Impact of analgesics on the risk of ovarian cancer: a systematic review and meta-analysis of cohort and case-control studies

Javad Sadeghi1, Saba Bazzazi2, Farinaz Fattahi3, Moloud Alsadat Mousavi4, Ardeshir Tajbakhsh5, Sadaf Rassouli5, Siavash Sangi6, Mahshad Ghezelbash7, Anna Ghorbani8

1Pain Clinic Manager, Be’sat Hospital, Faculty of Medicine, Aja University of Medical Sciences, Tehran, Iran
2Department of Gynecology and Obstetrics, Imam Hossein Hospital, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran
3Department of Emergency Medicine, School of Medicine, Milad Hospital, Isfahan University of Medical Sciences, Isfahan, Iran
4Anesthesia Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran
5Department of Gynecology and Obstetrics, Imam Khomeini Hospital, School of Medicine, Sari University of Medical Sciences, Sari, Iran
6Anesthesia Education Student, Department of Anesthesia Technology, School of Allied Medical Sciences, Iran University of Medical Sciences, Tehran, Iran
7Department of Anesthesiology, School of Medicine, Iran University of Medical Sciences, Tehran, Iran
8Department of Hematology-Medical Oncology, Shahid Beheshti University of Medical Sciences, Tehran, Iran

*Correspondence to Anna Ghorbani, Email: annaghorbani1367@gmail.com

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Abstract

Introduction: Ovarian cancer is the sixth leading cancer-related mortality cause in women worldwide. Analgesics may hinder the occurrence of ovarian cancer through inflammation relief. The present study seeks to examine the relationship between analgesic consumption and ovarian cancer risk through a systematic review and meta-analysis.

Materials and Methods: PubMed, Scopus, Web of Science, Cochrane databases, and Google Scholar search engines were searched for works published by May 2023 using standard keywords to collect the required data sources. Acquired data were then analyzed in STATA version 14, considering a significance level of P < 0.05 in statistical tests.

Results: The present meta-analysis comprised 21 studies (14 case-control and 7 cohort studies) performed on 53,755 subjects. Results indicated that taking aspirin reduced the risk of ovarian cancer by 8% (OR: 0.92; 95% CI: 0.87, 0.98), whereas other non-aspirin NSAIDs (non-steroidal anti-inflammatory drugs) did not significantly affect the ovarian cancer risk (OR: 0.91; 95% CI: 0.81, 1.02). Similar results were observed in the case of ibuprofen and acetaminophen, with non-significant relationships between the risk of ovarian cancer and with the consumption of both acetaminophen (OR: 0.95; 95% CI: 0.84, 1.08) and ibuprofen (OR: 0.76; 95% CI: 0.50, 1.14). Furthermore, the duration of analgesic consumption was not significantly linked to the risk of ovarian cancer in the case of all studied drugs.

Conclusion: Among aspirin, ibuprofen, acetaminophen, and non-aspirin NSAIDs, only aspirin was found to reduce the risk of ovarian cancer in women while the other studied drugs did not influence the studied risk. However, further research is recommended to confirm the results.

Registration: This study has been compiled based on the PRISMA checklist, and its protocol was registered on the PROSPERO (CRD42023434730) and Research Registry (UIN: reviewregistry1668) websites.

Introduction

Ovarian cancer is the sixth leading cancer-related mortality cause in women worldwide (1), and inflammation contributes significantly to ovarian cancer development (2,3). Local inflammation concurrent with ovulation may contribute to ovarian tumor genesis (4). The factors associated with epithelial disruption are thus known to be associated with ovarian cancer risk through ovulation (4,5), inflammation-associated exposures such as endometriosis, and pelvic inflammatory disease (6,7).

Analgesics such as aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) are associated with the reduced risk of several malignancies due to their anti-inflammatory properties (8,9). Acetaminophen is another conventional analgesic with a weak anti-inflammatory activity, but it may still reduce the risk of cancer through its anti-gonadotropic effects that may be specifically relevant to ovarian cancer (10).

The relationship between analgesics and the risk of ovarian cancer has long been investigated by researchers, yielding...
contradictory results. For instance, the results of 12 population-based case-control studies indicated that aspirin and non-aspirin NSAIDs might reduce the risk of ovarian cancer (11), while several other studies concluded that taking non-aspirin NSAIDs was a risk factor in ovarian cancer (12,13).

