

**Literature Review**

***Hormonal vs. Non-Hormonal Contraceptives for Women in Relation to Cervical Cancer:  
A Systematic Review***

**Alat Kontrasepsi Hormonal VS Non-Hormonal untuk Wanita Berkaitan dengan Kanker Serviks:  
Sebuah Tinjauan Sistematis**

*Annisa Adhnia Rusfandi, I Wayan Agung Indrawan*

*Department of Obstetrics and Gynecology Faculty of Medicine Universitas Brawijaya Malang*

**ABSTRACT**

*Recent global statistics indicate approximately 527,624 new cases of cervical cancer and 265,672 deaths annually. Additionally, recent research has identified a correlation between cervical cancer incidence and the use of hormonal or non-hormonal contraceptives. This systematic review aims to investigate this correlation. Articles meeting inclusion criteria from Google Scholar and PubMed within the last five years were searched. Eight eligible studies were included: six on hormonal contraceptives and two on non-hormonal contraceptives. The review findings suggest that the use of both non-hormonal and hormonal contraceptives increases the risk of cervical cancer. Non-hormonal contraception was associated with a slightly elevated risk, while hormonal contraceptives, especially oral contraceptive tablets used over an extended period, showed a clear link to increased cervical cancer risk.*

**Keywords:** *Cervical cancer, hormonal contraception, non-hormonal contraception*

**ABSTRAK**

Menurut statistik global terbaru, setiap tahun terdapat sekitar 527.624 kasus baru kanker serviks dan 265.672 kematian akibatnya. Penelitian terbaru menunjukkan adanya korelasi antara kejadian kanker serviks dengan penggunaan kontrasepsi hormonal atau non-hormonal. Tujuan dari penelitian ini adalah untuk mengidentifikasi korelasi ini melalui tinjauan sistematis. Google Scholar dan PubMed digunakan untuk mencari artikel-artikel yang memenuhi kriteria inklusi dan dipublikasikan dalam lima tahun terakhir. Ada delapan studi yang memenuhi syarat, terdiri dari enam studi tentang kontrasepsi hormonal dan dua studi tentang kontrasepsi non-hormonal. Tinjauan ini menemukan bahwa risiko kanker serviks meningkat dengan penggunaan kontrasepsi non-hormonal maupun hormonal. Risiko kanker serviks sedikit meningkat dengan penggunaan kontrasepsi non-hormonal. Di sisi lain, penggunaan kontrasepsi hormonal terkait secara signifikan dengan peningkatan risiko kanker serviks, terutama ketika menggunakan tablet kontrasepsi oral untuk jangka waktu yang lebih lama.

**Kata Kunci:** Kanker serviks, kontrasepsi hormonal, kontrasepsi non-hormonal

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*Correspondence: Annisa Adhnia Rusfandi. Departement of Obstetrics and Gynecology of Medicine Universitas Brawijaya, Jl. Veteran Malang 65145 Tel. +628181333018153 Email: annisa.obgjan23@gmail.com*

DOI: <http://dx.doi.org/10.21776/ub.jkb.2025.033.03.7>

## INTRODUCTION

Cancer is a global topic of concern due to its presence, impact, and aftereffects. It ranks as the leading cause of mortality among non-communicable diseases, with six million people dying from cancer each year (1,2). The 2017 Indonesia Demographic and Health Survey (IDHS) reported that 40% of married women aged 15 to 49 used a family planning method (3). Contraception, defined as the deliberate prevention of pregnancy during sexual activity through various means such as devices, agents, medicines, sexual practices, or surgery, is expected to reduce birth rates, especially in countries with rapid population growth (4,5,6). According to the 2017 IDHS, contraception use increased to 64% in 2017 from 62% in 2012, with 57% of users adopting modern contraception and 6% using traditional methods (3,7). The use of contraception is closely linked to women's reproductive health. Cervical cancer remains one of the most common cancers in women worldwide, with an estimated age-adjusted death rate of 7.3 per 100,000 person-years in 2020 (2,8). Although the exact relationship between contraceptive use and the presence of cervical precancerous lesions and Human Papillomavirus (HPV) infection remains unclear, it is thought that contraceptive use may contribute to the development of cervical cancer.

