 1998). Secondary analyses of randomised clinical trials of statin use and coronary heart disease have not had adequate statistical precision to evaluate comprehensively the association between statin use and ovarian cancer risk (Dale *et al*, 2006), and only four observational studies have specifically reported on the risk for ovarian cancer associated with statin use (Kaye and Jick, 2004; Friedman *et al*, 2008; Yu *et al*, 2009; Lavie *et al*, 2013). This prompted us to examine the association between statin use and ovarian cancer risk in a large nationwide case–control study.

## MATERIALS AND METHODS

**Study population and record linkage.** Our case–control study was nested in the entire Danish female population (population, 2.8 million), using data from seven nationwide registries. The registries were linked by use of the unique civil registration number assigned to all Danish citizens by the Danish Civil Registration System (Pedersen, 2011). From the Danish Cancer Registry (Gjerstorff, 2011), we identified all women aged 30–84 years with a histologically verified first diagnosis of well-defined epithelial ovarian cancer during 2000–2011. We required that the cases were resident in Denmark at the start of the Prescription Registry in 1995 and at the date of diagnosis, defined as the index date. We also required the cases to have no history of cancer (except non-melanoma skin cancer) before the index date. For each case, we randomly selected 15 age-matched female population controls using risk-set sampling and applying the same selection criteria as for the cases (Rothman *et al*, 2008; Pedersen, 2011). In addition, we required that the controls have no bilateral oophorectomy before the index date.

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All statin (ATC code C10AA) prescriptions redeemed by the cases and controls between January 1995 and 1 year before the index date were obtained from the Danish Prescription Registry (Kildemoes *et al*, 2011). We defined 'ever use' of statin as  $\geq 2$  prescriptions on separate dates and 'non-use' as  $< 2$  prescriptions. The duration of statin use was defined as the time between the first and last redeemed statin prescription plus 60 days and classified as short-term ( $< 5$  years) or long-term ( $\geq 5$  years). The intensity of use was defined as the cumulative number of defined daily doses (DDDs) (WHO, 2010) of statins divided by the duration of use in days and classified into approximate tertiles of low, medium or high intensity. Finally, we categorised statins by their lipid solubility into either 'exclusive use of lipophilic statins' (simvastatin, lovastatin, fluvastatin, atorvastatin and cerivastatin) or 'ever use of hydrophilic statins' (pravastatin and rosuvastatin).

**Statistical analysis.** We used conditional logistic regression to estimate age- and multivariable-adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for ovarian cancer associated with the use of statins. The reference group in all analyses was non-use of statins. Confounding factors were selected *a priori* and included age, parity, infertility, endometriosis, diabetes mellitus, chronic obstructive pulmonary disease or asthma, hysterectomy, tubal sterilisation, education, income, and the use of oral contraceptives, hormonal replacement therapy (HRT), paracetamol and low-dose aspirin. We stratified analyses according to duration and intensity of statin use and tested the combined exposure categories of duration and intensity for trend. All statistical analyses were performed with the statistical software R, version 3.0.2 (R Development Core Team, 2013).

A further description of the included registries, codes for identification of cases, drug use and other characteristics, and additional analyses are provided in the Supplementary text and Supplementary Table 1.

## RESULTS

We identified 4103 epithelial ovarian cancer cases (2731 serous, 650 endometrioid, 459 mucinous and 263 clear cell) and 58 706 controls. Only slight differences in characteristics were observed between the cases and controls (Table 1). The prevalence of ever use of statins was similar among cases (10.6%) and controls (11.0%). The vast majority of statin users were exclusive users of lipophilic statins (87.6%).

Ever use of statins was not associated with risk for overall epithelial (OR = 0.98, 95% CI = 0.87–1.10) or serous (OR = 1.03, 95% CI = 0.90–1.19) ovarian cancer (Table 2). No material risk variation was observed with increasing duration or intensity of statin use, and we found no apparent trends with the intensity of use within strata of short-term (epithelial overall:  $P$  trend = 0.22; serous:  $P$  trend = 0.98) or long-term (epithelial overall:  $P$  trend = 0.68; serous:  $P$  trend = 0.78) statin use (Table 2).

