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Review

# Ovarian microbiota and ovarian cancer: An overview and update meta-analysis

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**Abstract.** *Background and aim:* Ovarian cancer (OC) remains the most lethal gynecological malignancy, although advancements in treatment strategies. Emerging data suggested the potential role of ovarian microbiota in ovarian cancer pathogenesis. The objective of this review and meta-analysis is to analyze available literature to investigate this correlation. *Methods:* According to the recommendations in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement, the Pubmed database and the Embase database were searched in February 2024. No limitation of the countries was considered. *Results:* Twenty-seven studies met the inclusion criteria. Five thousand and fourteen ovarian carcinoma cases were included of which 1659 (33.1%) showed dysbiosis. The fixed-effect model and the random-effect model showed no significant correlation between ovarian cancer patients and dysbiosis ($p<0.001$ and $p<0.001$ with 95% Confidence Interval 0.21-0.35 and effect size 0.28, respectively). The heterogeneity between studies was high with an I2 of 95.76% ($p<0.001$). *Conclusions*: Our meta-analysis suggests no significant difference in dysbiosis prevalence between OC patients and controls. Considering the substantial heterogeneity found, more studies with control groups and precise methodologies are needed to further evaluate the potential role of the ovarian microbiota in the OC. (www.actabiomedica.it)

**Key words:** Ovarian cancer, ovarian microbiota, dysbiosis, human papillomavirus infection, Cytomegalovirus, *Chlamydia trachomatis*

## Introduction

Ovarian cancer is the most lethal gynecological malignancy in women worldwide and represents the fifth most common malignancy (1, 2) with a 5-year standardized survival rate of 30–40% (3). Patients often present with advanced-stage disease and intraperitoneal dissemination due to the asymptomatic clinical course, lack of effective screening methods, and not well defined etiologic factors (4). Except for the known association between BRCA1/2 mutations and increased ovarian cancer risk, which accounts for approximately 10-15% of ovarian cancers (5), current knowledge of ovarian carcinogenesis is sparse (6). More recently, the scientific gynecologic oncology community turned its attention to new potential

pathogenetic factors, highlighting the possible correlation between cancer and patterns of microbial organisms colonizing affected organs. In non-gynecological cancer, this correlation is well established for chronic inflammation such as *Helicobacter pylori*-related to gastric adenocarcinoma (7). In a gynecological setting, the focus is usually on the involvement of the vaginal microbiota, as evidenced by its role in the mediators mechanism of the persistence of human papillomavirus (HPV) infection (8). In this regard, dysbiosis, defined as a numerical and/or qualitative alteration of a microbial population, may represent a crucial factor in the development of ovarian cancer. Of particular interest is the potential role of bacterial presence. *Chlamydia trachomatis* is associated with salpingitis and pelvic inflammatory disease (PID) (9). These conditions have been shown to be associated with an increased risk of ovarian cancer(10), and this bacterium is often detected in ovarian tumor tissue (11). Ovarian "oncobiome" has also been used in terms of virus expression in the tumor tissue, suggesting the possibility of virus' implication in tumor carcinogenesis and progression. In this regard, some authors investigated the potential role of Cytomegalovirus (CMV) and Epstein-Barr virus (EBV) in ovarian cancer pathogenesis, based on the theory that these viruses are implicated in the development of non-gynecological malignancies (12). Lastly, the association between high-risk HPV infection and epithelial malignancies, such as cervical cancer (13) and squamous cell carcinoma of the head and neck (14), has been well established. However, its involvement in ovarian cancer is still controversial (15). On this evidence, it is unclear whether the dysbiosis may play a role in the etiopathogenesis of ovarian cancer. Thus, the goal of this review and meta-analysis is to collect and analyze available literature to offer an up-to-date and rigorous overview of this topic.

## Materials and methods

This systematic research has been performed in agreement with the Preferred reporting items for Systematic Reviews and Meta-analysis (PriSMa) statements (16). The study was registered with the International Prospective Register of Systematic Reviews (PROSPERO) under the registration number:CRD42024600403. A comprehensive literature research on electronic databases (MEDLINE and PubMed Databases) was conducted from inception until February 2024. The primary research strategy was identified with the use of a combination of the following medical relevant headings terms (MeSH) and keywords: "ovarian cancer and dysbiosis", "inflammatory disease and ovarian cancer", "infections and ovarian cancer", "HPV and ovarian cancer, "sexual infections and ovarian cancer", "microbiota and ovarian cancer" and "viral infections and ovarian cancer". Studies that were not in line with the aim of the study, case reports, papers based on animal models or laboratory studies, and non-English language articles were excluded. Titles and abstracts were screened. Articles reporting data on ovarian cancer and dysbiosis or infection disease were obtained in full for further evaluation. The electronic research and the eligibility of the studies were independently assessed by two of the authors (SMC, GC). In addition, references in the included articles were reviewed to identify additional eligible articles. Differences were discussed with a third reviewer (AE) for data extraction. The main findings considered in the present review were author, year of publication, the study design, the number of patients included in each study, and information about the infections (infection agents and type of sample). After the initial research, a total of 10278 titles were extracted from the Pubmed database and MEDLINE databases using the keywords previously mentioned. After the first revision, 505 unique studies were extracted. After further revision, 32 articles were selected, out of which 26 studies were ultimately eligible for the present metanalysis following a full-text evaluation. The selection process is illustrated in Figure 1.