Oral contraceptives (OC) have been identified by the International Agency for Research on Cancer (IARC) as a cause of cervical cancer (9). Numerous studies have documented the relationship between the usage of various forms of contraception and the prevalence of cancer. For example, the use of oral and injectable hormonal contraceptives increases the risk of developing breast and cervical cancer, whereas using oral tablets alone does not induce the same effects (10). It has been suggested that high estrogen content in oral contraceptives contributes to the development of cervical and breast cancer (11). Conversely, using an intrauterine contraceptive device (IUD) lowers the risk of developing cervical and endometrial malignancies (8). Modern contraceptive methods are safe, highly effective, and provide additional non-contraceptive advantages. Levonorgestrel-containing IUDs help manage heavy menstrual bleeding and the associated iron deficiency, and women who use non-hormonal IUDs have a decreased incidence of endometrial cancer (12).

With the global rising incidence of cancer cases, particularly in underdeveloped nations lacking widespread information on early detection and diagnostics, the scientific community must delineate which contraceptives increase or decrease the risk of various types of cancer (9,12-14).

This systematic review aims to investigate the role of contraceptive use in the development of cervical cancer.

## METHOD

### Literature Search Strategy

Literature was retrieved from PubMed and Google Scholar electronic databases with the following keywords: "hormonal contraception and cervical cancer", "non-hormonal contraception and cervical cancer", and "cervical cancer risk while using contraception".

### Inclusion and Exclusion Criteria

Following the Preferred Reporting Items for Systematic

Reviews and Meta-Analyses (PRISMA) guidelines, literature was screened using the PICOS (Population, Intervention, Comparator, Outcome, and Study Design) framework. Studies were considered feasible if they: 1) were observational studies, 2) involved subjects using hormonal or non-hormonal contraception, 3) included different human groups (users and non-users of contraception), and 4) assessed patients for cervical cancer. Case reports, abstracts only, report meetings, conference proceedings, editorial comments, reviews (systematic literature reviews and meta-analyses), irrelevant studies, inaccessible literature, duplicates, and non-English publications were excluded.

### Systematic Literature Review Process

Following the removal of irrelevant literature, abstracts and titles of relevant literature were assessed. Materials that met the inclusion criteria underwent detailed examination. Data extraction included author names, publication year, country of origin, study design, sample size, mean follow-up duration, overall success rate, and recurrence rate, presented in a tabular format. Figure 1 displays the PRISMA flow diagram outlining the literature selection and review process.

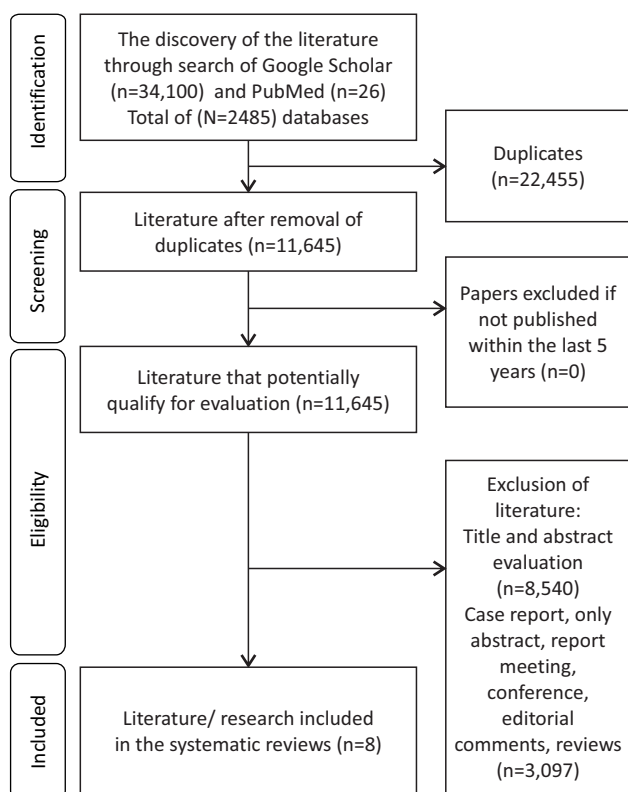


Figure 1. PRISMA diagram that describes the search process for literature review and literature selection

