

# Hormonal Contraception and Cervical Cancer Stage: Does Duration of Use Matter? Evidence from Indonesia

Meta Zulyati Oktora<sup>1\*</sup>, Niken Safitri<sup>1</sup>, Nadia Purnama Dewi<sup>1</sup>,  
Primadella Fegita<sup>1</sup>, Desi Aliefia<sup>1</sup>

<sup>1</sup> Medical Faculty of Baiturrahmah University, Padang, Indonesia

Email : [metazulyantioktora@fk.unbrah.aci.id](mailto:metazulyantioktora@fk.unbrah.aci.id)

## Abstract

**Background:** Cervical cancer remains a major public health problem in Indonesia, ranking as the second most common cancer among women. Hormonal contraceptives are widely used, and long-term exposure has been hypothesized to promote cervical carcinogenesis through hormonal modulation of HPV oncogene expression and epithelial proliferation. However, limited evidence is available on their association with the stage of cervical cancer at diagnosis in Indonesian populations. **Objective:** To examine the association between the duration of hormonal contraceptive use and the clinical stage of cervical cancer among patients at Dr. M. Djamil General Hospital, Padang, Indonesia. **Methods:** A cross-sectional analytic study was conducted involving 80 randomly selected patients from 222 cervical cancer cases in 2019. Data on age, age at marriage, parity, type and duration of contraceptive use, and cervical cancer stage (FIGO classification) were retrieved from medical records. Descriptive statistics were presented as frequencies and percentages, while bivariate associations were analyzed using the Mann–Whitney U test (SPSS v25). **Results:** The majority of patients were aged 46–55 years (38.6%), married after age 20 (57.1%), multiparous (80%), and predominantly used injectable contraceptives (62.9%). More than half had used hormonal contraceptives for <5 years (55.7%). Cervical cancer was most frequently diagnosed at stage III (47.1%). A statistically significant association was observed between longer duration of hormonal contraceptive use and more advanced cervical cancer stage ( $p = 0.008$ ). **Conclusion:** Prolonged hormonal contraceptive use is significantly associated with advanced cervical cancer stage at diagnosis. These findings highlight the need for targeted counseling and routine cervical cancer screening in women using long-term hormonal contraceptives to facilitate earlier detection and improve clinical outcomes.

**Keywords:** Cervical cancer, hormonal contraceptives, duration of use, FIGO stage, Indonesia

## Abstrak

**Latar Belakang:** Kanker serviks masih menjadi masalah kesehatan masyarakat utama di Indonesia, menempati peringkat kedua sebagai kanker tersering pada perempuan. Kontrasepsi hormonal banyak digunakan, dan paparan jangka panjang diduga memicu karsinogenesis serviks melalui modulasi hormonal ekspresi onkogen HPV dan proliferasi epitel. Namun, bukti yang tersedia mengenai hubungannya dengan stadium kanker serviks saat diagnosis pada populasi Indonesia masih terbatas. **Tujuan:** Untuk mengkaji hubungan antara durasi penggunaan kontrasepsi hormonal dan stadium klinis kanker serviks pada pasien di Rumah Sakit Umum Dr. M. Djamil, Padang, Indonesia. **Metode:** Sebuah studi analitik cross-sectional dilakukan dengan melibatkan 80 pasien yang dipilih secara acak dari 222 kasus kanker serviks pada tahun 2019. Data tentang usia, usia saat menikah, paritas, jenis dan durasi penggunaan kontrasepsi, dan stadium kanker serviks (klasifikasi FIGO) diambil dari rekam medis. Statistik deskriptif disajikan sebagai frekuensi dan persentase, sementara hubungan bivariat dianalisis menggunakan uji Mann–Whitney U (SPSS v25). **Hasil:** Mayoritas pasien berusia 46–55 tahun (38,6%), menikah setelah usia 20 (57,1%), multipara (80%), dan sebagian besar menggunakan kontrasepsi suntik (62,9%). Lebih dari separuh telah menggunakan kontrasepsi hormonal selama <5 tahun (55,7%). Kanker serviks paling sering didiagnosis pada stadium III (47,1%). Hubungan yang signifikan secara

statistik diamati antara durasi penggunaan kontrasepsi hormonal yang lebih lama dan stadium kanker serviks yang lebih lanjut ( $p = 0,008$ ). **Kesimpulan:** Penggunaan kontrasepsi hormonal jangka panjang berhubungan signifikan dengan stadium kanker serviks lanjut saat diagnosis. Temuan ini menyoroti perlunya konseling terarah dan skrining kanker serviks rutin pada perempuan yang menggunakan kontrasepsi hormonal jangka panjang untuk memfasilitasi deteksi dini dan meningkatkan luaran klinis.