### Statistical analysis

Continuous variables are reported as numbers and percentages. Random-effect and fixed-effect models are used for the analysis of the results. The event rate (presence of dysbiosis in ovarian cancer patients) is used as the effect size type. The Trim and Fill methods are used for the publication bias analysis. The variation

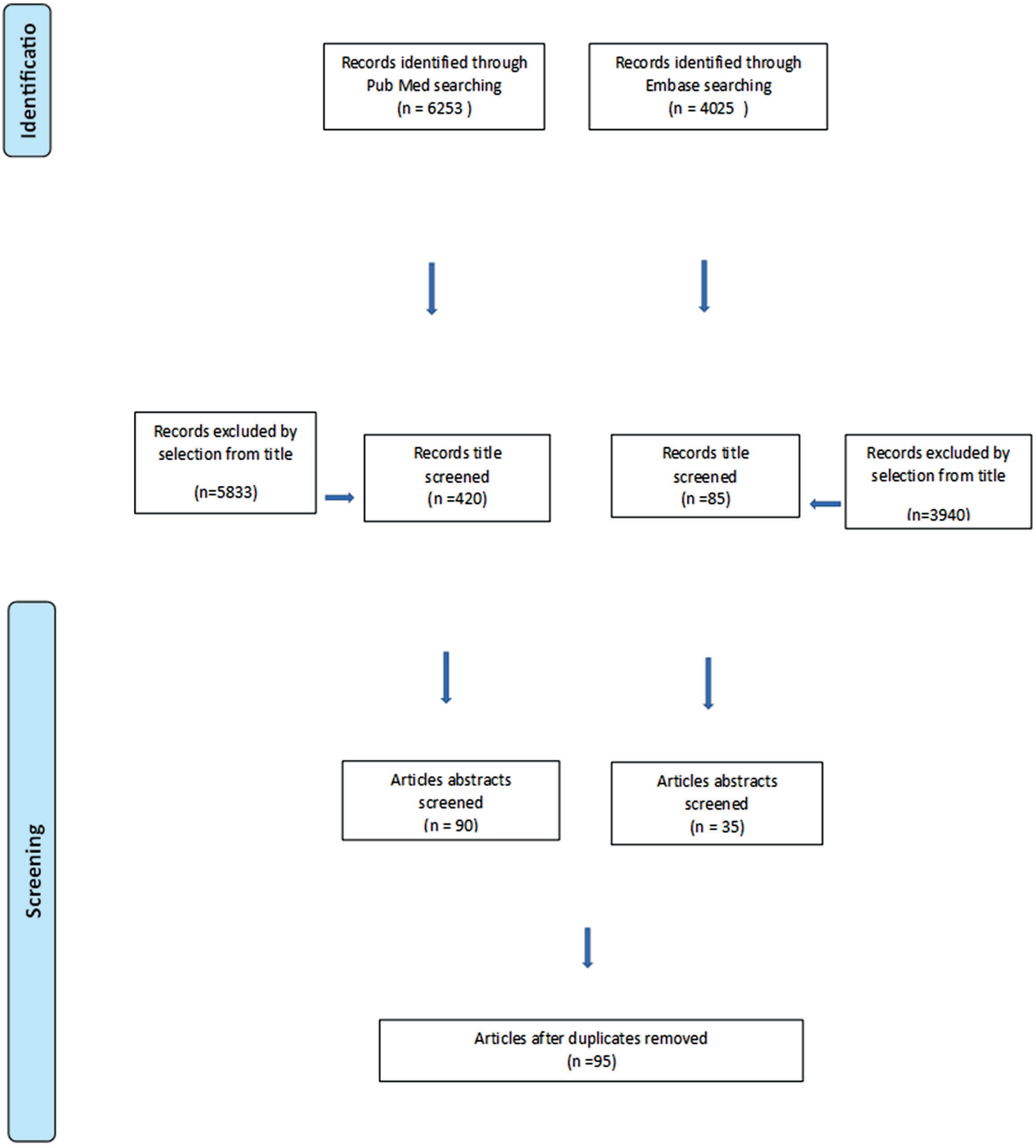


**Figure 1.** Prisma flow diagram.

in study outcomes between studies is evaluated by the I2 test in heterogeneity analysis. An I2 test < 50% was interpreted as low heterogeneity. Prometa Software version 3.0 was used for the analyses.

## Results

Of the 10278 studies initially screened, 27 met the inclusion criteria. Five thousand and fourteen

ovarian carcinoma cases were included of which 1659 (33.1%) showed dysbiosis. The fixed-effect model and the random-effect model showed no significant correlation between ovarian cancer patients and dysbiosis ($p<0.001$ and $p<0.001$ with 95% Confidence Interval 0.21-0.35 and effect size 0.28, respectively). Forest Plot is shown in Figure 2. The heterogeneity between studies was high with an I2 of 95.76% ($p<0.001$). Sensitivity analysis with both random and fixed models was statistically significant ($p<0.001$) for all the studies.

*Chlamydia trachomatis or other bacterial infections and ovarian cancer*

Among the studies selected in our metanalysis, 7 studies analyzed the correlation between chlamydia infection and ovarian cancer.

