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Aspirin use and ovarian cancer mortality in a Danish nationwide cohort study

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Background: Increasing data suggest that aspirin use may improve cancer survival; however, the evidence is sparse for ovarian cancer.

Methods: We examined the association between postdiagnosis use of low-dose aspirin and mortality in a nationwide cohort of women with epithelial ovarian cancer between 2000 and 2012. Information on filled prescriptions of low-dose aspirin, dates and causes of death, and potential confounding factors was obtained from nationwide Danish registries. We used Cox regression models to estimate hazard ratios (HRs) with 95% confidence intervals (CIs) for ovarian cancer-specific or other-cause mortality associated with low-dose aspirin use.

Results: Among 4117 patients, postdiagnosis use of low-dose aspirin was associated with HRs of 1.02 (95% CI: 0.87–1.20) for ovarian cancer mortality and 1.06 (95% CI: 0.77–1.47) for other-cause mortality. Hazard ratios remained neutral according to patterns of low-dose aspirin use, including prediagnosis use or established mortality predictors.

Conclusions: Low-dose aspirin use did not reduce mortality among ovarian cancer patients.

Despite some advances in treatment modalities, the survival of ovarian cancer has hardly improved for decades and identification of modifiable factors that can improve the prognosis of ovarian cancer patients remains a high priority (Allemani *et al*, 2015).

Several epidemiologic studies suggest improved cancer outcomes with regular aspirin use among patients with clinically manifest cancer, and a number of randomised clinical trials are currently ongoing to evaluate the role of aspirin in the treatment of common cancers, notably colorectal cancer (Coyle *et al*, 2016; Elwood *et al*, 2016). The exact mechanisms behind the anti-neoplastic effects of aspirin remain to be established (Thun *et al*, 2012; Umar *et al*, 2016). For ovarian cancer, some studies in murine models and human cell lines have demonstrated an interaction between platelets and proliferation, angiogenesis, and metastasis of ovarian tumours, suggesting a role for aspirin via the antiplatelet effect (Cooke *et al*, 2015; Cho *et al*, 2017); however, other mechanisms have also been suggested (Hudson *et al*, 2008; Gates *et al*, 2010). Only few epidemiologic studies of ovarian cancer patients have evaluated outcomes associated with aspirin use and the results have been too equivocal to allow efficient design of clinical trials (Minlikeeva *et al*, 2015; Nagle *et al*, 2015; Bar *et al*, 2016; Dixon *et al*, 2017; Verdoodt *et al*, 2017b). A pooled analysis of 12 studies within the Ovarian Cancer Association Consortium (OCAC) reported a neutral association between aspirin use and overall survival among ovarian cancer patients; however, aspirin exposure was self-reported and only prediagnosis use was evaluated (Dixon *et al*, 2017). The influence of postdiagnosis aspirin use, a clinically more relevant exposure, has been explored in only one small cohort study reporting a statistically significant 50% reduction in overall mortality with aspirin use (Bar *et al*, 2016). This prompted us to conduct a cohort study of postdiagnosis low-dose aspirin use and mortality among ovarian cancer patients in Denmark, using the unique Danish nationwide registries.

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MATERIALS AND METHODS

From the Danish Cancer Registry, we identified all women aged 30–84 years with incident primary epithelial ovarian cancer between 2000 and 2012 and no history of cancer (except non-melanoma skin cancer). Information on filled prescriptions for low-dose aspirin and other drugs, tumour and patient characteristics, comorbid conditions, and mortality outcomes were retrieved from nationwide demographic, prescription, and patient registries, using the unique civil registration number assigned to all Danish residents for linkage. The Supplementary Material provides a detailed description of the registries, with codes for ovarian cancer, drug exposure, and covariates.

The study outcomes were ovarian cancer-specific and other-cause mortality. Patients were followed from 1 year after ovarian cancer diagnosis until death, migration, or end of the study (31 December 2013).

We defined postdiagnosis use of low-dose (75–150 mg) aspirin as $\geqslant 1$ prescription filled after the ovarian cancer diagnosis. Prediagnosis use of low-dose aspirin was defined as $\geqslant 1$ prescription within 5 years before the ovarian cancer diagnosis. In the primary analysis, we assessed postdiagnosis use of low-dose aspirin as a time-varying covariate lagged by 1 year (Chubak *et al*, 2013). Thus, postdiagnosis low-dose aspirin users were regarded as non-users until 1 year after their first prescription.

