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

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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 version14, 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.

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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

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.

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 "anodynes, 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 (Anodynes[Title/Abstract] OR Analgesic[Title/Abstract] OR Anti-Inflammatory Agents, Non-Steroidal[Title/Abstract] OR NSAID[Title/Abstract] OR Aspirin Like Agent[Title/Abstract])

PICO elements

The PICO elements of the study are as follows: Population – women; Intervention – analgesic 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

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

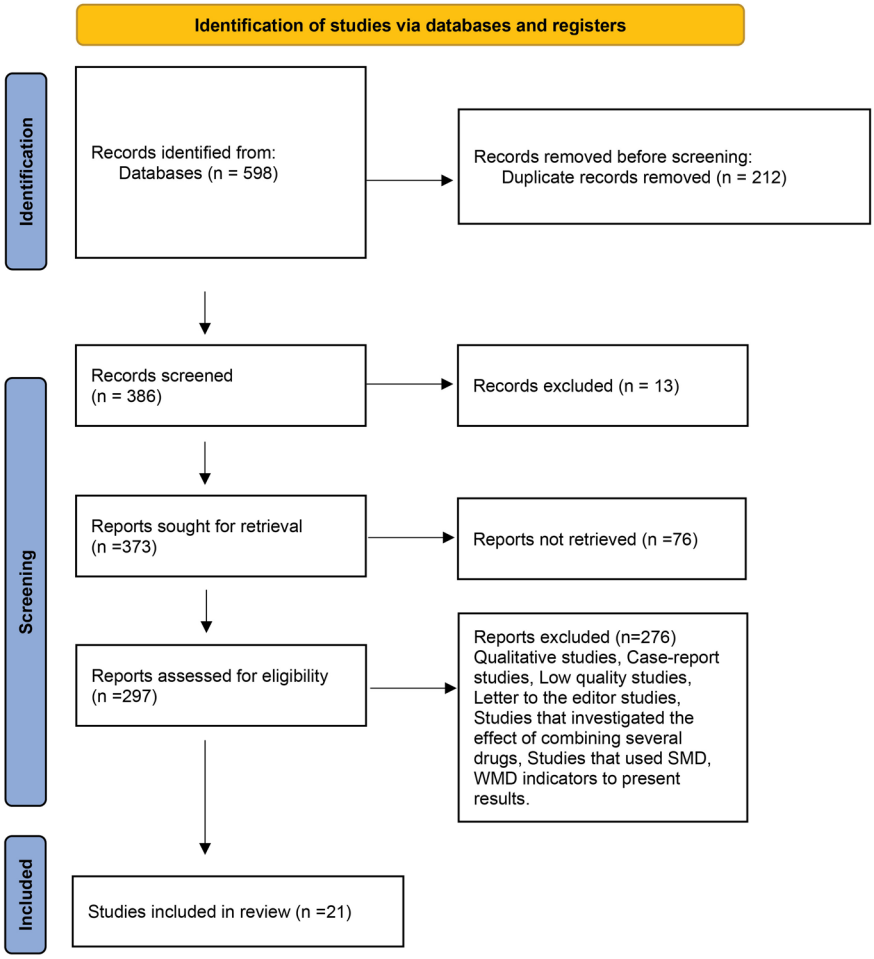

Figure 1. The process of entering the studies into the systematic review and meta-analysis.