## RESULT

The keywords "hormonal contraception and cervical cancer," "non-hormonal contraception and cervical cancer," and "cervical cancer risk while using contraception" resulted in a total of 34,126 articles in PubMed and Google Scholar. Exclusion criteria included case reports, abstracts, reports from meetings and

**Table 1. Studies in contraceptives associated with cervical cancer incidence**

No	Study	Year Published	Data Collection	Country
1	Arfailasufandi, <i>et al.</i> (15)	2019	2018	Indonesia
2	Dakhal, <i>et al.</i> (16)	2020	2014-2015	Iraq
3	Gul, <i>et al.</i> (13)	2022	2021-2022	Pakistan
4	Iversen, <i>et al.</i> (11)	2021	1995-2014	United Kingdom
5	Loopik, <i>et al.</i> (17)	2019	2017	Netherland
6	Trifitriana, <i>et al.</i> (18)	2019	2016	Indonesia
7	Zin, <i>et al.</i> (19)	2023	2019	Malaysia
8	Zuwariyah, <i>et al.</i> (20)	2021	2018	Indonesia

conferences, editorial comments, reviews, non-primary research, and studies without a summary of results. After screening, 8 articles met the criteria for review, involving a total of 2,607,739 individuals in observational studies assessing the relationship between oral contraceptives (OC) and/or intrauterine devices (IUDs) and the incidence of cervical cancer.

The majority of studies were on Asian middle-income countries, notably Indonesia, which has a significant population where contraception remains crucial. Studies by Trifitriana *et al.*, Zuwariyah *et al.*, and Arfailasufandi *et al.* have consistently reported on the association between hormonal contraceptive use, particularly OC, and increased cervical cancer risk (16,19,21).

Most of the reviewed articles examined hormonal contraceptives, including LNG-IUS, OC, injectables, and

implants. Researchers such as Arfailasufandi *et al.*, Trifitriana *et al.*, and Gul *et al.*, found a substantial correlation between oral contraception and cervical cancer risk (13,15,18). Studies by Iversen *et al.*, Zin *et al.*, and Zuwariyah *et al.*, also highlighted significant associations between hormonal contraceptives and cervical cancer or related infections observed during pap smear examinations (11,19,20).

Two studies explored the impact of non-hormonal contraceptives on cervical cancer risk. Dakhal *et al.*, reported higher rates of IUD-related dysplastic changes and an increased likelihood of cervical cancer progression with this method (16). Meanwhile, research by Loopik *et al.*, comparing hormonal and non-hormonal contraceptives indicated a significant risk of cervical cancer with both methods, with OC users showing a higher risk compared to IUD users (17).