**Kata kunci:** Kanker serviks, kontrasepsi hormonal, lama penggunaan, stadium FIGO, Indonesia

## I. INTRODUCTION

Cervical cancer remains a significant public health concern, ranking as the fourth most common cancer among women globally, with an estimated 604,000 new cases and 342,000 deaths in 2020—where 90% of cases occur in low- and middle-income countries<sup>1</sup>. A meta-analysis by Damayanti et al. (2023) demonstrated that long-term hormonal contraceptive use increased the risk of cervical cancer more than twofold (aOR=2.34, 95% CI=1.83–4.66), particularly for users of five years or longer<sup>2</sup>.

While human papillomavirus (HPV) infection is the primary etiological factor in cervical carcinogenesis, accumulating evidence suggests that long-term use of hormonal contraceptives may further elevate risk, especially in HPV-positive individuals.<sup>3</sup> A recent meta-analysis reported that women using hormonal contraceptives have more than twice the odds of developing cervical cancer (adjusted odds ratio [aOR] = 2.34; 95% CI: 1.83–4.66;  $p < 0.001$ ) compared to non-users.<sup>2</sup> Notably, this study underscores the magnitude of risk associated with exposure duration and reinforces the need for population-specific insight within Asia and Africa.<sup>2</sup>

Regionally, Kusmiyati et al. (2019) reported a more than fourfold increased risk of cervical cancer—after adjusting for age—among women who used hormonal contraception for over five years (OR  $\approx$  4.2; 95% CI: 1.01–5.69) in a hospital-based case-control study in Yogyakarta, Indonesia.<sup>4</sup> These findings are further supported by recent mechanistic and epidemiological studies, which demonstrated that oral contraceptive use is significantly associated with cervical cancer risk (e.g., OR ranging 1.5–3.3), particularly for durations exceeding five years and among HPV-positive women.<sup>3,5</sup> A 2025 study also highlighted the heightened risk of cervical intraepithelial neoplasia grades 2 and 3 (CIN 2/3) with oral

contraceptive use exceeding five years, reporting odds ratios up to 9.11 in some analyses.<sup>6</sup>

Despite this growing body of evidence, the association between duration of hormonal contraceptive use and the clinical stage at diagnosis of cervical cancer remains underexplored, particularly in the Indonesian setting. Understanding this relationship is clinically relevant, as advanced stage at diagnosis is strongly linked to poorer prognoses, limited treatment options, and higher mortality. Moreover, hormonal contraceptives are widely used in reproductive health programs across Indonesia, creating a critical need for evidence-based guidance for clinicians and policymakers.

Accordingly, this study investigates the association between the duration of hormonal contraceptive use and cervical cancer stage at diagnosis among patients treated at Dr. M. Djamil General Hospital, Padang. Such insight is essential to inform tailored prevention strategies, including screening protocols and patient counseling for long-term contraceptive users.

## II. METHODS

This study employed an analytical observational design with a cross-sectional approach and was conducted at Dr. M. Djamil General Hospital, Padang, Indonesia, a tertiary referral center for oncology services in West Sumatra. Data collection took place between September 2020 and April 2021. The study population consisted of all 222 patients diagnosed with cervical cancer in 2019, from which 80 patients were selected using a simple random sampling technique. Patients were included if they had a histopathologically confirmed diagnosis of cervical cancer and complete medical records documenting their reproductive history and contraceptive use. Patients with incomplete records or a history of

hysterectomy prior to diagnosis were excluded from the study.

