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Short communication

Aspirin, nonaspirin nonsteroidal anti-inflammatory drugs, acetaminophen and ovarian cancer survival

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ABSTRACT

Aspirin and nonaspirin nonsteroidal anti-inflammatory drugs (NSAIDs) have been shown to decrease tumor progression in pre-clinical models of ovarian cancer, however the influence of these drugs on survival in women following a diagnosis of ovarian cancer is unknown. We included 1305 Australian women diagnosed with incident invasive epithelial ovarian cancer, recruited into a population-based case–control study. Use of aspirin, nonaspirin NSAIDs and acetaminophen in the 5 years preceding ovarian cancer diagnosis was assessed from self-reports. Deaths were ascertained up to October 2011 via linkage with the Australian National Death Index. Cox proportional hazards regression models were used to calculate adjusted hazard ratios (HRs) and 95% confidence intervals (CI). During a mean follow-up time of 4.9 years (SD 2.8 years), there were 834 deaths, of which 779 (93% of deaths) were from ovarian cancer. We found uniformly inverse, but non-significant, HRs for ever use in the last five years of aspirin, nonaspirin NSAIDs and acetaminophen compared with no use (adjusted HRs 0.92 [95% CI 0.81–1.06], 0.91 [95% CI 0.80–1.05] and 0.91 [95% CI 0.69–1.20], respectively). There was no evidence of any dose response trends. The results remained unchanged when we limited the outcome to ovarian cancer mortality. Associations did not differ by histologic subtype, age at diagnosis or stage. Given current interest in the role of aspirin and nonaspirin NSAIDs in cancer survival these results are noteworthy given they are the first to investigate these associations in women with ovarian cancer. Our results provide no strong evidence that pre-diagnostic use of aspirin or nonaspirin NSAIDs are associated with improved survival in women with ovarian cancer.

1. Introduction

Ovarian cancer represents the leading cause of death among women with gynecological malignancies, with only approximately 40–45% of women alive 5 years after diagnosis [1]. About 75% of ovarian cancers are diagnosed at an advanced stage, acquired chemoresistance is common and there is a lack of new effective agents [2]. Most of the strongest known prognostic factors, such as stage of disease, tumor grade and age at diagnosis, are not modifiable. The search for ways to improve survival has lead to interest in identifying potentially modifiable factors that might improve prognosis.

Several lines of evidence suggest that ovarian cancer may be related to chronic inflammation [3]. Increasing evidence from the basic sciences, epidemiological studies and randomized controlled trials supports the effectiveness of aspirin, as well as other nonaspirin nonsteriodal anti-inflammatory drugs (NSAIDs) in reducing risk of cancer at several sites [4–7]. A recent analysis of pooled data from 12 population-based, case–control studies has suggested that aspirin and nonaspirin NSAIDs may reduce the risk of ovarian cancer [8]. There is also some evidence from laboratory studies [9–12] and animal models [13] suggesting that aspirin and NSAIDs can decrease the progression of ovarian cancer by inducing apoptosis and inhibiting angiogenesis.

We have followed a large cohort of women to report for the first time the association between the use of aspirin, nonaspirin NSAIDs,

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acetaminophen and mortality overall, and by histologic subtype and FIGO (International Federation of Gynecology and Obstetrics) stage.

2. Materials and methods

This study included 1305 women diagnosed with incident, primary, invasive epithelial ovarian cancer (including primary peritoneal and fallopian tube cancer) who originally participated in a national population-based case–control study: the Australian Ovarian Cancer Study (AOCS). Full details of the study have been provided elsewhere [14]. Briefly, information about socio-demographic, hormonal, reproductive and lifestyle factors was obtained via self-administered questionnaire at study enrollment. Women were asked how often, in the five years preceding their cancer diagnosis, they had taken aspirin, nonaspirin NSAIDs and acetaminophen medications. For this analysis frequency of use was categorized as never use, use ≤1/week and use >1/week.

Vital status was determined through data abstracted from medical records every 6–12 months, and linkage to the Australian National Death Index (NDI). Survival time was calculated from the date of histologic diagnosis to study exit due to death or censoring (31st October 2011). We also repeated analyses using age, rather than time, as the time metric. All-cause mortality was the endpoint for follow-up; however we repeated the analyses using ovarian cancer mortality as the endpoint.