Table 1. Studies included in the meta-analysis

First author	Study design	Study location	Number of women in the analgesics group	Mean age in analgesics group (year)	Number of women in compare group	Mean age in compare group (year)	Case definition	Exposure	Study period	Score of STROBE checklist
Cramer (10)	Case-control	USA	563	NR	523	NR	Epithelial ovarian cancer	Aspirin, Acetaminophen, Ibuprofen	1992-1997	27
Ammundsen (20)	Case-control	Denmark	756	57.8	1564	57.1	Epithelial ovarian cancer	Aspirin, Acetaminophen, Non-Aspirin NSAIDs	1995–1999	39
Fairfield (21)	Case-control	USA	333	30-55	41699	30-55	Epithelial ovarian cancer	Aspirin, Acetaminophen, Non-Aspirin NSAIDs	1976 - 1996	29
Barnard (12)	Cohort	USA	1054	30-55	205498	30-55	Epithelial ovarian cancer	Aspirin, Acetaminophen, Non-Aspirin NSAIDs	1980-2015	33
Peres (22)	Case-control	USA	541	NR	731	20-79	Epithelial ovarian cancer	Aspirin, Acetaminophen, Non-Aspirin NSAIDs	After December 2010	28
Rosenberg (23)	Case-control	USA	780	NR	4623	NR	Epithelial ovarian cancer	Aspirin, Acetaminophen, Non-Aspirin NSAIDs	1976–1998	38
Trabert (24)	Cohort	North America and Europe	3514	NR	755315	NR	Epithelial ovarian cancer	Aspirin, Acetaminophen, Non-Aspirin NSAIDs	NR	35
Moysich (16)	Case-control	USA	547	54.7	1094	54.5	Epithelial ovarian cancer	Aspirin, Acetaminophen,	1982 and 1998	30
Lacey (25)	Cohort	USA	31364	61.3	235420	61.3	Ovarian cancer	Aspirin, Acetaminophen, Non-Aspirin NSAIDs	1973-1980	40
Hannibal (13)	Case-control	USA	812	35-74	1313	35-74	Epithelial ovarian cancer	Aspirin, Acetaminophen, Non-Aspirin NSAIDs	2002-2005	36
Meier (26)	Case-control	UK	483	50–89	1877	50–89	Ovarian cancer	Acetaminophen, Non-Aspirin NSAIDs	1992-1997	35

Table 1. Continued

First author	Study design	Study location	Number of women in the analgesics group	Mean age in analgesics group (year)	Number of women in compare group	Mean age in compare group (year)	Case definition	Exposure	Study period	Score of STROBE checklist
Lo-Ciganic (27)	Case-control	USA	902	58.29	1802	57.02	Epithelial ovarian cancer	Aspirin, Non-Aspirin NSAIDs	2003-2008	37
Sasamoto (28)	Case-control	USA	1187	51.05	1225	18	Epithelial ovarian cancer	Aspirin, Acetaminophen, ibuprofen	1998 - 2008	40
Schildkraut (29)	Case-control	USA	586	20-74	627	20-74	Epithelial ovarian cancer	Acetaminophen, Non-Aspirin NSAIDs	1999-2003	33
Baandrup (30)	Case-control	Denmark	4103	30-84	58706	30-84	Epithelial ovarian cancer	Aspirin	2000–2011	38
Hurwitz (31)	Case-control	US, UK, and Australia	4476	58	6659	57	Epithelial ovarian cancer	Aspirin	1995-2009	39
Hurwitz (32)	Cohort	USA	223	55-74	41410	55-74	Ovarian cancer	Aspirin	1993-2001 and followed for cancer outcomes through 2014	35
Wernli (33)	Case-control	USA	276	55	1483	54	Epithelial ovarian cancer	Aspirin, Non-Aspirin NSAIDs, Ibuprofen	1998 -2001	29
Pinheiro (17)	Cohort	USA	666	30-55	NR	NR	Epithelial ovarian cancer	Aspirin, Acetaminophen, Non-Aspirin NSAIDs	1976-2005	30
Prizment (34)	Cohort	USA	314	67.5	NR	NR	Epithelial ovarian cancer	Aspirin, Non-Aspirin NSAIDs	1992–2006	32
Setiawan (15)	Cohort	USA	275	58.3	31938	58.8	Epithelial ovarian cancer	Aspirin, Acetaminophen, Non-Aspirin NSAIDs	1993-2008	34