In secondary analyses, we evaluated the influence of timing of low-dose aspirin use by developing a supplementary time-varying exposure matrix: (1) no pre- or postdiagnosis use (reference group), (2) prediagnosis use only, (3) pre- and postdiagnosis use, and (4) postdiagnosis use only.

In two sensitivity analyses with fixed exposure periods, low-dose aspirin use was assessed from time of diagnosis until the start of follow-up at 1 or 3 years following the ovarian cancer diagnosis, and was considered invariable thereafter (Verdoodt *et al*, 2017a).

We used Cox proportional hazard regression models to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between postdiagnosis low-dose aspirin use and ovarian cancer-specific and other-cause mortality. Minimally adjusted analyses included age at diagnosis, clinical stage, and year of diagnosis. Fully adjusted models further included tumour histology, chemotherapy, highest achieved education, disposable income, marital status, comorbid conditions, and non-aspirin drug use (Table 1 and Supplementary Material). The proportional hazards assumption was tested using scaled Schoenfeld residuals. Finally, we evaluated the influence of competing risks as a result of death from other causes using the subdistribution hazards model proposed by Fine and Gray adapted for time-dependent covariates (Fine and Gray, 1999).

All analyses were performed using the R statistical software version 3.2.3 and the survival package (R Foundation for Statistical Computing, 2015; Therneau, 2015). STROBE guidelines were used to outline this study (von Elm et al, 2007). The Danish Data Protection Agency and Statistics Denmark's Scientific Board approved the study. According to Danish law, ethical approval is not required for registry-based studies (Thygesen *et al*, 2011).

RESULTS

Among 5439 eligible women with a primary diagnosis of epithelial ovarian cancer, 4117 were alive 1 year after the diagnosis and included in our study. During a mean follow-up of 3.6 years (maximum 13 years), 2245 (55%) patients died and of these, 1903 (85%) women died from ovarian cancer. Characteristics of the study population are shown in Table 1.

In the primary, time-varying analysis, we saw no association between postdiagnosis use of low-dose aspirin and ovarian cancer (HR: 1.02, 95% CI: 0.87–1.20) or other-cause (HR: 1.06, 95% CI: 0.77–1.47) mortality (Table 2). Further, we observed no substantial variation in HRs according to estimated dose (tablet size), cumulative amount of postdiagnosis low-dose aspirin use, or with timing of use (Table 2). Stratification according to tumour histology (Table 3), age at diagnosis, clinical stage, or year of diagnosis (Online Supplementary eTable 2) did not materially influence the associations.

We also observed overall neutral associations for ovarian cancer-specific and other-cause mortality in sensitivity analyses, except for an increased HR with short duration of low-dose aspirin use in the 3-year analysis; however, these estimates were based on small numbers (Supplementary eTable 3). Finally, analyses accounting for competing risks (Fine and Gray) exhibited results similar to those of the primary analyses (data not shown).

DISCUSSION

Our finding of a null association between use of low-dose aspirin and mortality after ovarian cancer is compatible with the results of the OCAC study based on prediagnosis use, but our results are in contrast to a previous study reporting a substantial reduction in overall mortality among ovarian cancer patients with postdiagnosis aspirin use (Bar *et al*, 2016). However, besides a small sample size, the latter cohort study was prone to time-related bias which are likely to have influenced the estimates (Chubak *et al*, 2013).

In our study, we evaluated the influence of low-dose aspirin on mortality after ovarian cancer, assuming that one tablet was equivalent to daily use. Higher dosages of aspirin might be required to obtain a beneficial effect on ovarian cancer prognosis; however, this is not readily supported by analyses of various patterns of low-dose aspirin use in our study, or the similar associations for low-dose (<100 mg) and higher-dose (>100 mg) aspirin in the OCAC study (Dixon *et al*, 2017). Moreover, for cancer in general, there is no solid evidence that doses of aspirin higher than those used in cardioprotection (75–150 mg) would provide stronger anticancer effects (Coyle *et al*, 2016; Elwood *et al*, 2016).

