Gynecologic Oncology 142 (2016) 368–377

Contents lists available at ScienceDirect

Gynecologic Oncology

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

Review Article

Is aspirin use associated with a decreased risk of ovarian cancer? A systematic review and meta-analysis of observational studies with dose-response analysis

Dongyu Zhang [a,*], Bei Bai [b], Yuzhi Xi [a], Tengteng Wang [a], Yuqian Zhao [c]

[a] Department of Epidemiology, University of North Carolina at Chapel Hill Gillings School of Global Public Health, Chapel Hill, NC, USA
[b] Department of Science & Technology, West China Hospital, Sichuan University, Chengdu, Sichuan, China
[c] Cancer Hospital, Chinese Academy of Medical Sciences (CAMS) & Peking Union Medical College (PUMC), Beijing, China

HIGHLIGHTS

- We performed a systematic review and meta-analysis of 23 observational studies.
- We observed a moderate chemopreventive effect of aspirin usage to ovarian cancer.
- An inverse dose-response relationship was observed between aspirin and ovarian cancer.

ARTICLE INFO

Article history:
Received 14 March 2016
Received in revised form 28 April 2016
Accepted 30 April 2016
Available online 15 May 2016

Keywords:
Ovarian cancer
Aspirin
Chemoprevention
Systematic review and meta-analysis

ABSTRACT

Objective. Currently available epidemiologic evidences concerning the chemopreventive effect of aspirin on ovarian cancer are inconsistent. Therefore, we aimed to further explore the association by synthesizing evidence from population-based studies.

Methods. We searched PubMed, EMBASE, Web of Science, and Scopus using key words and controlled vocabularies. Title/abstract screening, full-text review, data extraction, and quality assessment were performed independently by reviewers, and a random-effects model was utilized for meta-analysis. Subgroup analysis was conducted based on study locale, and sensitivity analysis was performed by synthesizing studies that adjusted for certain covariates or studies with good quality. Dose-response relation was assessed by a two-stage linear dose-response model. Statistical heterogeneity was evaluated by the I-squared value and a chi-squared test for the Cochrane Q statistic.

Results. We identified 8 cohort studies and 15 case-control studies. In overall meta-analysis of risk ratios (RRs) of binary exposure, the synthesized RR was 0.89 (95% CI, 0.83–0.96), and no substantial statistical heterogeneity was observed ($I^2 = 22.5\%$, $P_{Cochrane} = 0.168$). After stratification by study design, the synthesized RR was 0.85 (95% CI, 0.77–0.94) and 0.95 (95% CI, 0.85–1.05) for case-control and cohort studies, respectively. In sensitivity analysis, the synthesized estimate of long-term use was not statistically significant, whereas the effect measure ($RR_{meta} = 0.60$, 95% CI, 0.39–0.93) was significant by synthesizing RRs of the highest frequency of use from 2 cohort studies. The dose-response analysis showed an inverse significant association between aspirin use and the risk ($RR_{per\ 1\ time/wk} = 0.94$, 95% CI, 0.89–1.00; n = 2). Egger's tests showed that publication bias existed for overall meta-analysis, meta-analysis for case-control studies, and studies conducted in the United States.

Conclusion. In summary, our study suggests that aspirin can reduce the risk of ovarian cancer. In addition, we observed a possible dose-response relation between frequency of use and ovarian cancer risk, but further studies are needed to examine this association.

* Corresponding author at: Department of Epidemiology, University of North Carolina at Chapel Hill Gillings School of Global Public Health, 170 Rosenau Hall, CB #7400, 135 Dauer Drive, Chapel Hill, NC 27599-7400, USA.
E-mail address: dzhang34@live.unc.edu (D. Zhang).

http://dx.doi.org/10.1016/j.ygyno.2016.04.543
0090-8258/

Contents

1. Introduction

Ovarian cancer is the sixth most common malignant tumor among women worldwide [1]. Annually, approximately 200,000 new cases are diagnosed globally [2], and over 100,000 patients will die of ovarian cancer [3]. The Surveillance, Epidemiology, and End Results (SEER) Program shows that, in the United States, about 80% of new ovarian cancer cases have the characteristic of regional or distant metastasis at the time of diagnosis. This leads to an unfavorable 5-year survival rate which can be lower than 50% [4]. In addition, it has been estimated that the total cost of ovarian cancer treatment and care will be $5.3 billion in the United States at 2020 [5], which is a substantial burden to the health system. Therefore, to reduce the incidence of ovarian cancer and burden of the disease, an effective and inexpensive primary preventive medication should be either developed or identified for women at risk.

