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Review Article

Non-steroidal anti-inflammatory drug use and risk of endometrial cancer: A systematic review and meta-analysis of observational studies

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HIGHLIGHTS

- Regular aspirin or NA-NSAID use was associated with a reduced risk of endometrial cancer.
- The reduction in endometrial cancer risk was consistent, albeit small.
- The reduction in endometrial cancer risk increased with frequency of NSAID use.

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ABSTRACT

Objective. Non-steroidal anti-inflammatory drug (NSAID) use has been linked to a reduction in the risk of several cancer types. For endometrial cancer, however, results have been inconsistent. To summarize the available evidence on the risk of endometrial cancer associated with use of aspirin or non-aspirin (NA-) NSAIDs, we performed a systematic review and meta-analysis of observational studies.

Methods. We conducted a bibliographic database search in PubMed, Embase and Cochrane Library. Relative risk estimates were extracted from eligible case–control and cohort studies and pooled using a random effects model.

Results. Six case–control and seven cohort studies were found eligible for our meta-analysis. We observed risk reductions in endometrial cancer associated with regular use of aspirin (case–control: 11%, cohort: 8%) and NA-NSAIDs (case–control: 9%, cohort: 6%), compared to non-use. However, the pooled risk ratios were not statistically significant. Higher risk reductions were seen with high frequency of notably aspirin use (case–control: 37%, cohort: 20%). The inverse association between regular aspirin use and endometrial cancer risk was strongest among women with a body mass index above 30 (case–control: 44%, cohort: 20%).

Conclusions. Regular use of aspirin or NA-NSAIDs was associated with a marginally reduced risk of endometrial cancer. Larger risk reductions were linked with high frequency of NSAID use and high BMI.

Contents

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1. Introduction

Effective chemopreventive measures against endometrial cancer could have an important impact on public health, given that endometrial cancer is the most common cancer of the female genital tract [1] and overall the fourth most common cancer in developed regions [2]. The high frequency of precursors of endometrial cancer requiring hysterectomy further contributes to the morbidity of the disease.

Aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) have received broad attention due to their potential anti-carcinogenic properties [3–5]. Although the precise anti-neoplastic mechanisms remain unclear, the anti-inflammatory effects of NSAIDs are likely involved. Various inflammatory processes have been shown to facilitate carcinogenesis and chronic inflammation is an established risk factor of several cancer types [6–8]. All NSAIDs are inhibitors of cyclooxygenase (COX), a group of enzymes involved in physiological and pathophysiological processes, including inflammation and platelet aggregation [9].

Current evidence of a chemopreventive effect of aspirin use is strongest for colorectal cancer [5,10–15], but consistent inverse associations with aspirin use have also been reported for upper gastrointestinal cancers, and cancers of the lung, breast, and prostate [5,12,13]. Overall, cancer sites with predominance of adenocarcinomas seem to be most susceptible to chemopreventive effects of aspirin and/or NA-NSAID use [16–18]. Hence, attention has been placed on the influence of NSAID use on risk of endometrial cancer, for which adenocarcinoma is the predominant type. Laboratory and pathological studies suggest that COX-enzymes are involved in endometrial carcinogenesis [19–22], and that the pathological processes can be inhibited by NSAIDs [23,24]. The biological plausibility of an anti-neoplastic effect of NSAIDs against endometrial cancer is further supported by interactions between NSAIDs and well-established risk factors of endometrial cancer, such as excess estrogen exposure [25,26], obesity [27,28], and inflammation [29,30].

A number of observational epidemiological studies have examined the association between overall use of NSAIDs, or of aspirin separately, and endometrial cancer risk. Three previous reviews have summarized the observational studies and provided pooled risk estimates [12,13,31]. However, only results for aspirin were presented in the reviews, and very limited attention was given to potential effect modification by other factors that may be of importance for the development of endometrial cancer. This prompted us to perform a systematic review and meta-analysis of NSAID use and the risk of endometrial cancer, evaluating the effect of both aspirin and NA-NSAIDs. In addition, we performed detailed analyses of potential effect measure modification according to study design, definition of use, and risk factors for endometrial cancer.

2. Materials and methods

2.1. Literature search and study selection

We performed a systematic literature search using the electronic bibliographic databases PubMed, Embase, and Cochrane Library (last search: October 12th, 2015). For each database, a search string was constructed, combining various text words and indexed terms on three topics: non-steroidal anti-inflammatory drugs, endometrium, and cancer. We applied no restrictions according to language or publication date in order to allow evaluation of all published studies. Additionally, we performed a manual search for relevant papers in reference lists of key papers.

Studies were eligible for inclusion if they fulfilled the following predefined criteria: (1) observational study (*e.g.* case–control or cohort), (2) evaluation of the association between use of aspirin and/or NA-NSAIDs and risk of endometrial cancer, (3) estimates of association were presented as relative risk measures (RR), *i.e.* incidence rate ratio (IRR), hazard ratio (HR), or odds ratio (OR), with associated confidence intervals (CIs). Studies based on individuals with predisposition for endometrial cancer were excluded. A 'preferred reporting items for systematic reviews and meta-analyses' (PRISMA) flow diagram was constructed to demonstrate the process of study evaluation [32].

2.2. Data extraction and statistical analysis

For each study, risk estimates and corresponding confidence intervals were extracted. When several estimates were presented, those adjusted for most covariates were chosen. Additionally, we extracted data on the study design (case–control or cohort), setting (population- or hospital-based), study population (selection, size, response-rate, matching variables in case–control studies), exposure (definition, characterization, ascertainment), outcome (definition, ascertainment), and measures that were performed to account for confounding and biases. The data extraction was performed by the first author (F.V.) and reviewed by two co-authors (V.A. and S.F). In the absence of a broadly accepted standardized tool to assess the quality of observational studies, and to avoid subjective weighing of the studies, no summary scores were assigned to individual studies [33,34]. Instead, the quality of included studies was evaluated and discussed using a set of signaling-questions based on the Newcastle–Ottawa Quality Assessment Scale for observational studies [35]. The quality of each included study was discussed at plenary meetings involving all five authors.

In a baseline analysis, regular use of aspirin or NA-NSAIDs was compared to non-use. Subsequently, four sensitivity analyses were performed, restricted to specific subgroups of users. These subgroups were defined according to maximal overall use, highest frequency of use, longest duration of use, and high body-mass index (BMI, ≥30), respectively. Additionally, for case–control studies, we performed a stratified analysis on study setting (population- or hospital-based). The reference in all analyses was non-use of aspirin or NA-NSAIDs, respectively.

Pooled RR (cohort studies) and OR (case–control studies) with corresponding 95% CI were calculated using METAN, a procedure in Stata. A random effects model was used to account for the variation between studies [36]. The statistical heterogeneity was assessed using the I^2 statistic, which estimates the proportion of variability between studies that is due to inter-study heterogeneity rather than chance [37].

Smaller studies are more prone to publication bias, whereas larger studies are more likely to be published even if results are insignificant, due to the more extensive investment of resources and time. This may lead to a 'small-study effect' where smaller studies in a meta-analysis show a larger treatment effect [38]. In the present meta-analysis, we evaluated publication bias by funnel plots of risk estimate against its standard error (Metafunnel, Stata). Quantitative assessment of publication bias was performed by a linear regression test for funnel plot asymmetry, using Egger's test [39]. Statistical significance was defined as p-values less than 5%. All analyses were performed using Stata 11 (StataCorp., College Station, TX, USA).