Among the strengths of our study were the nationwide cohort, large study size, high-quality and continuously updated registry data, and complete follow-up. The use of the Danish Prescription Registry ensured complete assessment of prescription drug use. The study design eliminated recall bias, and minimised selection bias and time-related biases.

A limitation of our study was the lack of data on over-the-counter (OTC) purchases of aspirin. However, in Denmark, most ($>90\%$) of the total sales of low-dose aspirin are prescribed (Schmidt *et al*, 2014), and this proportion may even be higher in cancer patients who are typically under close medical surveillance. High-dose (500 mg) aspirin preparations are mainly sold OTC in Denmark, and thus use of aspirin at this dose may have driven a possible slight inverse association towards the null given that high-dose aspirin is more likely to be used by non-users of low-dose aspirin than among users. However, high-dose aspirin is mainly used for short-term treatment of transient, non-cancer-related pain and therefore OTC use of high-dose aspirin likely resulted in at most minor misclassification of long-term aspirin use. Moreover, the absence of any material differences in associations with increasing dose and cumulative amount of low-dose aspirin indicates that OTC sales of high-dose aspirin likely did not have major impact on our results. Furthermore, in Denmark, regular use of drugs, including high-dose aspirin, is generally prescribed

because of at least 50% cost reimbursement and the need for medical surveillance for adverse effects (Schmidt *et al*, 2014). In our study population, only five patients filled a minimum of one prescription for high-dose aspirin, thus suggesting that use of aspirin at this dose was indeed only sporadical. Still, although we adjusted for several potential confounding factors, residual

Table 1. Characteristics of ovarian cancer patients surviving at least 1 year after the ovarian cancer diagnosis, according to post-diagnosis use of low-dose aspirin within the first year after diagnosis

		Non-users ($n = 3650$)	Post-diagnosis low-dose aspirin users ($n = 467$)
		No. (%)	No. (%)
Prediagnosis low-dose aspirin use	Use	179 (4.9)	374 (80.1)
	Non-use	3471 (95.1)	93 (19.9)
Year of diagnosis	2000–2003	1197 (32.8)	130 (27.8)
	2004–2007	1131 (31.0)	123 (26.3)
	2008–2012	1322 (36.2)	214 (45.8)
Age at diagnosis	Median (IQR)	60 (52–68)	70 (63–76)
Clinical stage	Localised	1470 (40.3)	171 (36.6)
	Non-localised	1913 (52.4)	247 (52.9)
	Unknown	267 (7.3)	49 (10.5)
Tumour histology	Serous	2164 (59.3)	279 (59.7)
	Endometrioid	484 (13.3)	72 (15.4)
	Mucinous	351 (9.6)	28 (6.0)
	Clear cell	204 (5.6)	20 (4.3)
	Other	447 (12.2)	68 (14.6)
Chemotherapy	Yes	2814 (77.1)	366 (78.4)
	No	836 (22.9)	101 (21.6)
Highest achieved education	Basic	99 (2.7)	11 (2.4)
	Vocational/short	2560 (70.1)	388 (83.1)
	Long/medium	898 (24.6)	54 (11.6)
	Unknown	93 (2.5)	14 (3.0)
Disposable income	Low	1088 (29.8)	190 (40.7)
	Medium	1208 (33.1)	186 (39.8)
	High	1354 (37.1)	91 (19.5)
Marital status	Divorced	460 (12.6)	51 (10.9)
	Married	2274 (62.3)	242 (51.8)
	Unmarried	418 (11.5)	35 (7.5)
	Widow	498 (13.6)	139 (29.8)
Comorbid conditions	Diabetes mellitus	137 (3.8)	69 (14.8)
	COPD	134 (3.7)	37 (7.9)
	Ischaemic heart disease	113 (3.1)	137 (29.3)
	Congestive heart disease	45 (1.2)	32 (6.9)
	Cerebrovascular disease	107 (2.9)	85 (18.2)
	Atrial fibrillation	92 (2.5)	50 (10.7)
Other drug use ($\geqslant$1 post-diagnosis prescription)	Non-aspirin NSAIDs	1050 (28.8)	157 (33.6)
	Antiplatelet drugs (other)[a]	32 (0.9)	55 (11.8)
	Anticoagulants (other)[b]	227 (6.2)	38 (8.1)
	Statins	287 (7.9)	186 (39.8)
	β-Blockers	300 (8.2)	166 (35.5)
	Calcium channel blockers	301 (8.2)	125 (26.8)
	ACE inhibitors	249 (6.8)	115 (24.6)
	ARBs	221 (6.1)	67 (14.3)
	Antihypertensives (other)[c]	915 (25.1)	232 (49.7)
	Cardiovascular drugs (other)[d]	83 (2.3)	79 (16.9)
	Insulin and analogues	38 (1.0)	27 (5.8)
	Metformin	56 (1.5)	31 (6.6)
	Oral antidiabetics (other)[e]	52 (1.4)	24 (5.1)
	Paracetamol	852 (23.3)	195 (41.8)
	Proton pump inhibitors	988 (27.1)	192 (41.1)
	Bisphosphonates	101 (2.8)	26 (5.6)
	Antihistamines	268 (7.3)	41 (8.8)
	Drugs against COPD	40 (1.1)	15 (3.2)
	High-dose aspirin[f]	5 (0)	0 (0)