It has been demonstrated that chronic inflammatory conditions (e.g., pelvic inflammatory disease) can increase the risk of ovarian cancer [6–8]; therefore, in theory, anti-inflammatory medications can lower the ovarian cancer risk. Among all kinds of nonsteroidal anti-inflammatory drugs (NSAIDs), aspirin is the most commonly used one, which can inhibit the activity of cyclooxygenase (COX). COX is a major pro-inflammatory factor that is responsible for the synthesis of prostaglandin (PG), and the latter is positively associated with epithelial carcinogenesis [9]. Therefore, aspirin may have the potential to reduce the risk of ovarian cancer.

Previous epidemiologic research found that long-term utilization of aspirin is associated with a reduced risk of colorectal cancer [10,11], esophageal cancer [12], and breast cancer [13]. However, current evidences derived from population-based research regarding the relation between aspirin utilization and the risk of ovarian cancer are inconsistent [14–17], which makes the association unclear.

Thus, to provide a conclusive evidence concerning the chemopreventive effect of aspirin on ovarian cancer, we searched for relevant observational epidemiologic studies and synthesized them qualitatively and quantitatively.

2. Methods

2.1. Search strategy

A systematic literature search was conducted on Nov 29th 2015. Four electronic databases were utilized for the search, and they were: PubMed, EMBASE, Web of Science, and Scopus. Controlled vocabularies and key words that were related to “ovarian cancer”, “aspirin”, and “neoplasm” were used in the search strategy (Supplementary A). In addition, we hand-searched the reference lists of previous systematic reviews of related topics in order to obtain more potentially eligible articles.

2.2. Study identification

We followed the instruction of *Meta-analysis of Observational studies in Epidemiology* (*MOOSE*) to identify and select eligible articles [18]. The identification process was constituted of two steps which were title/abstract screening and full-text review. Studies that met the following criteria were selected in the title/abstract screening: (1) observational epidemiology study (cross-sectional, cohort, case-control, nested case-control, and case-cohort study); (2) the exposure of interest was aspirin use; (3) the outcome of interest was the risk of ovarian cancer; and (4) written in English. The full-text review was performed for studies selected in title/abstract screening process. In full-text review, studies controlling for aspirin use in multivariable models without numerically reporting the measures of association were excluded; moreover, abstracts and incomplete studies were excluded in full-text review as well. Title/abstract screening and full-text review were conducted independently within reviewer pair (pair 1: D.Z. and B.B.; pair 2: Y.X. and T.W.), and all discrepancies were solved by discussion or consulting senior researchers. The details of study inclusion and exclusion are presented in a flow chart (Fig. 1) as per the guideline of *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* (*PRISMA*) [19].

2.3. Data extraction and quality assessment

Reviewers read the articles carefully and extracted relevant information of the study. Key characteristics (e.g., study design, locale, measurement, definition of user, and adjusted confounders) were recorded from each study. The studies were evaluated in aspect of methodological strengths and limitations. We referred to *The Newcastle-Ottawa Scale* (*NOS*) *for assessing the quality of nonrandomized studies in meta-analyses* [20] to evaluate the study quality and the risk of bias (e.g., representativeness, selection bias, measurement error, and statistical rationality). Odds ratios (ORs) were treated as proximate measures of risk ratios (RRs) because of the low prevalence of ovarian cancer among the population. Effect measures were calculated based on raw data in original study if an adjusted effect measure was not reported. In addition, effect measures that could not be calculated by this method were treated as missing; we did not utilize any other method to obtain the missing data. Data extraction and quality assessment were also conducted in an independent manner, and discrepancies were resolved by discussion.

2.4. Data synthesis

Before quantitative synthesis, a descriptive summary of study characteristics was performed qualitatively. In the following quantitative synthesis, RRs of binary exposure (aspirin user vs. non-user) were