The main independent variable was the duration of hormonal contraceptive use, categorized into <5 years and ≥5 years. The dependent variable was the stage of cervical cancer at diagnosis, which was classified based on the International Federation of Gynecology and Obstetrics (FIGO) 2018 staging system. Additional variables analyzed included patient age, age at marriage, parity, and type of hormonal contraceptive used. Data was collected from hospital medical records using a structured checklist, and all identifying information was removed to ensure confidentiality.

Data analysis was performed in two stages. First, descriptive statistics were used to present the frequency distribution of patient characteristics, contraceptive use, and cancer stage. Second, the relationship between the duration of hormonal contraceptive use and cervical cancer stage was examined using the Mann–Whitney U test, given the ordinal nature of staging data. A p-value <0.05 was considered statistically significant. Statistical analyses were performed using SPSS version 25.0 (IBM Corp., Armonk, NY, USA).

This study obtained ethical approval from the Research Ethics Committee of Universitas Baiturrahmah, Padang (approval number 050/ETIK-FKUNBRAH/03/04/2021) and research permission from the Director of Dr. M. Djamil General Hospital. All study procedures adhered to the ethical principles outlined in the Declaration of Helsinki (2013 revision).

### III. RESULTS

#### Patient Characteristics

Table 1 presents the distribution of cervical cancer patients according to demographic and reproductive characteristics. The majority of patients were aged 46–55 years (38.6%), with most having married at age

>20 years (57.1%). Multiparity was dominant, found in 80.0% of patients. Regarding contraceptive type, injectable contraceptives were the most common (62.9%), while oral pills and implants were less frequently reported. More than half of the patients had used hormonal contraceptives for <5 years (55.7%). At diagnosis, the majority of patients presented with stage III cervical cancer (47.1%).

**TABLE 1. DISTRIBUTION OF CERVICAL CANCER PATIENTS BY DEMOGRAPHIC AND CLINICAL CHARACTERISTICS (N=80)**

Variable	n	%
<b>Age group</b>		
26–35 years	13	18.6
36–45 years	20	28.6
46–55 years	27	38.6
≥56 years	20	14.2
<b>Age at marriage</b>		
≤20 years	30	42.9
>20 years	40	57.1
<b>Parity</b>		
Multiparous (≥3)	56	80.0
Primiparous (1–2)	14	20.0
<b>Type of hormonal contraceptive</b>		
Injectable	44	62.9
Oral pill	20	28.6
Implant	6	8.5
<b>Duration of contraceptive use</b>		
<5 years	39	55.7
≥5 years	31	44.3
<b>Stage of cervical cancer (FIGO)</b>		
Stage I	12	17.1
Stage II	23	32.8
Stage III	33	47.1
Stage IV	12	17.1

#### Association between Duration of Hormonal Contraceptive Use and Cancer Stage

Bivariate analysis using the Mann–Whitney U test demonstrated a statistically significant association between the duration of hormonal contraceptive use and cervical cancer stage (p = 0.008). Patients who used hormonal contraceptives for ≥5 years were more likely to be diagnosed at advanced stages (III–IV) compared to those with shorter duration (<5 years).

**TABLE 2. ASSOCIATION BETWEEN DURATION OF HORMONAL CONTRACEPTIVE USE AND CERVICAL CANCER STAGE**

Duration of use	Early stage (I-II)	Advanced Stage (III-IV)	p-value
<5 years (n=39)	22 (56,4%)	17 (43,6%)	0.008
≥5 years (n=31)	8 (25,8%)	23 (74,2%)	

The findings indicate that longer duration of hormonal contraceptive use is strongly correlated with more advanced stages of cervical cancer at diagnosis. Specifically, nearly three-quarters (74.2%) of women with contraceptive use ≥5 years were diagnosed at stage III or IV, compared to only 43.6% among those with <5 years of use. This suggests that prolonged hormonal exposure may play a role not only in cervical carcinogenesis but also in disease progression.

#### IV. DISCUSSION

In this hospital-based cross-sectional study, longer duration of hormonal contraceptive use (≥5 years) was significantly associated with a more advanced stage of cervical cancer at diagnosis (III–IV vs I–II; p=0.008). The direction and magnitude of this association are consistent with prior evidence that prolonged exposure to combined or progestin-only hormonal methods is linked to increased cervical cancer risk, particularly among women with persistent high-risk HPV infection. While most published work has focused on incidence rather than stage at presentation, our findings suggest that extended hormonal exposure may also be a correlate of later clinical stage at diagnosis in this Indonesian cohort.