In analyses of histological types of epithelial ovarian cancer, inverse associations were observed between ever use of statins and risk for endometrioid (OR = 0.80, 95% CI = 0.58–1.10) and, notably, mucinous tumours (OR = 0.63, 95% CI = 0.39–1.00). In contrast, we observed an elevated OR for clear cell ovarian cancer (OR = 1.48, 95% CI = 0.92–2.38) associated with ever statin use. Albeit based on small numbers, reduced ORs were observed for mucinous ovarian cancer with short-term (OR = 0.57, 95% CI = 0.33–0.96) or high-intensity (OR = 0.23, 95% CI = 0.07–0.74) statin use. High-intensity statin use was also associated with a reduced OR for endometrioid ovarian cancer (OR = 0.54, 95% CI = 0.30–0.96), whereas elevated ORs were found for clear cell ovarian cancer in all exposure categories, and notably  $\geq 5$  years of statin use (OR = 2.05, 95% CI = 0.98–4.29).

**Table 1. Characteristics of the study population**

Characteristic	Cases (n = 4103)	Controls (n = 58 706)
<b>Drug use</b>		
Statin	434 (10.6)	6445 (11.0)
Oral contraceptives	224 (5.5)	5070 (8.6)
Hormonal replacement therapy	1484 (36.2)	18 850 (32.1)
Paracetamol	587 (14.3)	9513 (16.2)
Low-dose aspirin	494 (12.0)	7536 (12.8)
<b>Age at diagnosis/index date (years)</b>		
30–39	104 (2.5)	1454 (2.5)
40–49	480 (11.7)	6879 (11.7)
50–59	1041 (25.4)	14 991 (25.5)
60–69	1233 (30.1)	17 632 (30.0)
70–84	1245 (30.3)	17 750 (30.2)
<b>Education</b>		
Basic	82 (2.0)	1522 (2.6)
Higher	853 (20.8)	11 576 (19.7)
Vocational	3026 (73.8)	43 606 (74.3)
Unknown	142 (3.5)	2002 (3.4)
<b>Personal income</b>		
Low	1427 (34.8)	19 854 (33.8)
Medium	1372 (33.4)	19 507 (33.2)
High	1304 (31.8)	19 345 (33.0)
<b>Parity</b>		
0	901 (22.0)	9528 (16.2)
1	797 (19.4)	10 641 (18.1)
2	1521 (37.1)	23 218 (39.5)
$\geq 3$	884 (21.5)	15 319 (26.1)
<b>Medical history</b>		
Infertility	163 (4.0)	1443 (2.5)
Endometriosis	71 (1.7)	857 (1.5)
Diabetes mellitus	189 (4.6)	2792 (4.8)
Chronic obstructive pulmonary disease or asthma	167 (4.1)	2882 (4.9)
Ischaemic cardio- or cerebrovascular disease	321 (7.8)	5666 (9.7)
<b>Previous surgical procedure</b>		
Hysterectomy	369 (9.0)	4772 (8.1)
Tubal sterilisation	200 (4.9)	3453 (5.9)

Restricting the overall analyses to use of lipophilic statins exclusively yielded risk estimates close to those in the main analysis (presented in Supplementary Table 2).

## DISCUSSION

Our large population-based case-control study did not support an association between statin use and risk for overall epithelial or serous ovarian cancer, and we observed no variation in risk for these cancers according to duration, intensity or lipophilicity of statin use. With respect to non-serous types of epithelial ovarian cancer, we found inverse associations between statin use and risks for mucinous and endometrioid tumours, whereas the risk estimates were increased for clear cell ovarian cancer. The inverse associations between statin use and mucinous and endometrioid ovarian cancer were largest for high-intensity statin use, whereas risk estimates for clear cell ovarian cancer increased with the duration of statin use; however, the results for non-serous tumours were based on small numbers, and our study did not allow full evaluation of the influence of statin use on risks for these types of ovarian cancer.

