Gynecologic Oncology xxx (2018) xxx–xxx

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

Non-aspirin NSAID use and ovarian cancer mortality

Freija Verdoodt [a], Christian Dehlendorff [b], Søren Friis [b,c], Susanne K. Kjaer [a,d,*]

[a] Virus, Lifestyle and Genes, Danish Cancer Society Research Center, Copenhagen, Denmark
[b] Statistics and Pharmacoepidemiology, Danish Cancer Society Research Center, Copenhagen, Denmark
[c] Department of Public Health, University of Copenhagen, Copenhagen, Denmark
[d] Department of Gynaecology, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark

HIGHLIGHTS

- Any postdiagnosis non-aspirin NSAID use was not associated with mortality among ovarian cancer patients overall.
- Non-aspirin NSAID use was, however, associated with improved survival among patients with serous tumor histology.
- A trend emerged towards a dose-response relationship.
- We found a suggestion of increased mortality with non-aspirin NSAID use among patients with non-serous histology.
- These histology-specific findings warrant further investigation.

ARTICLE INFO

Article history:
Received 19 April 2018
Received in revised form 12 June 2018
Accepted 15 June 2018
Available online xxxx

Keywords:
Ovarian neoplasms
Nonsteroidal anti-inflammatory drugs
Pharmacoepidemiology
Mortality
Gynecological cancer
Prescription registry

ABSTRACT

Objective. Preclinical studies suggest that non-aspirin non-steroidal anti-inflammatory drugs (NSAIDs) may improve survival of ovarian cancer. We examined the association between non-aspirin NSAID use and ovarian cancer mortality.

Methods. All women in Denmark with a first diagnosis of epithelial ovarian cancer between 2000 and 2012 were identified. We obtained information on drug use, mortality outcomes, and potential confounding factors from nationwide registries. Cox regression models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between postdiagnosis non-aspirin NSAID use (≥1 prescription) and ovarian cancer-specific or other-cause mortality compared with non-use (no prescriptions). The influence of competing risks was evaluated using the sub-distribution hazards model proposed by Fine and Gray.

Results. Among 4117 patients, any postdiagnosis use of non-aspirin NSAIDs was not associated with either ovarian cancer (HR = 0.97, 95% CI = 0.87–1.08) or other-cause (HR = 0.99, 95% CI = 0.77–1.27) mortality, however, inverse associations for ovarian cancer mortality were observed with high cumulative (HR = 0.75, 95% CI = 0.60–0.94) or high-intensity (HR = 0.86, 95% CI = 0.72–1.03) postdiagnosis use of non-aspirin NSAIDs. The associations differed substantially with histological subtype of ovarian cancer, with only inverse associations observed for serous ovarian cancer (HR = 0.87, 95% CI = 0.77–0.99). Among a smaller number of patients with a non-serous tumor, postdiagnosis non-aspirin NSAID use was associated with increased ovarian cancer mortality.

Conclusions. Any postdiagnosis use of non-aspirin NSAIDs did not influence ovarian cancer mortality overall, however, more intensive use was associated with improved survival of serous ovarian cancer.

1. Introduction

Identification of measures that may improve the prognosis of ovarian cancer patients has high priority, as ovarian cancer remains the most lethal gynecological malignancy in developed countries, with an average 5-year survival of only around 20% for serous ovarian cancer, the most common histological subtype [1, 2]. Aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) have been suggested to improve the prognosis of some cancer types [3–6]. Previously, we found no association between low-dose aspirin use and survival of ovarian cancer patients [7], however, a number of preclinical studies have demonstrated stronger anti-neoplastic effects of non-aspirin NSAIDs than of aspirin in ovarian cancer animal models and human cell lines [8–10]. While the anti-neoplastic effects of aspirin are thought to be mediated

* Corresponding author at: Virus, Lifestyle and Genes, Danish Cancer Society Research Center, Strandboulevarden 49, 2100 Copenhagen, Denmark.
E-mail address: susanne@cancer.dk (S.K. Kjaer).

https://doi.org/10.1016/j.ygyno.2018.06.018
0090-8258/

by mechanisms involving inhibition of both cyclooxygenase (COX)-1 and COX-2, and of platelet aggregation [11, 12], non-aspirin NSAIDs are suggested to exert their anti-neoplastic effect primarily through inhibition of COX-2 and suppression of inflammation [11, 13]. Compelling evidence has established a clear link between inflammation and cancer [14, 15], and overexpression of COX-2 has been demonstrated in ovarian malignant tumors and suggested to be a predictor of poor prognosis and chemotherapy resistance [16–19]. Furthermore, inhibition of COX enzymes has been reported to suppress estrogen biosynthesis *in vitro* [20] and a modest inverse association between NSAID use and circulating estrogen levels has been reported among post-menopausal women [21]. Since ample evidence implicates a role for estrogen and other reproductive hormones in ovarian carcinogenesis [22, 23], an anti-neoplastic effect of NSAIDs may be hypothesized.

Although the preclinical findings are intriguing, only few epidemiologic studies have examined the association between use of non-aspirin NSAIDs and ovarian cancer prognosis, and overall, were unable to comprehensively evaluate the influence of exposure patterns [24–29]. Furthermore, the majority of these studies did not provide separate estimates for histological subtypes of ovarian cancer, although there is general consensus that ovarian cancer in fact comprises several distinct diseases, with diverse etiology, prognosis and molecular characteristics [30, 31].

The above considerations prompted us to investigate the association between postdiagnosis use of non-aspirin NSAIDs and mortality in a nationwide cohort of epithelial ovarian cancer patients, evaluating potential effect modification by patterns of use and clinical parameters, including tumor histology.

