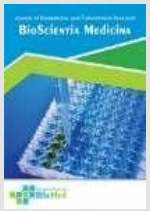
eISSN (Online): 2598-0580



Bioscientia Medicina: Journal of Biomedicine & Translational Research

Journal Homepage: www.bioscmed.com

Passive Smoking as a Significant Risk Factor of Cervical Dysplasia: A Novel Findings in Single Center Study in Denpasar, Bali, Indonesia

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ARTICLE INFO

Keywords:
Cervical cancer screening
Cervical dysplasia
Colposcopy
Risk factors

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All authors have reviewed and approved the final version of the manuscript.

https://doi.org/10.37275/bsm.v8i11.1126

A B S T R A C T

Background: Colposcopy is a diagnostic procedure evaluating the cervix following an abnormal screening test. It aims to identify and treat cervical cancer precursors. Risk stratification at the end of colposcopy helps differentiate those who can return to regular screening from those needing more frequent screening or surveillance. The study examined the characteristics and risk factors of patients undergoing colposcopy for cervical dysplasia in Denpasar, Bali, Indonesia. **Methods:** This was a cross-sectional study of women who underwent colposcopy at BaliMed Hospital, Denpasar, Bali, Indonesia, from January 2021-December 2022. Data were derived from medical records. The gynecology oncologist performed a colposcopy examination with a biopsy sample, which was later checked by the pathologist. Bivariate and multivariate analyses were used to identify the risk factors associated with cervical dysplasia**. Results:** 142 patients underwent colposcopy with a mean age of 37.28+10.1 years. Seventy-eight patients (54.9%) had a low-grade cervical lesion, and 9 (6.3%) had a high-grade cervical lesion. After adjusting the employment status and education level, factors associated with cervical dysplasia were age at first intercourse <20 years (aOR [adjusted odd ratio] 2.44, 95% CI [1.04-5.69]) and history of smoking, either actively or passively (aOR 8.91, 95% CI [3.52-22.54]). From the biopsy result, patients with abnormal cervical lesions were associated with evidence of CIN (aOR 9.03, 95% CI [2.49-32.77]). **Conclusion:** Early age first sexual intercourse and history of smoking have been identified as significant risk factors for cervical dysplasia. Additionally, passive smoking has been shown to increase the risk. This research provides a foundational reference for future studies in this area.

1. Introduction

Cervical cancer is a major health concern for women and ranks as the fourth most common type of cancer worldwide. According to the Global Cancer Incidence, Mortality and Prevalence (GLOBOCAN), there has been an increasing trend in the incidence and mortality rates of cervical cancer globally. This disease is responsible for approximately 527,624 new cases and 265,672 deaths each year.[1,2] Cervical cancer ranks as the second most prevalent cancer type among women in Southeast Asia and is a primary contributor to cancer-related fatalities, especially in low and middle-income countries (LMICs).[3]

In Indonesia, there has been a 17% increase in the number of women diagnosed with cervical cancer, rising from 7.4 to 8.7 cases per 100,000 women. Additionally, the prevalence rate has gone up by 20.8%, from 43.3 to 52.4 cases per 100,000 women. Despite these increases, the death rate has remained relatively steady, at 3.3 and 3.7 cases per 100,000

women, respectively.[4] The Indonesian Ministry of Health reported that the yearly incidence of cervical cancer was 100 out of 100,000 individuals. Without preventative measures, this number is projected to increase by 25% over the next decade. Given Indonesia's high incidence of cancer, collecting accurate data to inform future cancer prevention is crucial. As the fourth most populous country in the world with over 260 million people, improving Indonesia's cancer epidemiological data will make a valuable contribution to the GLOBOCAN model.[5,6]

Cervical dysplasia, also known as cervical intraepithelial neoplasm (CIN), is primarily caused by the human papillomavirus (HPV). The most high-risk types are HPV 16 and 18, which are responsible for 66% of cervical cancers. Other types, such as HPV types 31, 33, 45, 52, and 58, account for 15% of cases. Research indicates that smoking cigarettes can elevate the risk of developing cervical cancer, particularly when combined with HPV infection.[7] However, the correlation between smoking and HPV appears to decrease upon smoking cessation.[8,9] Precancerous lesions in the cervix are typically the result of an HPV infection and can be affected by multiple risk factors. These factors include older age, early marriage, multiple sexual partners, sexually transmitted infections, having numerous children, using contraception, smoking, and low socioeconomic status. These risk factors contribute to the development of abnormal cells that can lead to cervical cancer.[10,11] This study conducted a thorough analysis to investigate the distinguishing features and potential risk factors of patients who underwent colposcopy for cervical dysplasia in the Indonesian demographic. The aim was to gain a deeper understanding of this specific population and the factors that may contribute to the development of cervical dysplasia.