Another study argued that the regular consumption of aspirin reduced the risk of ovarian cancer by 13% regardless of other ovarian cancer risk factors (14). Still, some researchers believed that taking aspirin did not influence the risk of ovarian cancer (10,15). On the other hand, several studies suggested that ovarian cancer was prevented by consuming acetaminophen (10,16), whereas other studies rejected this hypothesis, arguing that acetaminophen did not affect ovarian cancer risk (15,17). Given the contradictory results in the literature, the question of whether or not analgesics reduce the risk of ovarian cancer remains an unsolved challenge. The present study thus performs a systematic review through a meta-analysis to investigate the relationship between taking analgesics (acetaminophen, aspirin, ibuprofen, and non-aspirin NSAIDs) and the risk of ovarian cancer development.

**Materials and Methods**

**Research protocol**

The study utilized PRISMA principles and followed registered protocols on the PROSPERO (CRD42023434730) and Research Registry (UIN: reviewregistry1668) website to investigate the impact of analgesics on ovarian cancer risk in women through a systematic review and meta-analysis.

**Statistical population**

The target population of the present study comprised women, who were subjected to no limitation applied in terms of race, age, and type of analgesics.

**Search strategy**

The present study explored PubMed, Scopus, Web of Science, and Cochrane databases as well as the Google Scholar search engine with no time limit using the standard mesh keywords, including “analgesics, analgesics, ovarian neoplasm, ovarian cancer, anti-inflammatory agents, non-steroidal, NSAIDs, and aspirin-like agent”. Various combinations of the keywords were searched using “And/Or” operators through advanced search in the mentioned databases (the search was updated until May 2023). For a manual search, the lists of references of all initially included studies were searched at the end of the PRISMA flowchart. The following indicates an example of the search strategy in the PubMed database: (Ovarian Neoplasm[Title/Abstract] OR Ovarian Cancer[Title/Abstract]) AND (Analgesics[Title/Abstract] OR Analgesic[Title/Abstract] OR Anti-Inflammatory Agents, Non-Steroidal[Title/Abstract] OR NSAID[Title/Abstract] OR Aspirin Like Agent[Title/Abstract])

**Key point**

In a review of the literature, we found that taking aspirin reduced the risk of ovarian cancer by 8%, whereas other non-aspirin non-steroidal anti-inflammatory drugs did not significantly affect the ovarian cancer risk.

**PICO elements**

The PICO elements of the study are as follows: Population – women; Intervention – analgesics consumption; Comparison – women not taking analgesics; and Outcomes – the impact of analgesics on the risk of ovarian cancer.

**Inclusion criteria**

Case-control and cohort studies on the influence of acetaminophen, aspirin, ibuprofen, and non-aspirin NSAIDs on the risk of ovarian cancer were included in this review study.

**Exclusion criteria**

Replicated and qualitative studies, case reports, low-quality studies, studies with incomplete data, conference articles, letters to the editor, studies examining the impact of combining several drugs, studies with unavailable full text, and studies using SMD and WMD indices to report results were excluded from the present work.

**Qualitative assessment**

Two of the authors evaluated independently the quality of the retrieved studies using the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) checklist (19), which contains 22 questions the score of which is a number between zero and 44. Studies scoring lower than 16 were considered low-quality and thus excluded from the review, while those scoring over 16 were considered of high quality and included in the next stage of the analysis.

**Data extraction**

Two researchers extracted data from the studies independently. The checklist designed by the researchers to extract data included the items of author's name, publication year, research design, location, the number of women, patients’ mean age, the type of disease, the type of drugs, research duration, and the odds ratio (OR) between analgesic consumption and the risk of ovarian cancer and its upper and lower limits.

**Statistical analysis**

The OR index was used to investigate the relationship between analgesics and ovarian cancer. The results of reviewed studies were consolidated using the OR logarithm reported by each study. The heterogeneity of the studies

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was assessed using the $I^2$ index. Fixed effects and random effects models were used for low and high heterogeneity, respectively. Acquired data were then analyzed in STATA v.14 considering a significance level of $P < 0.05$ in statistical tests.

Results
Study selection
Of 598 studies eventually retrieved from the examined databases, 212 studies with replicated titles were eliminated from the review. Among the reviewed abstracts of the remaining 386 articles, 13 cases were excluded from the study due to unavailable full texts. Out of the remaining 373 articles, 76 cases were excluded due to incomplete data, and 276 studies were eliminated due to the other exclusion criteria. A total of 21 high-quality articles were eventually included in the meta-analysis (Figure 1).