A duration–response relationship has been consistently reported. A meta-analysis by Damayanti et al. (2023) found that women with long-term hormonal contraceptive use had more than double the risk of cervical cancer compared to non-users (aOR=2.34, 95% CI=1.83–4.66) kontrasepsi. Similarly, Kusmiyati et al. (2019) in Yogyakarta

reported a fourfold increased risk among users exceeding five years kontrasepsi. More recent observational studies in Asia confirmed heightened odds of cervical intraepithelial neoplasia (CIN 2/3) and invasive cancer after ≥5 years of oral contraceptive use, with odds ratios ranging between 3 and 9, underscoring the cumulative effect of hormonal exposure.<sup>1,7</sup>

Biological plausibility for a hormonal cofactor in HPV-driven carcinogenesis is strong. Persistent infection with high-risk HPV (notably 16/18) facilitates viral DNA integration and expression of E6 and E7 oncoproteins, which inactivate p53 and Rb, deregulate the cell cycle, and promote genomic instability. Estrogen- and progesterone-responsive elements within the HPV long control region (LCR) and host pathways can up-modulate E6/E7 transcription, supporting persistence and progression from high-grade intraepithelial disease to invasion. Recent mechanistic reviews detail how steroid hormone signaling intersects with HPV gene regulation and the cervical microenvironment, offering a coherent framework that aligns with the observed epidemiology.<sup>8,9</sup>

Globocan 2023 reported 36,964 new cervical cancer cases and 20,708 deaths in Indonesia, reflecting the persistent challenge of late-stage presentation. In alignment with the WHO 2020 elimination strategy (“90–70–90” targets), integrating family planning services with HPV-based screening and follow-up could reduce advanced-stage diagnoses among long-term hormonal contraceptive users.<sup>10</sup>

Our study’s clinical implications are threefold. First, counseling for women considering or already using hormonal contraception long-term should incorporate balanced discussion of benefits and potential cancer risks, while emphasizing that risk is primarily mediated by HPV and may

diminish after cessation. Second, prioritizing routine HPV-based screening for long-term users—especially those aged  $\geq 35$  and multiparous—may facilitate earlier detection and improved outcomes. Third, aligning oncologic care pathways with the FIGO 2018 staging framework—now incorporating imaging/pathology for stage allocation—enhances staging accuracy and comparability across studies, a consideration for future multicenter Indonesian cohorts.<sup>11,12</sup>

Strengths of this work include the use of a clearly defined hospital cohort, random sampling from a well-characterized 2019 case frame, and staging according to FIGO 2018. However, limitations merit emphasis. The cross-sectional design precludes causal inference; lack of HPV status, sexual behavior variables, and screening history limits confounder control; and medical-record abstraction may introduce information bias. Given the observed association with stage at diagnosis, future research should adopt prospective designs with HPV genotyping, detailed contraceptive exposure histories (type, dose, cyclicality, cumulative duration), and multivariable adjustment for screening participation, parity, smoking, and socioeconomic factors.<sup>12</sup>

## V. CONCLUSION

This study demonstrates that prolonged hormonal contraceptive use ( $\geq 5$  years) is significantly associated with advanced cervical cancer stage at diagnosis among women treated at a tertiary referral hospital in West Sumatra, Indonesia. These findings provide local evidence that complements global data on the duration-dependent role of hormonal contraception in cervical carcinogenesis, particularly in HPV-endemic settings.

The results underscore the importance of integrating counseling into contraceptive choices with cervical cancer prevention strategies, including regular HPV-based

screening and timely follow-up. Strengthening the linkage between family planning and cancer control programs could help reduce late-stage presentation and improve patient outcomes.

Future research should employ prospective multicenter designs with HPV genotyping and more comprehensive assessment of contraceptive exposure to clarify causal mechanisms and guide public health recommendations. This study is limited by its cross-sectional design, absence of HPV status and screening history, and reliance on medical record abstraction, which may introduce bias.

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