**Table 2. Review from selected studies in contraceptives associated with cervical cancer incidence**

Study	Study Design	Type of Contraceptives	Methodology	Findings
Arfailasufandi, <i>et al.</i> (15)	Case-control	OC	A sample of 200 individuals was chosen, with 100 having cervical cancer and 100 not. Cervical cancer was the dependent variable, while obesity, oral contraceptive use, smoking exposure, parity, age at first sexual encounter, and family history were the independent variables. Data from medical records were analyzed using multiple logistic regression.	The use of oral contraceptives raises the risk of cervical cancer. (OR= 3.43; 95%CI= 1.27 to 9.25; p= 0.015)
Dakhal, <i>et al.</i> (16)	Cross-sectional	OC and IUD	In this study, 237 cases were examined and classified into three groups based on whether they had used OC, IUD, or other forms of contraception for a full year. Pap smears were performed and examined by a specialist cytopathologist.	There was no difference in age, parity, or contraceptive usage duration among the three groups. Most Pap smear results were normal, with 3% showing dysplastic changes and 12.2% showing inflammation. No malignancy was found. Women using non-IUD contraception had more benign dysplastic changes, while IUD users had more inflammatory changes. Dysplastic alterations were significantly correlated with age above 35.
Gul, <i>et al.</i> (13)	Case-control	OC, injectables, and implants	This study involved 300 female patients at various hospitals in Peshawar who had used hormonal contraception for over five years. Conducted between August 1, 2021, and January 30, 2022, the population was divided into two groups: non-users and regular users of hormonal contraception.	In the hormonal group, 98 (65.33%) used injectables, 40 (26.66%) used OCs, and 12 (8%) used implants. Among them, 120 (80%) had been using contraception for up to seven years, and 30 (20%) for longer. Abnormal smear results were found in 3 patients (2%) using

Table 2. Review from selected studies in contraceptives associated with cervical cancer incidence

Study	Study Design	Type of Contraceptives	Methodology	Findings
Gul, <i>et al.</i> (13)	Case-control	OC, injectables, and implants		injectables for over seven years, compared to 2 patients (1.33%) in the control group.
Iversen, <i>et al.</i> (11)	Cohort	OC	The study included all women aged 15 to 49 living in Denmark between 1995 and 2014 (n = 1,904,094), excluding those who moved to Denmark after 1995. Women with prior ovarian stimulating medication therapy, venous thrombosis, hysterectomy, or cancer (excluding non-melanoma skin cancer) were excluded. The final population (n = 1,853,542) was tracked until death, age 50, the end of follow-up on December 31, 2014, or a cervical cancer diagnosis (ICD-10 code C53).	Current or recent users of hormonal contraception have higher risks of cervical cancer: RR 1.30 (95% CI 1.20-1.42) and 1.40 (95% CI 1.28-1.53), but not for progestin-only contraception: RR 0.91 (95% CI 0.78-1.07). Users of chemical contraception were more likely to develop squamous cancer (RR 1.31, 95% CI 1.19-1.44) and adenocarcinoma (RR 1.29, 95% CI 1.05-1.60). Risk patterns increased with longer use and then decreased after cessation, taking longer for prolonged users. Products combining various progestins posed similar risks. Most women in the study were not vaccinated against HPV.
Loopik, <i>et al.</i> (17)	Cross-sectional	OC or IUCD	In this study, 702,037 women were followed for a median of 9.7 years. Dutch women aged 30 to 60 participate in a statewide cervical cancer screening program every five years. Women aged 29 to 44 who took part in the program between January 1, 2005, and December 31, 2009, had a normal cervical smear, and had at least five years of follow-up were included in this retrospective cohort analysis. Data was provided by the Dutch National Registry of Histopathology and Cytology (PALGA). Contraceptive use status was recorded as 'no contraceptive use,' 'oral contraceptive use,' 'IUD use,' 'other,' or 'unknown' on a cervical screening form.	During follow-up, 6705 (0.96%) women developed CIN3 and 559 (0.08%) developed cervical cancer. IUD use was linked to an increased risk of CIN3 (RR 1.51, 95% CI 1.32-1.74), while OC use was linked to an increased risk of both cervical cancer (RR 2.06, 95% CI 1.52-2.79) and CIN3 (RR 2.77, 95% CI 2.65-3.00). OC users had a higher risk of developing CIN3 and cervical cancer compared to IUD users (RR 1.83, 95% CI 1.60-2.09 and RR 1.70, 95% CI 1.00-2.90, respectively).
Trifitriana, <i>et al.</i> (18)	Case-control	OC	The sample included 52 individuals, 26 with cervical cancer and 26 without, from Dr. Mohammad Hosein Palembang Hospital's Obstetrics and Gynecology Department between September and November 2016. Data was primarily collected through interviews. A frequency distribution table was created after univariate analysis to determine correlation and OR.	Among the eight risk factors examined, significant correlations with cervical cancer were found for pathological vaginal discharge (p=0.0005, OR=∞), parity (p=0.0005, OR=22.7), age (p=0.0005, OR=19.2), long-term oral contraceptive use (p=0.0005, OR=12.4), age of first sexual contact (p=0.006, OR=6.1), and the husband's occupation (p=0.05, OR=3.6). Smoking and switching partners did not show significant correlations (p=1.0).
Zin, <i>et al.</i> (19)	Cross-sectional	OC	This study utilized secondary data from HPV DNA test registry books and laboratory request forms, involving 789 women aged 30-49 in 2019. Basic random sampling was employed, and data from the forms were gathered using a proforma and analyzed with SPSS. Results were categorized into HPV infection and non-HPV infection, and multivariable logistic analysis identified variable characteristics associated with HPV infection.	Among women in the new cervical screening, HPV infection prevalence was 8.4% (95% CI 6.4%, 10.3%). Having five or more parities (AdjOR 2.09; 95% CI 1.16, 3.78, p=0.014) and using hormonal contraception (AdjOR 7.48; 95% CI 4.07, 13.76, p<0.001) were significantly associated with HPV infection (AdjOR 2.82; 95% CI 1.58, 5.06, p<0.001).