2. Methods

This research was a cross-sectional study involving women who underwent colposcopy examinations at BaliMed Hospital in Denpasar, Bali, Indonesia, from January 2021 to December 2022. All information was obtained from medical records. Maternal medical history was documented through interviews and standard physical examinations. A gynecologist performed the colposcopy examination based on the recommended protocol. Later, a biopsy sample was taken by the gynecologist and checked by the pathologist. The inclusion criteria were all women who underwent colposcopy and were willing to participate during the research period. Patients with confirmed squamous cell carcinoma (SCC) or adenocarcinoma of the cervix were excluded. Each participant signed an informed consent approved by the Ethics Committee according to the Ethics Commission Faculty of Medicine Udayana University No.694/UN14.2.2.VII.14/LT/2023 with approval number from BaliMed Hospital Denpasar of 421/TU/RSBM/EXT/IV/2023 before enrolling in the study.

The population characteristics were divided based on demographic factors, maternal and medical history, and colposcopy results. The demographic factors included age (stated in mean + SD and <40 or >40 years old), body mass index or BMI (displayed in mean + SD, and normal with BMI <25 kg/m^2 or obesity with BMI >25 kg/m^2), in this study, BMI was calculated by dividing a person's weight in kilograms by the square of their height in meters, and it is used to assess the degree of obesity or underweight in individuals.[12] In this study, the Asia-Pacific BMI classification was used, which divides BMI into four categories based on the Asian-Pacific cut-off points: underweight (<18.5 kg/m^2), normal weight (18.5 –22.9 kg/m^2), overweight (23–24.9 kg/m^2), and obese (≥25 kg/m^2). Employment status (on a job or without a job), and education level (high education, if graduated from high school/equivalent, or low education, if graduated from less than high school/equivalent or not having an education at all). Maternal and medical history included age at first sexual intercourse (<20 or >20 years old), history of smoking (yes or no, with active smoking, if the patient actively smoked, and passive smoking, if there were any family members, specifically the patient's husband, who smoked while

residing in the same household), parity (nulliparous/<3 or >3 times), and blood pressure (normotension or hypertension). Hypertension was classified as systolic blood pressure (SBP) greater than 140 or diastolic blood pressure (DBP) greater than 90 mmHg, which follows the ESC hypertension guidelines 2018 and can be used across age groups. In this study, office blood pressure was measured using a pre-calibrated sphygmomanometer for blood pressure examination. Colposcopy results were divided into several categories: normal, low-grade squamous intraepithelial lesions (LSIL) or low-grade cervical lesions, high-grade squamous intraepithelial lesions (HSIL) or high-grade cervical lesions, cervical mass, or others (including cervical erosion).

Cervical dysplasia is an abnormal growth of cells on the surface of the cervix, known to be precancerous. We defined cervical dysplasia based on the pathologic anatomy report of the lesion biopsy. We classified the outcome into cervical dysplasia if it was categorized to CIN 1, CIN 2, or CIN 3, and non-cervical dysplasia for other results, including chronic cervicitis and cervical polyp. Our data were numerical, reported with mean ± standard deviation (SD), and categorical, narrated with n (%). We compared the characteristics of the study population to the outcome groups using the chi-square test. The risk factors associated with cervical dysplasia were identified using univariate and multivariable binary logistic regression analyses. The p-value for significant data was 0.05. There were also odds ratios (ORs) and a 95% confidence interval (CI) calculated. SPSS version 26 (IBM Corp., Armonk, NY, USA) was used for data analysis.