2. Methods

2.1. Study population and data sources

All patients in Denmark with incident epithelial ovarian cancer between 2000 and 2012 were identified from the nationwide Danish Cancer Registry. Patients were eligible if they were resident in Denmark at time of diagnosis, aged between 30 and 84 years, and had no previous history of cancer (except non-melanoma skin cancer). Information on prescription drug use, treatment, comorbid conditions, and socioeconomic parameters was obtained from nationwide registries and linked using the unique personal identification number assigned to all residents of Denmark. A detailed description of the registries with codes for tumor characteristics, drug exposure and comorbid conditions is provided in the online Supplementary Methods.

2.2. Follow-up and outcome assessment

The primary outcome was ovarian cancer-specific mortality, ascertained from the Register of Causes of Death. We evaluated other-cause mortality as a competing risk for ovarian cancer mortality. Follow-up started one year after ovarian cancer diagnosis and ended at death, migration, or end of the study (December 31, 2013), whichever occurred first. We did not include patients who died in the first year after diagnosis, as it seemed unlikely that postdiagnosis NSAID exposure would influence mortality within such a short period.

2.3. Assessment of non-aspirin NSAID use

Postdiagnosis use of non-aspirin NSAIDs was the primary exposure and assessed from prescription data in the Danish National Prescription Registry. We defined postdiagnosis use of non-aspirin NSAIDs as one or more prescriptions, and non-use as no prescriptions filled after the ovarian cancer diagnosis. Prediagnosis use was defined as one or more prescriptions within five years prior to the ovarian cancer diagnosis. Cumulative amount of non-aspirin NSAIDs was calculated as total amount of defined daily doses (DDDs) [32] filled after the ovarian cancer diagnosis. Intensity of use was defined as cumulative amount divided by the number of days between the first and the latest non-aspirin NSAID prescription after diagnosis. In a sensitivity analysis, duration of use was defined as the time between the first and last prescription in a fixed three-year exposure period after diagnosis. Further, we categorized postdiagnosis non-aspirin NSAID use as (1) COX-2–selective NSAIDs defined as selective COX-2 inhibitors and traditional non-aspirin NSAIDs with high COX-2 selectivity, and (2) non-selective NSAIDs comprising the remaining traditional NSAIDs (online Supplementary Methods). Finally, we evaluated the influence of timing of non-aspirin NSAID use, by developing a supplementary exposure matrix including both pre- and postdiagnosis non-aspirin NSAID use, *i.e.*, (1) no pre- or postdiagnosis use ('never use', reference category), (2) prediagnosis use only, (3) pre- and postdiagnosis use, and (4) postdiagnosis use only.

2.4. Statistical analysis

We used Cox proportional-hazard regression analyses to estimate hazard ratios (HRs) and two-sided 95% confidence intervals (CIs) for ovarian cancer and other-cause mortality. Minimally adjusted analyses included age at diagnosis, clinical stage, and year of diagnosis. Fully adjusted models additionally included tumor histology, chemotherapy, highest achieved education, disposable income, marital status, use of other drugs, and history of selected chronic diseases (characterized as in Table 1). Covariates were selected based on current knowledge of prognostic predictors for ovarian cancer and data available in the nationwide health and demographic registries. A description of covariates is provided in the online Supplementary Methods. The proportional hazards assumption was tested using scaled Schoenfeld residuals [33].

In the main analysis, postdiagnosis non-aspirin NSAID use was assessed as a time-varying covariate, allowing patients to become users throughout follow-up. We implemented a lag-time of one year after the first postdiagnosis prescription, to minimize the influence of changes in exposure as part of end-of-life clinical care [34] and to allow a reasonable induction period. Additionally, we evaluated associations according to timing, intensity and cumulative amount of use, and we tested effect modification by stratification of results according to tumor histology, clinical stage, age at diagnosis, and year of diagnosis. Cumulative amount and intensity of use were updated at each prescription of non-aspirin NSAIDs during follow-up.

In secondary analyses with fixed exposure-periods, postdiagnosis non-aspirin NSAID use was assessed prior to the start of follow-up, and was considered invariable thereafter, mimicking a postdiagnosis 'intention-to-treat' analysis. Follow-up was started at one or three years, respectively, after the ovarian cancer diagnosis, the latter analysis being conditioned on survival until three years after diagnosis. We also evaluated associations according to cumulative amount used and duration of use in the three-year exposure period.

In *post hoc* analyses, we evaluated the influence of patterns of postdiagnosis non-aspirin NSAID use (*i.e.*, cumulative amount, intensity, and duration) separately in (1) patients with serous ovarian cancer, in (2) patients with well-defined non-serous ovarian cancer, in (3) prediagnosis users and non-users of non-aspirin NSAIDs, and (4) according to COX-2 selectivity of non-aspirin NSAIDs. Evaluations of exposure patterns were not performed separately for patients with endometrioid, mucinous or clear cell histology because of low patient numbers.

Finally, we evaluated the influence of competing risks as a result of death from other causes using the sub-distribution hazards model proposed by Fine and Gray adapted for time-dependent covariates [35].

All analyses were performed using R statistical software version 3.2.3 using the survival package [36, 37]. STROBE guidelines were used to outline the manuscript [38].

Please cite this article as: F. Verdoodt, et al., Non-aspirin NSAID use and ovarian cancer mortality, Gynecol Oncol (2018), https://doi.org/10.1016/j.ygyno.2018.06.018