**Table 2. Review from selected studies in contraceptives associated with cervical cancer incidence**

Study	Study Design	Type of Contraceptives	Methodology	Findings
Zuwariyah, <i>et al.</i> (20)	Cross-sectional	OC	In this study, 30 responders were purposively sampled, with cervical cancer incidence as the dependent variable and hormonal contraceptive usage as the independent variable. Medical data and questionnaires were employed. Data analysis utilized the Rank-Spearman test at $\alpha = 0.05$ significance level.	Most responders (63.3%) used hormonal contraception, with 46.7% classified under pap smear grade 2. Hormonal contraceptive use was associated with increased cervical cancer risk ( $p=0.005$ ).

**Note:** Oral Contraceptive, OC; Intrauterine contraceptive device, IUD.

## DISCUSSION

Research primarily focused on the relationship between the usage of hormonal contraceptives and cervical cancer predominated our search results. Numerous studies have implicated oral contraceptive (OC) use as a cofactor associated with cervical cancer, alongside factors such as immunosuppression, sexual behavior, obesity, and nulliparity (21). However, there is limited evidence demonstrating an overall increase in cancer risk or cancer-related mortality among OC users. Cohort studies are particularly useful for analyzing the overall ratio of benefits and risks associated with OC exposure. In our analysis, Iversen *et al.*, conducted a cohort study of Danish women aged 15 to 49 residing in Denmark from 1995 to 2014 (11). Using the International Classification of Diseases (ICD) 10th edition, the study monitored the entire population until the initial diagnosis of cervical cancer. The study found higher risks of cervical cancer among current or past users of hormonal contraception: RR 1.30 (95% CI 1.20-1.42) and RR 1.40 (95% CI 1.28-1.53), respectively, compared to non-users. Interestingly, there was no significant increase in risk observed among users of progestin-only contraception: RR 0.91 (95% CI 0.78-1.07). It is important to note that the majority of participants in these studies were not vaccinated against HPV (11).

Six publications explore the relationship between hormonal contraception and cervical cancer risk. All these studies consistently found a positive correlation between the duration of hormonal contraceptive use and the risk of cervical cancer. Participants using oral contraceptives (OC) face a significant risk of developing cervical cancer, with those using them for longer durations at notably higher risk. These findings align with a systematic review and meta-analysis conducted by Asthana *et al.*, that also identified a positive association between OC use and cervical cancer (22). They reported significant risks of invasive cancer associated with OC use, with odds ratios (OR) (95% CI) of 1.35 (1.35, 1.68) for unknown HPV status and 1.66 (1.24, 2.21) for known HPV status. They also found substantial correlations with OR (95% CI) of 1.77 (1.40, 2.24), 1.29 (1.18, 1.42), and 1.70 (1.18, 2.44) for adenocarcinoma, squamous cell carcinoma, and carcinoma in situ, respectively. Their findings emphasized that longer-term use of OC tablets significantly increases the risk of cervical cancer, particularly adenocarcinoma (22).