Our findings for epithelial ovarian cancer are compatible with those reported by Kaye *et al* (2004) in a population-based case-control study based on prescription data in the General

**Table 2. Risk for epithelial ovarian cancer overall and histological types according to ever use of statins and stratified by duration and intensity of use**

Statin use	Epithelial OC				Serous OC				Endometrioid OC				Mucinous OC				Clear cell OC		
	Cases	Controls	Adjusted OR <sup>a</sup> (95% CI)		Cases	Controls	Adjusted OR <sup>a</sup> (95% CI)		Cases	Controls	Adjusted OR <sup>a</sup> (95% CI)		Cases	Controls	Adjusted OR <sup>a</sup> (95% CI)		Cases	Controls	Adjusted OR <sup>a</sup> (95% CI)
	Non-use	3669	52261	1.00 (reference)		2411	34513	1.00 (reference)		593	8306	1.00 (reference)		434	6023	1.00 (reference)		231	3419
Ever use	434	6445	0.98 (0.87–1.10)		320	4559	1.03 (0.90–1.19)		57	998	0.80 (0.58–1.10)		25	545	0.63 (0.39–1.00)		32	343	1.48 (0.92–2.38)
<b>Duration</b>																			
< 5 years	310	4683	0.96 (0.84–1.10)		227	3307	1.01 (0.87–1.18)		45	708	0.88 (0.62–1.24)		17	415	0.57 (0.33–0.96)		21	253	1.32 (0.77–2.24)
≥ 5 years	124	1764	1.04 (0.85–1.27)		93	1252	1.11 (0.88–1.40)		12	290	0.57 (0.31–1.07)		8	130	0.85 (0.39–1.83)		11	90	2.05 (0.98–4.29)
<b>Intensity<sup>b</sup></b>																			
Low	162	2108	1.11 (0.93–1.32)		117	1494	1.15 (0.94–1.41)		20	310	0.89 (0.54–1.45)		11	179	0.83 (0.43–1.58)		14	125	1.76 (0.93–3.33)
Medium	130	2209	0.86 (0.71–1.04)		88	1567	0.82 (0.65–1.03)		24	345	0.98 (0.62–1.54)		11	188	0.81 (0.42–1.56)		7	109	1.01 (0.44–2.32)
High	142	2128	0.98 (0.81–1.17)		115	1498	1.13 (0.92–1.39)		13	343	0.54 (0.30–0.96)		3	178	0.23 (0.07–0.74)		11	109	1.62 (0.80–3.26)
<b>Short-term use<sup>c</sup></b>																			
Low	119	1515	1.14 (0.93–1.38)		82	1062	1.14 (0.93–1.38)			NA <sup>d</sup>				NA <sup>d</sup>				NA <sup>d</sup>	
Medium	91	1598	0.83 (0.66–1.03)		60	1139	0.83 (0.66–1.03)			NA <sup>d</sup>				NA <sup>d</sup>				NA <sup>d</sup>	
High	100	1570	0.93 (0.75–1.15)		85	1106	0.93 (0.75–1.15)			NA <sup>d</sup>				NA <sup>d</sup>				NA <sup>d</sup>	
P trend			0.22				0.98												
<b>Long-term use<sup>c</sup></b>																			
Low	43	593	1.05 (0.76–1.45)		35	432	1.05 (0.76–1.45)			NA <sup>d</sup>				NA <sup>d</sup>				NA <sup>d</sup>	
Medium	39	611	0.95 (0.68–1.33)		28	428	0.95 (0.68–1.33)			NA <sup>d</sup>				NA <sup>d</sup>				NA <sup>d</sup>	
High	42	558	1.12 (0.81–1.54)		30	392	1.12 (0.81–1.54)			NA <sup>d</sup>				NA <sup>d</sup>				NA <sup>d</sup>	
P trend			0.68				0.78												

Abbreviations: OC = ovarian cancer; OR = odds ratio; CI = confidence interval; NA = not available. Italics are used to indicate P-values.

<sup>a</sup>Adjusted for age (by matching), parity (0, 1, 2, ≥ 3), use of oral contraceptives (ever/never), use of hormonal replacement therapy (ever/never), hysterectomy (ever/never), infertility (ever/never), endometriosis (ever/never), diabetes mellitus (ever/never), chronic obstructive pulmonary disease/asthma (ever/never), education (basic, higher, vocational, unknown), income (low, medium, high), use of paracetamol (ever/never) and use of low-dose aspirin (ever/never).

<sup>b</sup>Intensity of use was defined as the cumulative number of defined daily doses (DDD) divided by the duration of use in days and classified into approximate tertiles among controls into low, medium or high intensity. The cut-off values for low-, medium- and high-intensity statin use were 0.59 and 1.01 DDD.