In a nested case-control study, Skarga et al. (17) investigated the role of sexually transmitted infections, specifically *Chlamydia trachomatis* (CT), in ovarian cancer risk. Authors measured antibodies to CT and *Mycoplasma Genitalium* (MG) in serum samples of 484 patients matched 1:1 to controls; no correlation was found between seropositivity and ovarian cancer subtypes, except for a positive association between MG seropositivity and Mucinous Ovarian Cancer ($p<.001$). Similarly, Jonsson et al. (18) in a prospective case-control study matched the serology of 92 women with high-grade serous ovarian cancer with 359 controls. Authors highlighted no significant correlations between previous *Chlamydia* infection and OC occurrence. The same evidence was found by Ness et al. (19) in a large case series including 521 patients versus 766 controls. In contrast, R. Fortner et al. (11) in a case-control study included 377 cases, showed that seropositivity to CM infection was associated with a two-fold increased risk of ovarian cancer (RR: 2.07). A similar result was found by M. Laban et al. (20) analyzing 77 paraffin block specimens retrieved from patients with serous ovarian cancer (30 cases), primary tubal serous cancer (25 cases), and

| | ES | W | Sig. | N |
|---|---|---|---|---|
| Al-Shabanah et al. 2014 | 0.36 | 4.28% | 0.000 | 200 |
| Ashrafian et al. 2015 | 0.77 | 4.08% | 0.000 | 100 |
| Atalay et al. 2008 | 0.09 | 3.68% | 0.000 | 94 |
| Bilyk et al. 2011 | 0.17 | 3.69% | 0.000 | 53 |
| Dadashi et al. 2017 | 0.36 | 4.04% | 0.018 | 70 |
| Fortner et al. 2019 | 0.39 | 4.33% | 0.000 | 337 |
| Giordano et al. 2008 | 0.02 | 1.77% | 0.000 | 50 |
| Hammou et al. 2019 | 0.11 | 3.66% | 0.000 | 70 |
| Hassan et al. 2017 | 0.10 | 3.79% | 0.000 | 100 |
| Holster et al. 2023 | 0.25 | 4.21% | 0.000 | 162 |
| Idahl et al. 2020 | 0.41 | 4.38% | 0.000 | 791 |
| Ingerslev et al. 2016 | 0.01 | 1.78% | 0.000 | 198 |
| Jonsson et al. 2020 | 0.16 | 3.95% | 0.000 | 92 |
| Kuscu et al. 2005 | 0.33 | 4.04% | 0.006 | 72 |
| Laban et al. 2019 | 0.45 | 3.98% | 0.501 | 55 |
| Malisic et al. 2012 | 0.07 | 3.16% | 0.000 | 54 |
| Mukhtarulina et al. 2006 | 0.76 | 3.94% | 0.000 | 67 |
| Nenè et al. 2019 | 0.59 | 4.27% | 0.016 | 176 |
| Ness et al. 2008 | 0.48 | 4.36% | 0.274 | 521 |
| Roos et al. 2015 | 0.01 | 3.54% | 0.000 | 405 |
| Shokouh et al. 2020 | 0.29 | 4.00% | 0.001 | 68 |
| Skarga et al. 2023 | 0.67 | 4.35% | 0.000 | 484 |
| Wu et al. 2003 | 0.33 | 3.93% | 0.016 | 54 |
| Yang et al. 2010 | 0.43 | 4.18% | 0.152 | 109 |
| Yang et al. 2020 | 0.25 | 4.31% | 0.000 | 310 |
| Zhang et al. 2016 | 0.20 | 4.29% | 0.000 | 322 |
| Overall (random-effects model) | 0.28 | 100.00% | 0.000 | 5014 |