Iversen *et al.*'s study linked cervical cancer to the use of oral contraceptives for an average of 5.87 years. The levonorgestrel-releasing intrauterine system (LNG-IUS)

and desogestrel-containing progestin-only pills are more commonly used by parous women, distinguishing them from other progestin-only products. The increased risk is mainly associated with combined hormonal contraceptives (containing estrogen and progestin), rather than other types. The risk is higher in current or recent users compared to those who have ever used hormonal contraceptives. A key strength of the study is its large cohort of over 1.8 million women, observed for over 21 million person-years. However, the data on progestin-only contraceptives is less clear, and the lingering effects of prior combined contraceptive use make it difficult to reach definitive conclusions (11).

The study by Gut *et al.* found that women who used oral contraceptives for at least 10 years had a fourfold higher risk of cervical cancer compared to those with shorter or no use. However, only three patients using injectable contraceptives for over seven years showed atypical smear results. The study found no link between birth control use and abnormal Pap smear results, indicating the need for further prospective research (13).

The analysis by Arfailasufandi *et al.*, found a significant link between oral contraceptive use and a higher risk of cervical cancer, with women using oral contraceptives for more than five years having a 3.43 times greater risk. However, the study has limitations, as it only shows an association, not causality. Confounding factors like HPV infection and recall bias due to the study's retrospective design could affect the results. Despite the large sample size, the findings may not apply universally. Therefore, further longitudinal research is needed to confirm the results and investigate the causal relationship more thoroughly (15).

Similarly to the previous study, Dakhal *et al.*, observed that women using non-IUD contraception experienced more benign dysplastic changes, while those using IUDs showed more inflammatory changes in their Pap smears. The study suggests that while the use of IUCD and OCP may affect Pap smear results, further research is needed to establish definitive causal links and to account for other potential factors, such as HPV infection (16).

Loopik *et al.*'s study suggested that the use of hormonal contraceptives (OC) is more strongly linked to an increased risk of CIN3+ and cervical cancer compared to intrauterine device (IUD) use with a usage duration of at least 5 years. While both forms of contraception are associated with a heightened risk, oral contraceptive pill users face a higher level of risk than those using IUDs. A possible confounding

factor could be variations in sexual behavior between individuals who use contraception and those who do not (17).

The research by Trifitriana *et al.*, indicated that prolonged use of oral contraceptives (over 4 years) is associated with a significantly higher risk of cervical cancer, with women using birth control pills for more than four years having a 12.4 times greater risk compared to those who used them for a shorter duration or never used them. However, similar to previous studies, the research may be influenced by recall bias, especially regarding sensitive information like sexual behavior or contraceptive use. Additionally, confounding factors such as HPV infection, smoking, and sexual behavior might not have been fully controlled for (18).

The study by Zin *et al.* found that women with five or more children, as well as those using hormonal contraception, were more likely to have HPV infection. These factors were significantly associated with the presence of the virus among participants in the cervical screening program. However, one limitation of the study is the potential for bias, along with the lack of longitudinal data, which makes it difficult to track how long-term exposure to factors like hormonal contraception and the number of children influences the development of HPV infection over time (19).

The study by Zurwariyah *et al.*, demonstrated a link between the use of hormonal contraceptives and the incidence of cervical cancer at the Wisnuwardhana Cancer Foundation in Surabaya. However, this study didn't specify the duration of use or the types of contraceptives that were used. Additionally, without accounting for potential confounding variables, such as HPV status, the study's conclusions may not fully capture the complexities of cervical cancer risk. Further research is needed to clarify these factors (20).