<sup>c</sup>Short-term defined as < 5 years; long-term defined as ≥ 5 years.

<sup>d</sup>Analysis not possible due to limited number of cases.

Practice Research Database. Three other register-based studies (Friedman *et al*, 2008; Yu *et al*, 2009; Lavie *et al*, 2013) reported statistically non-significant inverse associations between statin use and ovarian cancer risk, and a recent meta-analysis (Liu *et al*, 2014) of the previous studies suggested an inverse relationship between increasing duration of statin use and ovarian cancer risk. In our study; however, we found no risk variation according to the duration of statin use and our evaluation of the risk for epithelial and serous ovarian cancer according to both duration and intensity of use also did not reveal any dose–response patterns.

To the best of our knowledge, our study is the first to report on the association between statin use and specific histological types of epithelial ovarian cancer. Due to the heterogeneous biology of epithelial ovarian cancer (Risch *et al*, 1996; Kurman and Shih, 2010), any antineoplastic effect of statin use would conceivably vary between individual histological types. We have no ready explanation for the consistent increase in clear cell ovarian cancer in nearly all categories of statin use. In contrast, some evidence may support our finding of an inverse association between statin use and mucinous ovarian cancer as mucinous tumours differ from non-mucinous types of epithelial ovarian cancer with regard to several risk factors (Risch *et al*, 1996; Soegaard *et al*, 2007) and tissue of origin (Kurman and Shih, 2010).

In line with the results of a meta-analysis of randomised controlled trials (Dale *et al*, 2006), we found no apparent difference in the risk estimates according to the lipophilicity of statins. Other pharmacodynamic aspects include the hepatoselectivity and large hepatic first-pass effect of statins leading to low systemic bioavailability (Gazzerro *et al*, 2012). Thus, the serum levels of statins during the treatment of hypercholesterolaemia may not be sufficiently high to achieve antineoplastic effects. This might explain the discrepancy between the results of observational studies and those of experimental studies demonstrating apparent anti-neoplastic effects of statins (Liu *et al*, 2009; Matsuura *et al*, 2011).

Our study had several strengths. First, it is the largest of the association between statin use and ovarian cancer risk. Moreover, information was derived from national registries of high quality with complete coverage on all Danish residents. As statins are available only by prescription in Denmark, we captured all statin use from 1995, and the register-based design eliminated selection or recall bias. Furthermore, the distribution of ovarian cancer risk factors among cases and controls were compatible with the literature, providing further reassurance about study validity.

Our study also had limitations. Information on drug use before 1995 was not available, raising a possibility of left truncation prescription data bias. However, the impact of exposure truncation was likely minimal for statins as the use of these agents was limited in Denmark until the mid-1990s (Scandinavian Simvastatin Survival Study Group, 1994; Riahi *et al*, 2001). Non-compliance constituted another source of exposure misclassification. However, we believe that non-compliance had little impact on our results as we defined statin use as  $\geq 2$  prescriptions redeemed on separate dates and the prescription records are based on drugs that are actually purchased at pharmacies (only part of the cost of drugs is reimbursed in Denmark). Adherence to preventive drug therapy is known to be associated with behaviour for improving or maintaining health, that is, the healthy-user effect (Dormuth *et al*, 2009). Although we evaluated the potential confounding effect of socioeconomic status by adjusting for education and income, we had no information on health-seeking behaviour, such as regular gynaecological examinations, and we cannot rule out potentially important residual confounding by this or other unmeasured factors associated with both statin use and ovarian cancer risk. Finally, our exposure period might have been too short and the statistical precision in estimates of long-term statin exposure too low to appropriately assess the influence of statin use on ovarian cancer risk.

In conclusion, statin use was not associated with risk for overall epithelial or serous ovarian cancer in our study, and we found no consistent trend in ovarian cancer risk with increasing duration or intensity of statin use. Our observation of an inverse association between statin use and risk for mucinous ovarian cancer may be a chance finding; however, as mucinous cancers differ from the other ovarian cancer types in many respects, this finding may warrant further investigation.

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## CONFLICT OF INTEREST

The authors declare no conflict of interest.

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