Specifications of the reviewed articles
The present meta-analysis assessed 21 case studies (14 case-control and seven cohort studies) on 53,755 patients using analgesics (Table 1). Figure 2 reveals that 19 studies examining aspirin consumption reported the prevention of ovarian cancer in women using aspirin (OR: 0.92; 95% CI: 0.87, 0.98). However, the analysis results based on the duration of consumption indicated no significant difference in terms of ovarian cancer risk in women who consumed aspirin for less than 5 years (seven studies, Figure 3) (OR: 0.92; 95% CI: 0.84, 1.01). Besides, aspirin did not affect the risk of ovarian cancer in women who consumed it for over 5 years according to 11 studies (Figure 4) (OR: 0.97; 95% CI: 0.85, 1.11). The difference in the number of reviewed studies (Figures 2-4) can explain the reason for the overall ovarian cancer prevention by aspirin, however it left no significant impact on however based on the duration of consumption.

Figure 5 demonstrates that the consumption of non-aspirin NSAIDs left no overall statistically significant impact on the risk of ovarian cancer (OR: 0.91; 95% CI: 0.81, 1.02). Women who consumed non-aspirin NSAIDs for less than 5 years did not have a lower risk of ovarian cancer (OR: 0.87; 95% CI: 0.69, 1.09) (Figure 6). No statistically significant effect was observed in women who consumed non-aspirin NSAIDs for over 5 years (OR: 0.82; 95% CI: 0.61, 1.10) (Figure 7).

Taking acetaminophen left no overall impact on the

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**Figure 1.** The process of entering the studies into the systematic review and meta-analysis
<table>
<thead>
<tr>
<th>First author</th>
<th>Study design</th>
<th>Study location</th>
<th>Number of women in the analgesics group</th>
<th>Mean age in analgesics group (year)</th>
<th>Number of women in compare group</th>
<th>Mean age in compare group (year)</th>
<th>Case definition</th>
<th>Exposure</th>
<th>Study period</th>
<th>Score of STROBE checklist</th>
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<tbody>
<tr>
<td>Cramer (10)</td>
<td>Case-control</td>
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<td>563</td>
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<td>523</td>
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<td>Denmark</td>
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<td>1564</td>
<td>57.1</td>
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<td>Aspirin, Acetaminophen, Non-Aspirin NSAIDs</td>
<td>1995-1999</td>
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</tr>
<tr>
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<td>333</td>
<td>30-55</td>
<td>41699</td>
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<td>Aspirin, Acetaminophen, Non-Aspirin NSAIDs</td>
<td>1976 - 1996</td>
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<tr>
<td>Barnard (12)</td>
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<td>1054</td>
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<td>30-55</td>
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<td>Aspirin, Acetaminophen, Non-Aspirin NSAIDs</td>
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<td>NR</td>
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<td>20-79</td>
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<td>4623</td>
<td>NR</td>
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<td>1976–1998</td>
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<td>755315</td>
<td>NR</td>
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<td>NR</td>
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<td>1094</td>
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<td>50–89</td>
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<td>Acetaminophen, Non-Aspirin NSAIDs</td>
<td>1992-1997</td>
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<td>Number of women in compare group</td>
<td>Mean age in compare group (year)</td>
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<td>Exposure</td>
<td>Study period</td>
<td>Score of STROBE checklist</td>
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<td>1802</td>
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<td>1993-2008</td>
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ovarian cancer risk (OR: 0.95; 95% CI: 0.84, 1.08) (Figure 8). The risk of ovarian cancer in women who consumed acetaminophen for less and more than 5 years was as (OR: 0.97; 95% CI: 0.83, 1.13) and (OR: 1.05; 95% CI: 0.89, 1.24), respectively, none of which were significant statistically (Figures 9 and 10).

Similarly, the ovarian cancer risk was not influenced by taking ibuprofen (OR: 0.76; 95% CI: 0.50, 1.14) (Figure 11).

**Discussion**

The results of the present meta-analysis indicated that 19 out of the 21 reviewed studies examined the effect of aspirin on ovarian cancer risk, revealing that aspirin consumption played a protective role for women against ovarian cancer. However, no statistically significant relationship was observed between the risk of ovarian cancer and the consumption of non-aspirin NSAIDs, acetaminophen, and ibuprofen. Similar studies were published in the past; however, the present work has overviewed such studies more recently, presenting more up-to-date results. Our study classified the results based on the duration of drug administration and the type of analgesic to minimize heterogeneity and draw conclusions on each drug separately. However, challenges such as different doses and the frequency of consumed doses are among the issues that may have led to heterogeneity and less accurate results. Additionally, the age group of patients and the study type varied across the studied works, which...
Risk of ovarian cancer

...may have somehow impacted the results of the present meta-analysis.

