Investigation of the Association Between HSV-2 Virus and the Risk of Ovarian Cancer

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Abstract- Ovarian cancer is among the most lethal gynecologic malignancies, and its etiology remains poorly understood. Viral infections, including herpes simplex virus type 2 (HSV-2), have been hypothesized as potential risk factors. This study aimed to evaluate the association between HSV-2 infection and ovarian cancer risk in an Iranian population. A case-control study was conducted at Fatemieh Hospital, Hamadan, Iran, from 2021 to 2022, involving 38 women with histologically confirmed ovarian cancer and 38 age- and marital status-matched healthy controls. Data on demographic characteristics, obstetric history, sexually transmitted diseases (STDs), and family history of genital cancers were collected. HSV-2 serology was assessed using enzyme-linked immunosorbent assay (ELISA). Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using univariate and multivariate logistic regression. A post-hoc power analysis was performed. Baseline characteristics were similar between cases and controls. Among cases, 52.6% had epithelial ovarian cancer, 26.3% serous tumors, and 21.1% borderline tumors. Univariate analysis indicated increased odds of ovarian cancer with *Chlamydia trachomatis* (OR 4.2, 95% CI: 1.04-16.6), HSV-2 (OR 3.1, 95% CI: 0.7-12.8), and STDs overall (OR 4.8, 95% CI: 1.8-12.7). In multivariate analysis adjusting for age, menopausal status, family history, and urban residence, STDs remained significantly associated (adjusted OR 4.8, 95% CI: 1.7-13.2, *P*=0.003). No significant associations were observed between infections and cancer subtypes. Post-hoc power analysis indicated approximately 35% power to detect the observed HSV-2 difference. Sexually transmitted infections may contribute to ovarian cancer etiology. However, due to low statistical power, the non-significant finding for HSV-2 should be interpreted with caution. Further studies with larger sample sizes are needed to clarify the role of HSV-2 infection.

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Introduction

Cancer is a leading global cause of mortality and a major public health concern, characterized by complex epidemiology due to its multifactorial etiology. Among non-communicable diseases, cancers impose a major burden on society (1) The ovaries are responsible for producing oocytes and the hormones estrogen and progesterone (2). Ovarian cancer is often diagnosed at an advanced stage, after it has spread beyond the ovaries to the pelvis or abdomen (3), with early-stage treatment, typically surgery and chemotherapy—offering better outcomes (4). It is one of the deadliest gynecologic cancers, primarily due to late detection, and mainly affects women aged 40-65 years (5). Lifetime risk in U.S. women is 1.4-1.8%, with epithelial ovarian cancer (EOC) being the most common subtype (6). The incidence is approximately 1 in 55 women, with a mortality rate of about 1 in 100. Early symptoms are vague (e.g., pelvic discomfort, bloating, early satiety, urinary frequency),

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leading to advanced-stage diagnosis with prominent signs like abdominal swelling and nausea. Staging reflects extent of spread (7).

The precise etiology of ovarian cancer remains unclear, which limits the development of effective preventive strategies. Sexually transmitted infections (STIs) are linked to pelvic inflammatory disease and tubal damage; many ovarian cancers originate in the fallopian tubes, increasing risk in women with tubal infertility (8). A hypothesis posits STIs, including herpes simplex virus type 2 (HSV-2), may contribute to ovarian carcinogenesis (9-10). HSV-2 infection is associated with higher rates of other STIs and HIV (11). Despite these associations, the evidence remains inconclusive.

This study aims to investigate the potential association between HSV-2 infection and the risk of ovarian cancer in an Iranian population.

Materials and Methods

A case-control study was conducted at Fatemieh Hospital in Hamadan, Iran, from 2021 to 2022. The study population included 38 women diagnosed with primary ovarian cancer based on pathological confirmation, referred to Fatemieh Hospital or its affiliated clinics, and 38 healthy women matched for age and marital status as controls. Patients with incomplete medical records or those unwilling to participate were excluded.