Abbreviations: ACE = angiotensin-converting enzyme; ADP = adenosine diphosphate; ARB = angiotensin II receptor blocker; COPD = chronic obstructive pulmonary disease; IQR = interquartile range; NSAIDs = non-steroidal anti-inflammatory drugs.

[a]Dipyridamole and ADP receptor antagonists.

[b]Vitamin K antagonists, heparin group, direct thrombin inhibitors, and direct factor Xa inhibitors.

[c]Antiadrenergic drugs and diuretics.

[d]Cardiac glycosides, antiarrhythmic agents, cardiac stimulants, vasodilators, and prostaglandins.

[e]Sulfonylureas, α-glucosidase inhibitors, thiazolinediones, dipeptidyl-peptidase-4 inhibitors, and other blood glucose-lowering drugs.

[f]Not included in multivariable-adjusted analysis due to low numbers.

Table 2. Association between postdiagnosis low-dose aspirin use and ovarian cancer-specific and other-cause mortality, using time-varying analysis

	Ovarian cancer-specific mortality				Other-cause mortality			
Low-dose aspirin	**Person years**	**Deaths**	**HR basic adjustment[a] (95% CI)**	**HR full adjustment[b] (95% CI)**	**Person years**	**Deaths**	**HR basic adjustment[a] (95% CI)**	**HR full adjustment[b] (95% CI)**
Non-use	12914	1661	1	1	12914	272	1	1
Post-diagnosis use	1832	242	1.07 (0.93–1.23)	1.02 (0.87–1.20)	1832	70	1.24 (0.93-1.66)	1.06 (0.77–1.47)
Dose (tablet size)								
75–100 mg	1368	179	1.03 (0.88–1.21)	0.98 (0.82–1.17)	1368	45	1.08 (0.77–1.51)	0.95 (0.66–1.38)
150 mg	325	52	1.23 (0.93–1.64)	1.20 (0.90–1.61)	325	14	1.52 (0.86–2.68)	1.31 (0.73–2.37)
Mixed	139	11	1.07 (0.58–1.97)	0.87 (0.47–1.63)	139	11	2.28 (1.16–4.48)	1.53 (0.74–3.15)
Cumulative amount (tablets)								
1–365	620	114	1.12 (0.92–1.37)	1.07 (0.87–1.32)	620	25	1.45 (0.94-2.22)	1.29 (0.83–2.00)
366–1095	681	78	0.89 (0.71–1.13)	0.87 (0.67–1.11)	681	23	1.19 (0.76–1.86)	0.99 (0.61–1.60)
⩾1096	531	50	1.34 (0.98–1.84)	1.22 (0.88–1.70)	531	22	1.07 (0.64–1.77)	0.87 (0.50–1.49)
Timing[c]								
Never use	12378	1552	1	1	12378	253	1	1
Prediagnosis use only	536	109	1.03 (0.84–1.26)	0.92 (0.74–1.13)	536	19	1.11 (0.68–1.80)	0.91 (0.54–1.51)
Post-diagnosis use only	841	74	1.07 (0.83–1.36)	1.00 (0.77–1.29)	841	26	0.99 (0.63–1.56)	0.89 (0.56–1.42)
Pre- and postdiagnosis use	992	168	1.07 (0.91–1.27)	1.01 (0.84–1.22)	992	44	1.44 (1.02–2.03)	1.18 (0.79–1.75)
Prediagnosis cumulative amount (tablets)[d]								
1–999	506	80	0.99 (0.79–1.25)	0.95 (0.74–1.22)	506	17	1.15 (0.69–1.91)	1.01 (0.58–1.75)
⩾1000	486	88	1.16 (0.93–1.44)	1.07 (0.84–1.36)	486	27	1.72 (1.12–2.63)	1.34 (0.82–2.17)