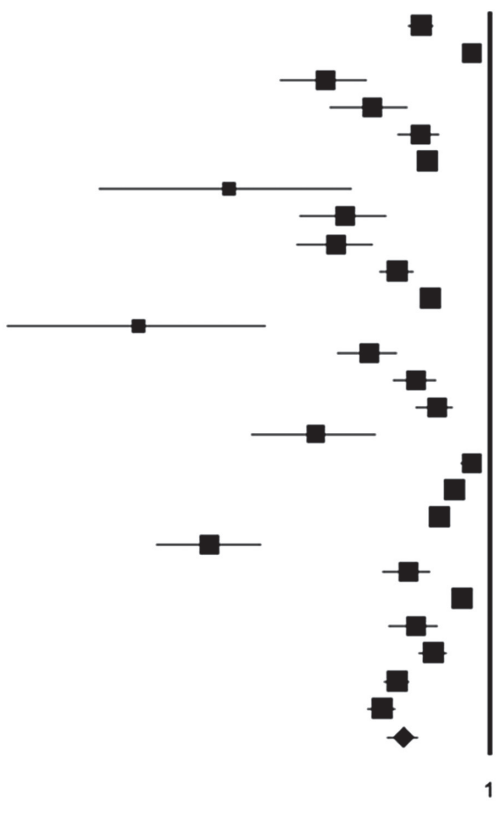


**Figure 2.** Forest Plot Analysis. ES: Effect Size; W: Weight; Sig.: Significance; N: Number of cases.

control specimens. CT- DNA was detected in 84% of high-grade tubal serous cancer, 16.7% of high-grade serous ovarian cancer, and 13.3% in controls (p=0.0005). In a retrospective cohort study, Holster et al. (21) explored the role of CT infection in epithelial ovarian cancer (EOC) by analyzing chlamydial TroA, HtrA and major outer membrane protein(MOMP) IgG serum antibody responses. Results showed that women with immunological markers of persistent CT infection had better response to the first-line platinum-taxane treatment and better 3-Y-survival.In a large retrospective study A. Idahl et al. (22) investigated the hypothesis that past sexual -infection, particularly *Chlamydia trachomatis*, is associated with higher EOC risk, analyzing a cohort of 791 cases and 1669 matched controls, also using serum antibodies against CT and MG. Results highlighted that positive serology to CT- Pgp3 antibodies was not associated with EOC risk overall, but with a higher risk of the mucinous histotype (RR = 2.30 [95% CI = 1.22-4.32]). Lastly, H. Yang et al. (23) analyzed the expressions of 16S rRNA and P37 protein from *Mycoplasma hyorhinis* in specimens obtained from 109 patients with ovarian cancer. The difference in the mycoplasma infection ratio between ovarian cancer tissues and normal samples was extremely significant (P < 0.001).

*HPV and ovarian cancer*

Eighteen studies included in our analysis exclusively explored the potential association between HPV infection and ovarian cancer. Seven studies focused on the detection of high-risk types of HPV (type 16-18) and p53 expression in OC tissues. In a small retrospective control study, O.O. Bilyk et al. (24) used HPV 16 and 18 E6-specific semiquantitative PCR in ovarian tissues to screen the incidence of HPV in 20 women at risk of developing ovarian cancer, showing a higher presence of HPVs in the upper genital tract of this group than 10 controls (p<.001). Similarly, M. Dadashi (25) in a larger retrospective study reported the presence of HPV-16 in a population of 70 women with malignancy and 70 patients with benign gynecologic tumors. Data suggested an incidence of 36.0% vs 2.8% of HPV positivity in cases vs. controls (p=.002). In contrast, K. Ingerslev et al.(26) and E. Kuscu et al. (27) exploring HPV 16-18 in 198 and 40 ovarian tissues of patients with EOC, respectively, concluded that high-risk HPV is unlikely to be associated with EOC. P. Roos et al. (28) reported an incidence of 1.5% in 405 women with ovarian cancer, concerning HPV -positive ovarian samples. Among these HPV-positive ovarian cancer samples, all reads were type HPV-18. Likewise, M. Shokouh (29) reported the presence of HPV 16-18 in 208 specimens, including 68 malignant, 27 borderline, 65 benign, and 45 normal tissues, through DNA extraction and PCR amplification. Lastly, Q. Wu et al. (30), using in situ hybridization (ISH) and immunohistochemistry (IHC) to detect the presence of HPV-16 and p53 expression, tested 54 cases of ovarian tissue blocks (50 are epithelial cancer, 4 are non-epithelial cancer) and 30 controls. Authors found that HPV-16 infection was significantly higher in cancer tissues compared to controls (p < .01), but a non-significant correlation between HPV-16 infection and histological types of cancer was found (P > 0.05). Three of the included studies analyzed the role of HPV 16-18, and 33 infection in ovarian cancer. In 94 patients with ovarian cancer included by F. Atalay et al. (31), HPV was found to be positive in 8 patients (8.5%), 6 patients had HPV type 16, and the remaining 2 patients had HPV type 33. The same results were obtained by Z. Hassan (32), showing in a cohort of 100 women with EOC, an HPV-prevalence of 10% with HPV-16 and HPV-18 as predominant genotypes, followed by HPV–33. Lastly, P. Zhang (33) collected paraffin-embedded ovarian tissue from 322 patients with EOC, 99 with ovarian benign tumors, and 199 controls. Using PCR and direct sequencing to identify the HPV 18-33 types in the samples, the authors showed a higher prevalence of HPV18 and HPV33 in EOC group than in the normal group (p<.001). Finally, 6 of the included articles explored the role of a wide range of HPV subtypes in ovarian cancer patients. In summary, the authors showed a higher presence of HPV in patients with EOC than controls, suggesting a possible key role in ovarian cancer development.

## Discussion

Despite advancements in treatment strategies, OC remains a significant challenge due to its high

mortality rate (34). Our investigation aimed to analyze the available results about a potential correlation between OC and microbiota. Based on our updated meta-analysis of 27 studies and 5014 women [n=1659 (33.1%) patients with dysbiosis], there is no significant correlation between ovarian cancer patients and dysbiosis, while we found a high heterogeneity between studies.