Data were collected using a standardized checklist that captured demographic information, obstetric history, and serologic test results for HSV-2. Serologic testing was performed using enzyme-linked immunosorbent assay (ELISA) under standard laboratory conditions at Fatemieh Hospital. To encourage participation, serologic testing was provided free of charge to the control group. A census sampling method was used, including all eligible ovarian cancer patients during the study period.

The composite variable "STDs overall" was defined as seropositivity for any of the following infections tested in this study: Chlamydia trachomatis, HSV-2, or co-infection with both. This broad categorization was used to explore the cumulative effect of any sexually transmitted infection, acknowledging that it does not differentiate between specific etiologies.

Statistical analysis was performed using SPSS version 16. Descriptive statistics (mean, standard deviation, proportions, and percentages) were used to summarize the data. Inferential statistics, including the independent t-test, chi-square test, or Fisher's exact test, were applied to compare baseline characteristics and risk factors between groups. Univariate and multivariate logistic regression models were used to estimate odds ratios (ORs) with 95% confidence intervals (CIs). Multivariate models adjusted for age, menopausal status, family history of genital cancer, and urban residence. A P of <0.05 was considered statistically significant. A post-hoc power analysis was performed using G*Power software. With the observed prevalence of HSV-2 (21.1% in cases vs. 7.9% in controls), a sample size of 38 per group, a two-sided alpha level of 0.05, the statistical power to detect a significant difference was approximately 35%, highlighting the risk of type II error. Thus, the non-significant finding for HSV-2 should be interpreted with caution.

Ethical approval was obtained from the Ethics Committee of Hamadan University of Medical Sciences (IR.UMSHA.REC.1401.801), and written informed consent was obtained from all participants. Confidentiality of personal data was strictly maintained throughout the study.

Results

This case-control study included 38 women diagnosed with ovarian cancer between 2021 and 2022 at Fatemieh Hospital, along with 38 age- and marital status-matched healthy controls. Baseline characteristics were comparable between the two groups, with no statistically significant differences in mean age, urban residence, family history of genital cancer, or menopausal status (Table 1).

Among the ovarian cancer cases, 20 patients (52.6%) had epithelial ovarian cancer (EOC), 10 (26.3%) had serous tumors, and 8 (21.1%) had borderline tumors.

The prevalence of *Chlamydia trachomatis* infection and sexually transmitted diseases (STDs) was significantly higher in the case group compared to the control group. Univariate logistic regression analysis showed increased odds of ovarian cancer associated with *C. trachomatis* (OR 4.2, 95% CI: 1.04-16.6), HSV-2 (OR 3.1, 95% CI: 0.7-12.8), and STDs overall (OR 4.8, 95% CI: 1.8-12.7). After adjustment for potential confounders in multivariate analysis, STDs remained independently associated with a 4.8-fold increased odds of ovarian cancer. In multivariate logistic regression analysis adjusting for age, menopausal status, family history of genital cancer, and urban residence, STDs remained independently associated with a 4.8-fold increased odds of ovarian cancer (adjusted OR 4.8, 95% CI: 1.7-13.2, P=0.003). For Chlamydia trachomatis, the adjusted OR was 3.9 (95% CI: 0.9–16.1, P=0.062). For HSV-2, the adjusted OR was 2.8 (95% CI: 0.6–12.4, P=0.174) (Table

2).

No statistically significant associations were observed between these infectious risk factors and specific histologic subtypes of ovarian cancer (Table 3).