Abbreviations: CI = confidence interval; HR = hazard ratio.
[a]Adjusted for age at diagnosis, year of diagnosis, and clinical stage.
[b]Adjusted for age at diagnosis, year of diagnosis, clinical stage, tumour histology, chemotherapy, highest achieved education, disposable income, marital status, use of non-aspirin drugs, and comorbid conditions.
[c]A supplementary exposure matrix including both pre- and postdiagnosis low-dose aspirin use was developed, using four time-varying categories: (1) no pre- or postdiagnosis use ('never use', reference), (2) prediagnosis use only, (3) postdiagnosis use only, and (4) both pre- and postdiagnosis use.
[d]Evaluation according to cumulative number of prediagnosis low-dose aspirin tablets among patients with both pre- and postdiagnosis use, compared with never use.

Table 3. Association between post-diagnosis low-dose aspirin use and ovarian cancer-specific and other-cause mortality, using time-varying analysis and stratified by tumour histology

		Ovarian cancer-specific mortality				Other-cause mortality			
Tumour histology	**Low-dose aspirin**	**Person years**	**Deaths**	**HR basic adjustment[a] (95% CI)**	**HR full adjustment[b] (95% CI)**	**Person years**	**Deaths**	**HR basic adjustment[a] (95% CI)**	**HR full adjustment[b] (95% CI)**
Serous	Non-use	6643	1123	1	1	6643	150	1	1
	Post-diagnosis use	917	162	1.04 (0.87–1.24)	0.98 (0.81–1.19)	917	33	1.22 (0.80–1.86)	0.95 (0.61–1.50)
Endometrioid	Non-use	2209	153	1	1	2209	35	1	1
	Post-diagnosis use	332	27	1.30 (0.82–2.07)	1.26 (0.79–2.02)	332	9	0.49 (0.19–1.24)	0.50 (0.20–1.30)
Mucinous	Non-use	1757	64	1	1	1757	34	1	1
	Post-diagnosis use	238	8	1.06 (0.44–2.56)	0.92 (0.37–2.25)	238	14	1.91 (0.85–4.30)	1.52 (0.66–3.48)
Clear-cell	Non-use	803	71	1	1	803	11	1	1
	Post-diagnosis use	151	10	0.68 (0.30–1.55)	0.72 (0.31–1.63)	151	5	2.46 (0.57–10.60)	1.87 (0.45–7.86)
Other	Non-use	1502	250	1	1	1502	42	1	1
	Post-diagnosis use	194	35	1.06 (0.70–1.59)	1.02 (0.67–1.54)	194	9	1.43 (0.60–3.42)	1.37 (0.55–3.42)

Abbreviations: CI = confidence interval; HR = hazard ratio.
[a]Adjusted for age at diagnosis, year of diagnosis, and clinical stage.
[b]Adjusted for age at diagnosis, year of diagnosis, clinical stage, chemotherapy, highest achieved education, disposable income, marital status, use of non-aspirin drugs, and comorbid conditions.

confounding could have been introduced by lifestyle factors, such as physical activity, smoking and obesity, or other unmeasured factors potentially associated with both low-dose aspirin use and ovarian cancer mortality.

In conclusion, we found no evidence of reduced mortality among ovarian cancer patients associated with postdiagnosis use of low-dose aspirin.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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