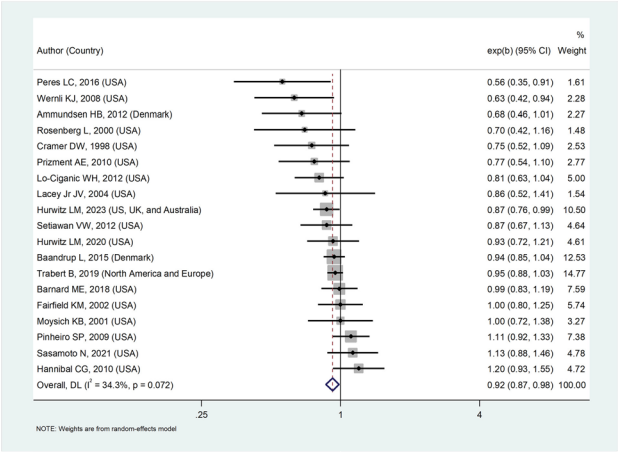

Figure 2. Forest plot showing the overall effect of aspirin consumption on the risk of ovarian cancer in women along with its 95% CI.

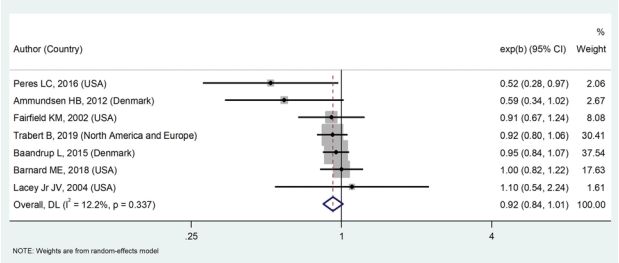

Figure 3. Forest plot showing the effect of aspirin use for less than 5 years on the risk of ovarian cancer in women along with its 95% CI.

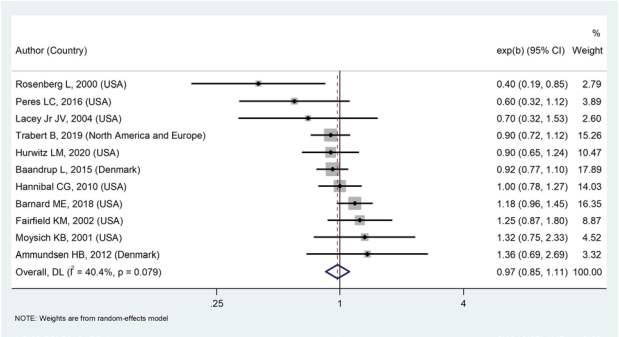

Figure 4. Forest plot showing the effect of aspirin use for more than 5 years on the risk of ovarian cancer in women along with its 95% CI.

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

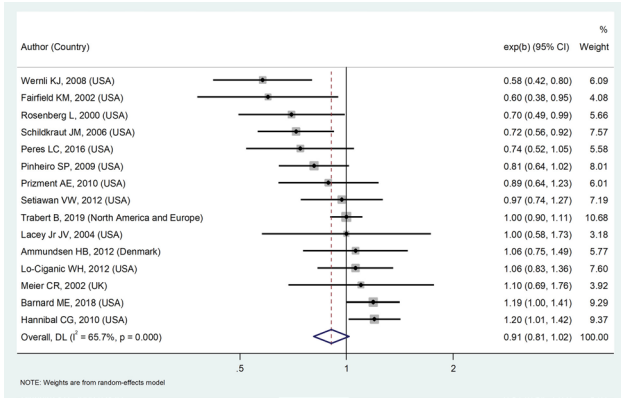

Figure 5. Forest plot showing the effect of non-aspirin NSAID use for less than 5 years on the risk of ovarian cancer in women along with its 95% CI.

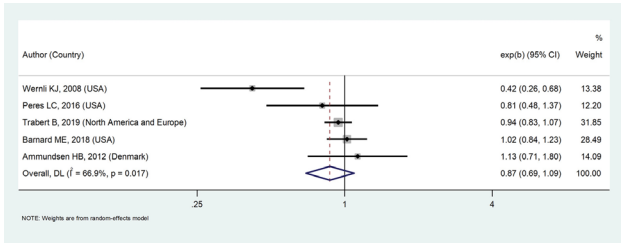

Figure 5. Forest plot showing the effect of non-aspirin NSAID use for less than 5 years on the risk of ovarian cancer in women along with its 95% CI.