Recently, numerous researchers have emphasized the potential strong correlation between diseases and specific arrangements of bacteria colonizing various organs (8).Dysbiosis appears to be associated with the development of various tumors, including colonrectal cancer and gastric malignancy(35,36). In the gynecological field, gut-dysbiosis has been observed in epithelial OC patients, including significant alteration of microbial composition, increased opportunistic pathogens, and decreased beneficial bacteria (37). Resident microbes likely contribute to the multifactor process of tumorigenesis by modulating the complex pathways underlying the cell proliferation and progression of tumorigenesis (38). Although the precise immunological mechanisms are still unclear, numerous evidence have highlighted the key role of inflammatory cytokines in the development of a protumorigenic microenvironment that stimulates angiogenesis and tissue remodeling in OC (39). In these intricate cellular signal pathways, the intestine could affect the systemic production of inflammatory factors such as C-reactive protein (CRP),interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF) (40). Additionally, the microorganisms that populate the organs locally have been studied for possible interactions with the development of cancer. Specifically, vaginal microbiota and in particular the presence of *Lactobacillus crispatus* is closely related to some benign pathologies including vaginal infections and inflammatory processes, modulating immune response mechanisms or increasing pathogenic strains (41). Although the relationship between the vaginal microbiome and gynecological cancers is still in its infancy, recent studies have shown a possible interconnection (42). In particular, vaginal microbiota dominated by *Lactobacillus gasseri,* was associated with increased clearance of HPV (43) and therefore a lower risk of neoplastic transformation. Microbiotas characterized by a low *Lactobacilli* rate or a high amount of *Atopobium* were associated with a lower virus elimination capacity (44). Even for endometrial cancer, some authors suggested the possible link between particular composition of the vaginal or uterine microbiota and chronic endometrial inflammation, highlighting significant differences between patients with endometrial hyperplasia and healthy controls (45). Similarly, the risk of ovarian cancer could be connected to alteration in vaginal microbiota with altered metabolite configurations as described in cancer mouse models (46). Noteworthy, a study included in our analysis remarked that patients with OC or known risk factors (BRCA1 germline mutations) were significantly associated with a subtype of vaginal microbiota in which lactobacilli accounted for less than 50% of the species present, suggesting a potential therapeutic role in vaginal supplements of *Lactobacilli* (47). Interestingly, the microbial population of the vaginal environment could interfere with the microenvironment of the upper female genital tract. The existence of an ovarian microbiome is a topic as new as it is extremely lacking, as well as its potential role in tumor genesis. The available data suggest that the ovarian microbiota differs significantly from the vaginal microbiota in both composition and quantity, being considered a low-abundance site (48). However, data in the literature are extremely heterogeneous and contrasting. This heterogeneity is reflected in the results of the studies included in our meta-analysis. One of the hypotheses outlined the mutual influence between the microbiome and the cancer environment under the assumption that a specific microenvironment may be an optimal niche for specific bacterial growth and vice versa, bacteria and their biological metabolites may be a substrate for the development or spreading of cancer cells (8). In particular, *Clamidya trachomatis* (CT), as the most common pathogenic bacteria of the female reproductive tract, is one of the primary pathogens associated with pelvic inflammatory disease (49). The correlation between CT and the increased risk of ovarian cancer development remains a widely debated and unclear topic, considering the contrasting findings. CT may cause DNA doublestrand breaks (50), interfere with the DNA damage-repair mechanism, and prevent host cell apoptosis,

that may have a direct impact on the development of ovarian cancer (17). In addition, CT and other pathogens, including *Mycoplasma genitalium* (MG), may indirectly promote tumorogenesis by increasing the inflammatory state of the genital tract (51). These infections play a significant role in the development of salpingitis and other tubal diseases that might increase the risk of ovarian cancer, regulating the activation of pro-oncogenic mediators (52). This may be particularly relevant for the high-grade serous ovarian histotype that has been found to originate from the tube epithelium (53). In contrast, in two studies of our series authors found a positive association between CT and MG infections and mucinous OC histotype (17,22) but mechanisms linking MG specifically to mucinous OC are not clear and need further research. Although epidemiological studies have proposed the existence of a link between PID and the risk of ovarian cancer (54), to date no firm conclusions can be drawn. The results of our meta-analysis do not support a strong association between genital infection and OC and are consistent with the results of previous studies (55). Similarly, it is important to note that the findings are burdened by the high heterogeneity across studies analyzed. In particular, these differences concern the diagnostic tests used, the type of sample, and the antibodies measured. Not least, the comparison of studies specifically focused on the association between ovarian cancer and antibodies to *Chlamydia* is limited by the higher cross-reactivity of antibodies with other chlamydial and bacterial infections (56), the timing of antibody analysis, possible subsequent infections manifested in the interval between blood sample and diagnosis, treatments or the proportion of women with a history of infection but did not seroconvert. Moreover, most of the studies included in our meta-analysis have evaluated the association between HPV infection and OC, considering that HPV has been identified as an etiological agent of numerous proliferative epithelial malignancies, including the lower genital tract (57). Since the first report on HPV in ovarian cancer was found in 1987, its role in the development of OC is still under debate (58). Several plausible mechanisms have been investigated to explain the contribution of HPV infection and ovarian carcinogenesis. For example, HPV may rise from the cervix to infect the upper genital tract (59), and the expression of viral oncogenes E6 and E7 may impair the function of host-cell tumor suppressors p53, promoting malignant transformation (60). Despite the different etiopathological hypotheses proposed, S. Cherif et al. (15) in a meta-analysis of 2280 patients with OC, suggested a great difference in the prevalence of HPV detected in OC, which is not seen in strongly HPV-associated cancers such as cervical cancer. Similarly, Rosa et al. founded a high prevalence of HPV in women with OC, but its role in carcinogenesis remains inconclusive (61). In line with these observations, our findings did not reveal a significant association between ovarian cancer and HPV.