Associations between aspirin, nonaspirin NSAIDs and acetaminophen use, overall and ovarian cancer specific mortality were estimated using Cox proportional hazards regression; multivariate hazard ratios (HR) and 95% confidence intervals (CIs) were generated using SAS (SAS, version 9.2; SAS Institute, Cary, NC). Multivariate models were adjusted for age at diagnosis (continuous), FIGO stage at diagnosis (I, II, III, IV) and grade (well, moderately, poorly/undifferentiated, unknown), residual disease after surgery (nil, ≤1 cm, >1 cm/not resected, unknown) and the presence of other major co-morbidities (yes/no) (based on co-morbidities included in the Charlson Index [15], with the exception of peptic ulcers and the inclusion of other major co-morbidities which may impact survival e.g. multiple sclerosis). Survival models were left-truncated at the date of study co\nsent as women had to survive to this point to be eligible for inclusion. Test for proportional hazard between each of these variables and survival was assessed using univariate proportional hazards regression. Where the proportional hazards assumption was violated a time-variable interaction term was included in the multivariate model. We also conducted subgroup analyses to examine whether the associations between aspirin, non aspirin NSAIDs or acetaminophen and survival were modified by histologic subtype (serous vs. non-serous), age at diagnosis (<60 and ≥60 years) or stage (I/II and III/IV). The statistical significance of any observed stratum differences was assessed by including a cross-product term in survival models. Ethics approval and informed consent were obtained prior to study enrollment.

3. Results

The descriptive characteristics of the women are shown in Table 1. Briefly, 834 (64%) women died during the follow-up period, of which 779 (93%) died due to ovarian cancer. For women who were alive at the end of follow-up, the mean time of follow-up from date of diagnosis was 4.9 years (interquartile range 2.3–7.3 years) and the 5-year survival of the entire cohort was 48%. As expected, women who were older, had late stage, higher grade disease, serous histology, residual disease or co-morbidities experienced worse survival in crude analyses.

Table 1
Baseline characteristics and 5-year survival in women with ovarian cancer.

	Baseline (*n*)	Crude 5-year survival % (% survived)	*P* value[a]
Age group (at diagnosis, years)			<0.0001
<50	236	59	
50 to <60	412	50	
60 to <70	411	46	
70+	246	35	
FIGO stage			<0.0001
I	245	87	
II	121	74	
III	801	35	
IV	131	25	
Histologic subtype			<0.0001
Serous	911	41	
Mucinous	51	74	
Endometrioid	140	77	
Clear cell	87	64	
Other	116	40	
Tumor grade			<0.0001
Well differentiated	121	71	
Moderately differentiated	247	48	
Poorly/undifferentiated	851	43	
Unknown	86	60	
Residual disease			<0.0001
No residual disease	563	73	
≤1 cm	295	33	
>1 cm/not resected	319	22	
Unknown	128	35	
Co-morbidities (Charlston)[b]			0.0048
No co-morbidity	888	50	
One or more co-morbidities	355	43	

[a] *P* value = Log-rank test of equality over strata.
[b] Based on co-morbidities included in the Charlson Index [14] with the exception of peptic ulcers and the inclusion of other major co-morbidities which may impact survival e.g. multiple sclerosis.

Multivariate analyses identified no significant associations between use or increasing frequency of use of aspirin, nonaspirin NSAIDs or acetaminophen and mortality (Table 2). The HRs were uniformly inverse and non-significant for users vs. never users of aspirin (HR = 0.92), nonaspirin NSAIDs (HR = 0.91) and acetaminophen (HR = 0.91). Results were not appreciably different for users of both aspirin and nonaspirin NSAIDs or a combined group of users of either aspirin or nonaspirin NSAIDs (compared to women who used neither aspirin nor nonaspirin NSAIDs). These results were unchanged when we used age as the time metric, ovarian cancer mortality as the end point and did not vary appreciably across the different histologic subtypes of ovarian cancer (serous, non-serous), age at diagnosis (<60 and ≥60 years) or by cancer stage (I/II vs. III/IV) (results not shown).

4. Discussion

Despite promising pre-clinical results, in this study of just over 1300 women with invasive ovarian cancer we found no evidence that use of aspirin or nonaspirin NSAIDs during the 5-years pre-diagnosis was associated with better survival outcomes. To our knowledge, no prior study has examined the association between aspirin, non aspirin NSAIDs and ovarian cancer mortality, however some epidemiologic evidence from other cancers, notably breast and colon, suggests that post-diagnostic use of aspirin/nonaspirin NSAIDs may be important in terms of survival [16,17]. The fact that our study was limited to pre-diagnostic use might explain our null