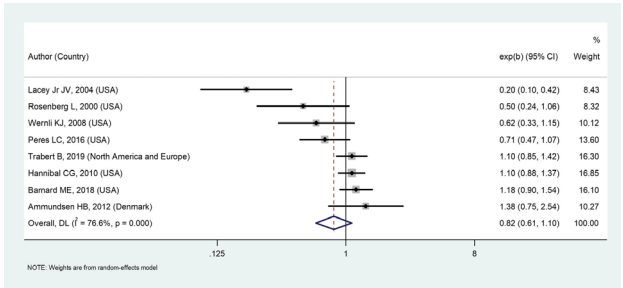

Figure 7. Forest plot showing the effect of non-aspirin NSAID use for more than 5 years on the risk of ovarian cancer in women along with its 95% CI.

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

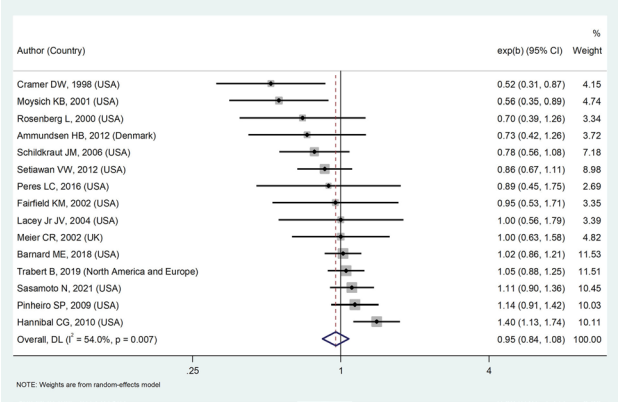

Figure 8. Forest plot showing the overall effect of acetaminophen consumption on the risk of ovarian cancer in women along with its 95% CI.

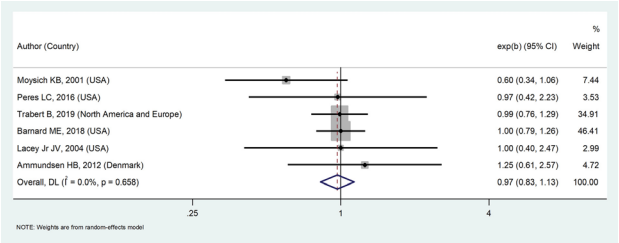

Figure 9. Forest plot showing the effect of acetaminophen use for less than 5 years on the risk of ovarian cancer in women along with its 95% CI.

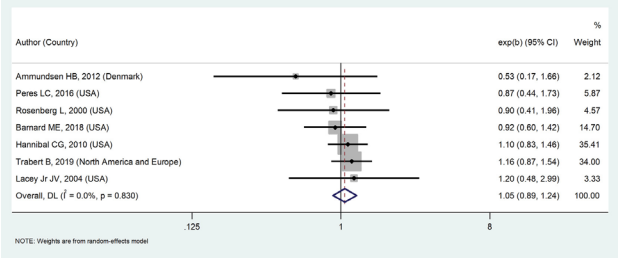

Figure 10. Forest plot showing the effect of acetaminophen use for more than 5 years on the risk of ovarian cancer in women along with its 95% CI.

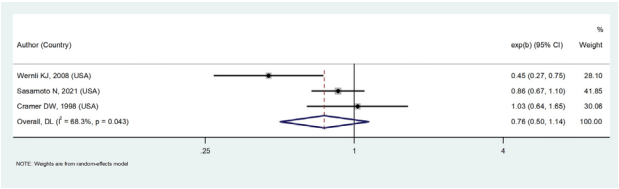

Figure 11. Forest plot showing the overall effect of ibuprofen consumption on the risk of ovarian cancer in women along with its 95% CI.

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: 0.89; 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 Ardeshir 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 Ardeshir 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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