Our analysis pointed out the extreme complexity of this debated topic, highlighting the discrepancy between the results present in the literature and the inherent limits of the conducted studies. Overall, the interplay between OC and dysbiosis remains unclear, focusing further research and attracting the attention of the scientific community. Despite being the most comprehensive meta-analysis to date, methodological inconsistencies across studies pose a significant limitation to our findings. Several biases related to diagnostic methods employed, type of sample, environmental factors, and patient characteristics should be considered when interpreting the results. However, the strength of this meta-analysis can be found in the rigor of research, which provides a significant update and wide overview of this controversial topic.

## Conclusion

Despite promising findings linking the microbiota to cancer pathogenesis, our study does not support a significant association between dysbiosis and ovarian cancer. Taking into account the extreme heterogeneity of studies included, standardization of methodologies in further research is needed to evaluate an effective correlation between microbiota of the female genital tract and the risk of ovarian cancer.

**Ethic Approval:** This article does not contain any studies with human participants or animals performed by any of the authors.

Following our institution's rules and the ethics committee's statement, no approval was required for this study since it is a meta-analysis review.

**Conflict of Interest:** Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

**Authors Contribution:** MCDD: Conceptualization; GC: Methodology; MCS: Writing, original draft; VAC: Data curation; IR: Methodology; AE: Review and editing; ASL: Review and editing; CR:Review;ES: Review; PR: Review and editing; VP: Review; SC: Editing; RB: Validation; VC: Validation.

**Declaration on the Use of AI:** None.

## References


1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. CA Cancer J Clin. 2015;65(1):5-29. doi: 10.3322/caac.21254
2. Torre LA, Islami F, Siegel RL, Ward EM, Jemal A. Global cancer in women: burden and trends. Cancer Epidemiol Biomarkers Prev. 2017;26(4):444-57. doi: 10.1158/1055-9965.EPI-16-0858
3. Di Donna MC, Cucinella G, Zaccaria G, et al. Concordance of radiological, laparoscopic and laparotomic scoring to predict complete cytoreduction in women with advanced ovarian cancer. Cancers (Basel). 2023;15(2):500. doi: 10.3390/cancers15020500
4. Janavičius R. Founder BRCA1/2 mutations in Europe: implications for hereditary breast-ovarian cancer prevention and control. EPMA J. 2010;1(3):397-412. doi: 10.1007/s13167-010-0037-y
5. Carlson JW, Miron A, Jarboe EA, et al. Serous tubal intraepithelial carcinoma: its potential role in primary peritoneal serous carcinoma and serous cancer prevention. J Clin Oncol. 2008;26(25):4160-5. doi: 10.1200/JCO.2008.16.4814
6. Chambers LM, Bussies P, Vargas R, et al. The microbiome and gynecologic cancer: current evidence and future opportunities. Curr Oncol Rep. 2021;23(8):92. doi: 10.1007/s11912-021-01079-x
7. Cazzaniga M, Cardinali M, Di Pierro F, Bertuccioli A. Ovarian microbiota, ovarian cancer and the underestimated role of HPV. Int J Mol Sci. 2022;23(24):16019. doi: 10.3390/ijms232416019
8. Price MJ, Ades AE, Welton NJ, Simms I, Horner PJ. Pelvic inflammatory disease and salpingitis: incidence of primary and repeat episodes in England. Epidemiol Infect. 2017;145(1):208-15. doi: 10.1017/S0950268816002065
9. Zhou Z, Zeng F, Yuan J, et al. Pelvic inflammatory disease and the risk of ovarian cancer: a meta-analysis. Cancer Causes Control. 2017;28(5):415-28. doi: 10.1007/s10552-017-0873-3
10. Fortner RT, Terry KL, Bender N, et al. Sexually transmitted infections and risk of epithelial ovarian cancer: results from the Nurses' Health Studies. Br J Cancer. 2019;120(8):855-60. doi: 10.1038/s41416-019-0422-9
11. Ingerslev K, Høgdall E, Skovrider-Ruminski W, et al. The prevalence of EBV and CMV DNA in epithelial ovarian cancer. Infect Agents Cancer. 2019;14:1. doi: 10.1186/s13027-019-0223-z
12. Zur Hausen H. Papillomaviruses in the causation of human cancers: a brief historical account. Virology. 2009;384(2):260-5. doi: 10.1016/j.virol.2008.11.046
13. Wai KC, Strohl MP, van Zante A, Ha PK. Molecular diagnostics in human papillomavirus-related head and neck squamous cell carcinoma. Cells. 2020;9(2):500. doi: 10.3390/cells9020500
14. Cherif S, Amine A, Thies S, et al. Prevalence of human papillomavirus detection in ovarian cancer: a meta-analysis. Eur J Clin Microbiol Infect Dis. 2021;40(9):1791-802. doi: 10.1007/s10096-021-04282-7
15. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009;6(7):e1000097. doi: 10.1371/journal.pmed.1000097
16. Skarga E, Surcel HM, Kaaks R, Waterboer T, Fortner RT. Sexually transmitted infections and risk of epithelial ovarian cancer: results from the Finnish Maternity Cohort. J Infect Dis. 2023;228(11):1621-9. doi: 10.1093/infdis/jiad171
17. Jonsson S, Lundin E, Elgh F, Ottander U, Idahl A. Chlamydia trachomatis and anti-MUC1 serology and subsequent risk of high-grade serous ovarian cancer: a population-based case–control study in northern Sweden. Transl Oncol. 2020;13(1):86-91. doi: 10.1016/j.tranon.2019.09.007
18. Ness RB, Shen C, Bass D, et al. Chlamydia trachomatis serology in women with and without ovarian cancer. Infect Dis Obstet Gynecol. 2008;2008:219672. doi: 10.1155/2008/219672
19. Laban M, Ibrahim EA, Hassanin AS, et al. Chlamydia trachomatis infection in primary fallopian tube and high-grade serous ovarian cancers: a pilot study. Int J Womens Health. 2019;11:199-205. doi: 10.2147/IJWH.S188938
20. Holster T, Urpilainen E, Paavonen J, Puistola U, Puolakkainen M. Immunological markers of Chlamydia trachomatis infection in epithelial ovarian cancer. Anticancer Res. 2023;43(9):4037-43. doi: 10.21873/anticanres.16592
21. Idahl A, Le Cornet C, González Maldonado S, et al. Serologic markers of Chlamydia trachomatis and other sexually transmitted infections and subsequent ovarian cancer risk: results from the EPIC cohort. Int J Cancer. 2020;147(8):2042-52. doi: 10.1002/ijc.32999
22. Yang H, Zhang J, Shou C. Detection of Mycoplasma hyorhinis infection in ovarian cancer with in situ hybridization