Studies suggest that combined oral contraceptives (which contain both estrogen and progestin) may be associated with a higher risk of cervical cancer, especially with long-term use. Progestin-only contraceptives, while still showing some risk, generally have a lower association compared to combined methods. The link between estrogen doses in combined oral contraceptives and cervical cancer risk is not fully agreed upon in research. Most of the studies included in the analysis focused on the risk of cervical cancer among the first generation of combined oral contraceptive users. These users were exposed to formulations containing high (50µg or more) or medium (30-35µg) doses of estrogen, combined with older progestins. However, higher estrogen doses in older contraceptive formulations have been associated with greater risks, while lower doses (20-35µg) tend to carry less risk. Modern low-dose contraceptives (20-30mcg) show reduced risk but still present some risk, particularly with prolonged use and the presence of HPV infection. Meanwhile, the risk of cervical cancer related to progestin doses in hormonal contraceptives is less clear compared to estrogen (11).

The transformation zone is where the majority of cervical cancers originate. Persistent infections resulting from HPV-DNA integration into the host genome may result in high-grade cervical lesions and eventually progress to invasive cervical cancer, whereas episomal HPV infections typically manifest as low-grade cervical lesions with a lower risk of progression. The HPV genome consists of late genes encoding the capsid proteins, early genes (E1, E2,

E4, E5, E6, E7) important in controlling the vegetative and productive stages of the virus life cycle, along with a non-coding regulatory region involved in transcription regulation and viral replication (9,23). Human papillomavirus (hrHPV) oncogenic strains, commonly referred to as high-risk strains, such as types 16, 18, 31, 33, 35, 45, 52, and 58, are required but not sufficient causes of cervical cancer. Cervical dysplasia can be identified and treated early by screening for hrHPV types and immunization, although not all women receive these services (1,2). Despite the effectiveness of these preventive measures, implementing outreach initiatives in regions with inadequate healthcare systems, including many middle-income nations, presents challenges. Efforts to expand vaccination and screening coverage are strongly advocated. OC usage is one factor that has been linked to an increased risk of hrHPV infection progressing to cervical dysplasia or cancer (2,4,11).

The proximity of the cervical canal to the device may influence the malignant potential of an intrauterine device (IUD). The transformation zone not only serves as a primary site for cell-mediated immune responses but is also a target for HPV. During IUD insertion, alterations to the tissue beneath the transformation zone could potentially trigger an immunological response. Damage to tissue during insertion may activate a cellular immune response that could help eradicate preinvasive lesions and persistent HPV infections (8,24).

According to Loopik *et al.*, the use of levonorgestrel IUD marginally increases the incidence of CIN2, but there is no correlation between CIN3 and cervical cancer (16). In contrast, the use of copper IUDs shows no correlation with cervical intraepithelial neoplasia 2 (CIN2) or 3 (CIN3) and is associated with a decreased risk of cervical cancer. This may be due to the low-grade, persistent, and sterile inflammation described by Castellsagué *et al.*, which enhances localized cervical immunity. Additionally, the copper IUD may create an environment unfavorable for HPV survival. A meta-analysis by Cortessis *et al.*, also found that women using IUDs had a lower incidence of cervical cancer (summary odds ratio 0.64, 95% confidence interval 0.53–0.77) (25).

The studies suggest that both non-hormonal and hormonal contraception increase the risk of cervical cancer. Levonorgestrel IUDs slightly increase the risk of CIN2 but not CIN3 or cervical cancer, while copper IUDs do not increase cancer risk. Hormonal contraceptives, especially oral contraceptives, are linked to a higher risk, particularly with long-term use. Injectable and implantable hormonal contraception also raise cervical cancer risk, though research on these methods is limited. Limitations of the studies include lack of data on contraceptive doses, duration, and insufficient control for confounding factors like HPV, requires further investigation.

#### ACKNOWLEDGMENTS

The authors would like to thank Dr. I Wayan Agung Indrawan, Sp.O.G., Subsp. Obygynsos, FisQua, for his guidance and support.

#### FUNDING

*The authors received no financial support for the research,*

authorship, and/or publication of this article.

#### CONFLICT OF INTEREST

The authors declare no conflict of interest.

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