Table 1. Comparison of baseline characteristics between study groups

Variable	Control group	Case group	*P*
Age (years), Mean ± SD	55.5 ± 5.8	54.5 ± 5.9	0.479
Urban Residence, n (%)	22 (57.9)	27 (71.0)	0.231
Family History of Genital Cancer, n (%)	3 (7.9)	5 (13.2)	0.711
Menopause, n (%)	20 (52.6)	22 (57.9)	0.645

Table 2. Prevalence of sexually transmitted infections and their association with ovarian cancer – univariate and multivariate analysis

Variable	Control (n=38)	Case (n=38)	Univariate OR (95% CI)	Multivariate OR (95% CI)	*P*
C. trachomatis	3 (7.9)	10 (26.3)	4.2 (1.04–16.6)	3.9 (0.9–16.1)	0.062
HSV-2	3 (7.9)	8 (21.1)	3.1 (0.7–12.8)	2.8 (0.6–12.4)	0.174
STDs	10 (26.3)	24 (63.2)	4.8 (1.8–12.7)	4.8 (1.7–13.2)	0.003

OR: odds ratio, CI: confidence interval, HSV-2: herpes simplex virus type 2, STDs: sexually transmitted diseases. Multivariate model adjusted for age, menopausal status, family history of genital cancer, and urban residence

Table 3. Frequency of risk factors in case group by cancer type

Risk Factor	Serous, n=10 (%)	Borderline, n=8 (%)	Epithelial, n=20 (%)	*P* (chi²)
Chlamydia trachomatis	2 (20.0)	2 (25.0)	6 (30.0)	0.838
HSV-2	3 (30.0)	2 (25.0)	3 (15.0)	0.607
STDs	8 (80.0)	5 (62.5)	11 (55.0)	0.408

HSV-2: herpes simplex virus type 2, STDs: sexually transmitted diseases

Discussion

The findings of this study suggest that recurrent *Chlamydia trachomatis* infection is a potential risk factor for ovarian cancer. Previous studies have indicated that *Chlamydia trachomatis* increases the risk of pelvic inflammatory disease (PID), which may elevate the risk of ovarian cancer through DNA damage, oxidative stress, cytokine production, and pro-inflammatory responses (12-13). A recent meta-analysis by Hosseininasab-Nodoushan *et al*., (11), analyzing 18 studies with a total of 8,207 patients, reported a 32.6% prevalence of *Chlamydia trachomatis* in ovarian cancer patients, increasing the risk by 1.34 times. Trabert *et al*., (14) in 2019 in Poland found that positive *Chlamydia trachomatis* antibodies were associated with a 1.63-fold increased risk in a case-control study (244 cases, 556 controls) and a 1.38-fold increased risk in a prospective nested case-control study (160 cases, 159 controls). Fortner *et al*., (15) in 2019 in Germany reported a 2-fold increased risk with *Chlamydia trachomatis* antibodies in 377 ovarian cancer patients and 377 controls. Idahl *et al*., (16) in 2020 found that positive serology for *Chlamydia trachomatis* (using heat shock protein 60) was associated with a 1.36-fold increased risk for epithelial ovarian cancer and a 1.44-fold increased risk for serous ovarian cancer. Idahl *et al*., (17) in 2011 suggested that *Chlamydia* and *Mycoplasma* antibodies may be associated with epithelial ovarian cancer, supporting the hypothesis of a link between genital infections and ovarian cancer.

Moreover, a 2024 Mendelian randomization (MR) study by Perrott and Kar (18) provided causal evidence linking genetically predicted seropositivity to C. trachomatis (specifically the momp D antibody) with an increased risk of epithelial ovarian cancer (EOC). The study, which analyzed data from over 25,000 EOC cases and 40,000 controls, found a statistically significant association between C. trachomatis and both overall EOC (OR 1.06; 95% CI 1.02-1.10) and high-grade serous EOC (OR 1.08; 95% CI 1.01-1.16). These findings were replicated in independent cohorts, further strengthening the evidence for a causal relationship.

In this study, a higher prevalence of HSV-2 infection was observed in the ovarian cancer group compared to the control group (21.1% vs. 7.9%), though this was not statistically significant (OR 3.1, 95% CI: 0.7-12.8). The wide confidence interval reflects the imprecision of the estimate due to the small sample size. A post-hoc power analysis indicated that the study had only 35% power to detect the observed difference, meaning that a true association could easily be missed (type II error). A larger sample might have yielded a significant association. The relationship between HSV-2 and ovarian cancer remains controversial. Trabert *et al*., (14) found no significant association, while Fortner *et al*., (15) reported a 1.38-fold

increased risk. Idahl *et al.*, (16) in 2020 reported a 2.35-fold increased risk of epithelial ovarian cancer with HSV-2.