and immunohistochemistry. Cancer Res. 2010;7(5):294-8. doi: 10.1007/s11805-010-0534-8
23. Bilyk OO, Pande NT, Pejovic T, Buchynska LG. The frequency of human papillomavirus types 16, 18 in upper genital tract of women at high risk of developing ovarian cancer. Exp Oncol. 2014;36(2):121-4. PMID: 24980768
24. Dadashi M, Eslami G, Faghihloo E, et al. Detection of human papillomavirus type 16 in epithelial ovarian tumor samples. Arch Clin Infect Dis. 2017;12(1):e39666. doi: 10.5812/archcid.39666
25. Ingerslev K, Hogdall E, Skovrider-Ruminski W, et al. High-risk HPV is not associated with epithelial ovarian cancer in a Caucasian population. Infect Agents Cancer. 2016;11:39. doi: 10.1186/s13027-016-0087-4
26. Kuscu E, Ozdemir BH, Erkanli S, Haberal A. HPV and p53 expression in epithelial ovarian carcinoma. Eur J Gynaecol Oncol. 2005;26(6):642-5.
27. Roos P, Orlando PA, Fagerstrom RM, Pepper JW. In North America, some ovarian cancers express the oncogenes of preventable human papillomavirus HPV-18. Sci Rep. 2015;5:8645. doi: 10.1038/srep08645
28. Shokouh MR, Safaei A, Moattari A, Sarvari J. Association of human papillomavirus and Epstein-Barr virus with ovarian cancer in Shiraz, southwestern Iran. Iran J Pathol. 2020;15(4):292-8. doi: 10.30699/ijp.2020.119681.2306
29. Wu QJ, Guo M, Lu ZM, Li T, Qiao HZ, Ke Y. Detection of human papillomavirus-16 in ovarian malignancy. Br J Cancer. 2003;89(4):672-5. doi: 10.1038/sj.bjc.6601172
30. Atalay F, Taskiran C, Taner MZ, Pak I, Or M, Tuncer S. Detection of human papillomavirus DNA and genotyping in patients with epithelial ovarian carcinoma. J Obstet Gynaecol Res. 2007;33(6):823-8. doi: 10.1111/j.1447-0756.2007.00663.x
31. Hassan ZK, Hafez MM, Kamel MM, Zekri ARN. Human papillomavirus genotypes and methylation of CADM1, PAX1, MAL and ADCYAP1 genes in epithelial ovarian cancer patients. Asian Pac J Cancer Prev. 2017;18(1): 169-76. doi: 10.22034/APJCP.2017.18.1.169
32. Zhang PP, Zhou L, Cao JS, et al. Possible epithelial ovarian cancer association with HPV18 or HPV33 infection. Asian Pac J Cancer Prev. 2016;17(6):2959-64.
33. Penny SM. Ovarian cancer: an overview. Radiol Technol. 2020;91(6):561-75.
34. Polk DB, Peek RM. Helicobacter pylori: gastric cancer and beyond. Nat Rev Cancer. 2010;10(6):403-14. doi: 10.1038 /nrc2857
35. Quaglio AEV, Grillo TG, Oliveira ECS De, Stasi LC Di, Sassaki LY. Gut microbiota, inflammatory bowel disease and colorectal cancer. World J Gastroenterol. 2022;28(30): 4053-60. doi: 10.3748/wjg.v28.i30.4053.
36. Hu X, Xu X, Zeng X, et al. Gut microbiota dysbiosis promotes the development of epithelial ovarian cancer via regulating Hedgehog signaling pathway. Gut Microbes. 2023;15(1):2221093. doi: 10.1080/19490976.2023.2221093
37. Fulbright LE, Ellermann M, Arthur JC. The microbiome and the hallmarks of cancer. PLoS Pathog. 2017;13(9):e1006480. doi: 10.1371/journal.ppat.1006480
38. Comen EA, Bowman RL, Kleppe M. Underlying causes and therapeutic targeting of the inflammatory tumor microenvironment. Front Cell Dev Biol. 2018;6:56. doi: 10.3389 /fcell.2018.00056
39. Mahoney DE, Chalise P, Rahman F, Pierce JD. Influences of gastrointestinal microbiota dysbiosis on serum proinflammatory markers in epithelial ovarian cancer development and progression. Cancers (Basel). 2022;14(12):3022. doi: 10.3390/cancers14123022
40. Ravel J, Gajer P, Abdo Z, et al. Vaginal microbiome of reproductive-age women. Proc Natl Acad Sci U S A. 2011; 108(Suppl 1):4680-7. doi: 10.1073/pnas.1002611107
41. Champer M, Wong A, Champer J, et al. The role of the vaginal microbiome in gynaecological cancer. BJOG. 2018;125(3):309-15. doi: 10.1111/1471-0528.14631
42. Brotman RM, Shardell MD, Gajer P, et al. Interplay between the temporal dynamics of the vaginal microbiota and human papillomavirus detection. J Infect Dis. 2014;210(11): 1723-33. doi: 10.1093/infdis/jiu330
43. Gao W, Weng J, Gao Y, Chen X. Comparison of the vaginal microbiota diversity of women with and without human papillomavirus infection: a cross-sectional study. BMC Infect Dis. 2013;13(1):271. doi: 10.1186/1471-2334 -13-271
44. Walther-António MRS, Chen J, Multinu F, et al. Potential contribution of the uterine microbiome in the development of endometrial cancer. Genome Med. 2016;8(1):122. doi: 10.1186/s13073-016-0368-y
45. Li C, Feng Y, Yang C, et al. Association between vaginal microbiota and the progression of ovarian cancer. J Med Virol. 2023;95(7):e28898. doi: 10.1002/jmv.28898
46. Nené NR, Reisel D, Leimbach A, et al. Association between the cervicovaginal microbiome, BRCA1 mutation status, and risk of ovarian cancer: a case-control study. Lancet Oncol. 2019;20(8):1171-82. doi: 10.1016/S1470 -2045(19)30340-7
47. Łaniewski P, Ilhan ZE, Herbst-Kralovetz MM. The microbiome and gynaecological cancer development, prevention and therapy. Nat Rev Urol. 2020;17(4):232-50. doi: 10.1038/s41585-020-0286-z
48. Jennings LK, Krywko DM. Pelvic inflammatory disease. StatPearls [Internet]. 2024.
49. Chumduri C, Gurumurthy RK, Zadora PK, Mi Y, Meyer TF. Chlamydia infection promotes host DNA damage and proliferation but impairs the DNA damage response. Cell Host Microbe. 2013;13(6):746-58. doi: 10.1016/j.chom .2013.05.010
50. Chan PJ, Seraj IM, Kalugdan TH, King A. Prevalence of Mycoplasma conserved DNA in malignant ovarian cancer detected using sensitive PCR–ELISA. Gynecol Oncol. 1996;63(2):258-60. doi: 10.1006/gyno.1996.0316
51. Shanmughapriya S, SenthilKumar G, Vinodhini K, Das BC, Vasanthi N, Natarajaseenivasan K. Viral and bacterial aetiologies of epithelial ovarian cancer. Eur J Clin Microbiol Infect Dis. 2012;31(9):2311-7. doi: 10.1007/s10096 -012-1570-5