Moreover, most studied works examined the impact of analgesics on ovarian cancer in terms of drugs taken for less and more than 5 years, but no significant relationship was found between the consumption of analgesics and the occurrence of ovarian cancer in this meta-analysis.

Baandrup et al performed a meta-analysis to investigate the relationship between NSAIDs and the risk of ovarian cancer. They suggested that the relationship between ovarian cancer and aspirin (RR: 0.93; 95% CI: 0.84–1.02) and non-aspirin NSAIDs (RR: 0.94; 95% CI: 0.84–1.06) was statistically non-significant (35). In a meta-analysis by Bonovas et al examining ten studies on the relationship between NSAIDs including aspirin, no association was found between aspirin consumption and the risk of ovarian cancer (RR: 0.92; 95% CI: 0.80, 1.06). No evidence was also found on the relationship between non-aspirin NSAIDs and ovarian cancer (RR: 0.86; 95% CI: 0.68, 1.08) (36). Results of a meta-analysis by Ni et al also indicated no relationship between ovarian cancer and the consumption of aspirin (RR: 0.91; 95% CI: 0.82, 1.01) or non-aspirin NSAIDs (RR: 0.86; 95% CI: 0.74, 1.08) (37). All three studies concluded that NSAIDs left no significant impact on ovarian cancer risks and were inconsistent with the present study in terms of the impact of aspirin while they disagreed with our results regarding the effect of NSAIDs.

A meta-analysis performed by Trabert et al on case-control studies examined the relationship between aspirin, non-aspirin NSAIDs, and acetaminophen consumption and the risk of invasive epithelial ovarian cancer, suggesting an association between the consumption of aspirin and reduced ovarian cancer risk (OR: 0.91; 95% CI: 0.84 to 0.99). However, the risk of ovarian cancer was not significantly related to using NSAIDs or acetaminophen (11), which is in full agreement with our results. In contrast, the meta-analysis conducted by Bonovas et al suggested that the “regular use” of acetaminophen was associated with a 30% significant decline in ovarian cancer risk (RR: 0.70; 95% CI: 0.51, 0.95) (38). Such a contradicting result accentuates the need for further meta-analyses. The contradiction may also stem from the fact the present work reviewed the impact of four different analgesics including aspirin, acetaminophen, ibuprofen, and non-aspirin NSAID.

Conclusion

Aspirin consumption reduced the risk of ovarian cancer slightly, which is a promising result for women, especially those prone to ovarian cancer. However, medications such as acetaminophen, ibuprofen, and non-aspirin NSAIDs were found to not affect the reduction of ovarian cancer risk. The heterogeneities mentioned in research limitations may have impacted our final results. Further research is thus imperative to explore the relationship between analgesics and ovarian cancer in women.

Limitations of the study

Most of the reviewed articles did not report the dose and frequency of doses. Most studies were performed in the USA, while some countries presented no studies. The analysis could be performed based on the type of the studies given the diversity of the studied drugs and their classification based on the duration of consumption. No
analysis could be performed on the age of the women as some studies did not disclose the age of the patients, and others reported multi-decade age periods. The role of age in ovarian cancer thus remained unexplored.

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Authors’ contribution
Conceptualization: Javad Sadeghi and Farinaz Fattahi.
Data curation: Siavash Sangi and Mahshad Ghezelbash.
Formal analysis: Moloud Alsadat Mousavi and Ardesher Tajbakhsh.
Investigation: Anna Ghorbani and Javad Sadeghi.
Methodology: Saba Bazzazi.
Project management: Anna Ghorbani.
Resources: Sadaf Rassouli and Saba Bazzazi.
Supervision: Javad Sadeghi.
Validation: Moloud Alsadat Mousavi.
Visualization: Mahshad Ghezelbash.
Writing—original draft: Saba Bazzazi, Farinaz Fattahi, Anna Ghorbani, and Mahshad Ghezelbash.
Writing—reviewing and editing: Javad Sadeghi, Moloud Alsadat Mousavi, Siavash Sangi, Sadaf Rassouli, and Ardesher Tajbakhsh.

Conflicts of interest
There are no competing interests.

Ethical issues
This study has been compiled based on the PRISMA checklist, and its protocol was registered on the PROSPERO (International Prospective Register of Systematic Reviews) website with ID: CRD42023434730 and Research Registry website (UIN: reviewregistry1668). Besides, ethical issues (including plagiarism, data fabrication, and double publication) have been completely observed by the author.

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References