Consistent with prior evidence, sexually transmitted diseases (STDs) showed the strongest association with ovarian cancer in this study, possibly due to the synergistic effect of viral and bacterial infections. We acknowledge that the "STDs overall" variable is a composite measure that combines viral (HSV-2) and bacterial (Chlamydia trachomatis) infections. While this approach allowed us to assess the cumulative risk associated with any STI exposure, it precludes attribution of the effect to any single pathogen. The strong association observed (OR 4.8, 95% CI: 1.8-12.7) may reflect synergistic biological effects or simply the higher prevalence of multiple infections in the case group. Future studies should examine individual pathogens separately with adequate power.

The global incidence of STDs, including Chlamydia trachomatis, is rising, with approximately 90 million new cases annually, many of which are asymptomatic and thus undiagnosed or untreated (19). Identifying the consequences of these infections is critical for public health policies and cancer control programs (20). STIs, including bacterial infections like *Chlamydia trachomatis* and *Mycoplasma genitalium* and viral infections like HPV and HSV-2, can cause persistent changes in the female reproductive tract. As modifiable risk factors, their diagnosis and treatment could be key strategies for ovarian cancer control (5).

The mean age of patients in this study was approximately 55 years, with most in their fifth decade, consistent with studies by Janbabaei *et al*., (21) where most ovarian cancer cases were aged 40-60 years. The increased risk with age is expected, as over 80% of new ovarian cancer diagnoses occur in women over 45 years. Younger patients generally have a better prognosis (22).

Menopause, family history of ovarian or breast cancer, and epithelial ovarian cancer with serous or mucinous histology were common in this study, aligning with previous findings. Epithelial ovarian cancer accounts for 80-95% of cases, with serous being the most common subtype. Janbabaei *et al.*, (21) reported 71% epithelial origin, and Rodriguez-Velazquez *et al.*, (23) in 2018 in Puerto Rico found 64.71% serous histology in 170 cases.

The most important limitation of this study is the small sample size, which resulted in low statistical power (approximately 35% for HSV-2). The observed odds ratio of 3.1 for HSV-2, while not statistically significant, suggests a potential effect that may reach significance in a larger cohort. Therefore, our findings should be considered exploratory rather than definitive. Additional limitations include the single-center design, which may limit generalizability to other populations; the reliance on serology without confirmatory PCR testing; the lack of data on duration and recurrence of infections; and the inability to control for all potential confounders such as sexual history, number of partners, and HPV co-infection status. Furthermore, the cross-sectional nature of serology testing cannot establish temporality between infection and cancer development. The small number of cases within each histologic subtype (serous n=10, borderline n=8, epithelial n=20) precluded meaningful subtype-specific analyses. Future studies with sample sizes calculated a priori to achieve adequate power (e.g., at least 150 cases and 150 controls assuming similar effect sizes) are necessary to confirm or refute the association between HSV-2 and ovarian cancer.

Collectively, these findings underscore the potential role of chronic bacterial and viral infections in the pathogenesis of ovarian cancer, highlighting the need for further longitudinal studies to establish causality and inform preventive strategies.

Ovarian cancer imposes a heavy global burden, with unclear etiology. This exploratory study, limited by small sample size, suggests potential associations between C. trachomatis, HSV-2, and STDs with ovarian cancer risk, possibly mediated through chronic inflammation. However, the non-significant finding for HSV-2 should not be interpreted as evidence of no effect given the low statistical power. The observed odds ratio of 3.1, if confirmed in larger studies, would represent a clinically meaningful association. As potentially modifiable factors, STI management could inform prevention strategies, but larger prospective cohort studies with adequate sample sizes are essential before drawing definitive conclusions about HSV-2 and ovarian cancer risk.

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