52. Kurman RJ, Shih IM. The origin and pathogenesis of epithelial ovarian cancer: a proposed unifying theory. Am J Surg Pathol. 2010;34(3):433-43. doi: 10.1097/PAS.0b013e3181cf3d79
53. Paavonen J, Turzanski Fortner R, Lehtinen M, Idahl A. Chlamydia trachomatis, pelvic inflammatory disease, and epithelial ovarian cancer. J Infect Dis. 2021;224(Suppl 2): S121-7. doi: 10.1093/infdis/jiab017
54. Capozzi VA, Incognito GG, Scarpelli E, et al. Exploring the relationship between ovarian cancer and genital microbiota: a systematic review and meta-analysis. J Pers Med. 2024;14(4):351. doi: 10.3390/jpm14040351
55. Casson N, Entenza JM, Greub G. Serological cross-reactivity between different Chlamydia-like organisms. J Clin Microbiol. 2007;45(1):234-6. doi: 10.1128/JCM.01867-06
56. Nour NM. Cervical cancer: a preventable death. Rev Obstet Gynecol. 2009;2(4):240-4.
57. Kaufman RH, Bornstein J, Gordon AN, Adam E, Kaplan AL, Adler-Storthz K. Detection of human papillomavirus DNA in advanced epithelial ovarian carcinoma. Gynecol Oncol. 1987;27(3):340-5. doi: 10.1016/0090-8258(87)90256-3
58. Svahn MF, Faber MT, Christensen J, Norrild B, Kjaer SK. Prevalence of human papillomavirus in epithelial ovarian cancer tissue: a meta-analysis of observational studies. Acta Obstet Gynecol Scand. 2014;93(1):6-19. doi: 10.1111/aogs.12254
59. Chen Y, Williams V, Filippova M, Filippov V, Duerksen-Hughes P. Viral carcinogenesis: factors inducing DNA damage and virus integration. Cancers (Basel). 2014;6(4): 2155-86. doi: 10.3390/cancers6042155
60. Rosa MI, Silva GD, de Azedo Simões PWT, et al. The prevalence of human papillomavirus in ovarian cancer: a systematic review. Int J Gynecol Cancer. 2013;23(3):437-41. doi: 10.1097/IGC.0b013e318280f3e0.

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