3. Results

A total of 142 patients were included in the analysis. The average age of the population was 37.28+10.1 years, and the majority were under 40 (58.4%). The patients' average body mass index (BMI) was 21.86+2.16 kg/m^2. The majority of patients had a high level of education and under-employment. The incidence of cervical dysplasia in our population was 21.2%, with the most common dysplasia found were low-grade squamous intraepithelial lesions (LSIL) in 78 patients (54.9%), followed by high-grade squamous intraepithelial lesions (HSIL) in 9 patients (6.3%), cervical mass in 7 patients (4.9%). From the cervical dysplasia biopsy results, CIN 1 was the most common and seen in 19 patients (63.3%), followed by CIN 2 in 9 patients (30%) and CIN 3 in 2 patients (6.7%). In the non-cervical dysplasia group, chronic cervicitis is the most common abnormal finding (45.5%). Table 1 compares the patients' baseline characteristics between the different outcome groups. Bivariate analysis showed significant risk factors for cervical dysplasia, such as earlier first sexual intercourse (p-value=0.037) and smoking history (p-value=0.000).

Table 2 shows the multivariate analysis for cervical dysplasia risk factors. From the crude analysis, factors associated with cervical dysplasia were age at first intercourse (crude odds ratio [cOR] 2.39, 95% CI [1.04-5.48]) and history of smoking (COR 8.45, 95% CI [3.42-20.88]). After adjusting the employment status and education level, factors associated with cervical dysplasia were age at first intercourse <20 years (aOR [adjusted odd ratio] 2.44, 95% CI [1.04-5.69]) and history of smoking, either actively or passively (aOR 8.91, 95% CI [3.52-22.54]). From the biopsy result, patients with high-grade cervical lesions were associated with evidence of CIN (aOR 9.03, 95% CI [2.49-32.77]). This study also investigated whether there were any notable differences between patients who actively smoke and those exposed to secondhand smoke, generally called passive smokers. The results showed a significant correlation between passive smokers and non-smokers, with a cOR of 25.04, 95% CI (6.28-99.71) and aOR of 24.77, 95% CI (6.19-99.03).

Table 1. Bivariate analysis of the study population characteristic and the colposcopy result.

Variable		Non-cervical dysplasia		Cervical dysplasia		p-value
		n= 112	%	n= 30	%	
Age	Mean: 37.28±10.1					
	<40 years	65	58.0	18	60	0.846
	≥40 years	47	42.0	12	40	
BMI	Mean: 21.86±2.16					
	Normal	100	89.3	25	83.3	0.372
	Obesity	12	10.7	5	16.7	
Employment	On a job	80	71.4	21	70.0	0.878
	Without job	32	28.6	9	30.0	
Education	High education	77	68.8	20	66.7	0.828
	Low education	35	31.2	10	33.3	
Age at first intercourse	≥20 years	82	73.2	16	53.3	0.037
	< 20 years	30	26.8	14	46.7	
Smoking	Non-smoker	89	79.5	4	13.3	0.000
	Active smoker	15	13.4	17	56.7	
	Passive smoker	8	7.1	9	30.0	
Parity	<3	84	75.9	21	70.0	0.580
	≥3	28	25.0	9	30.0	
Blood pressure	Normal	95	84.8	26	86.7	0.800
	Hypertension	17	15.2	4	13.3	
Colposcopy	Normal	42	37.5	1	3.3	0.006
	Low grade	54	48.2	24	80.0	
	High grade	6	5.4	3	10.0	
	Cervical mass	6	5.4	1	3.3	
	Others	4	3.6	1	3.3	
Pathology anatomy	CIN 1	0	0	19	63.3	0.000
	CIN 2	0	0	9	30.0	
	CIN 3	0	0	2	6.7	
	Chronic cervicitis	51	45.5	0	0	
	Others	10	8.9	0	0	
	Did not performed	51	45.5	0	0	

Note. BMI: body mass index; CIN: cervical-intraepithelial neoplasm.

Table 2. Multivariate analysis of the study population characteristics with cervical dysplasia incidence.

Variables	cOR (95% CI)	p-value	aOR (95% CI)	p-value
Age (years) - ≥40	0.92 (0.41-2.09)	0.846	0.92 (0.41-2.10)	0.849
BMI - Obesity	1.66 (0.53-5.16)	0.376	1.68 (0.54-5.27)	0.367
On a job – Without a job	1.07 (0.44-2.58)	0.878	Adjusted	-
Education - Low	1.10 (0.46-2.59)	0.828	Adjusted	-
Age at first intercourse (years)- <20	2.39 (1.04-5.48)	0.040	2.44 (1.04-5.69)	0.039
Smoking - Active Smoker	8.45 (3.42-20.88)	0.000	8.91 (3.52-22.54)	0.000
Active vs Passive Smoker	1.01 (0.31 - 3.27)	0.990	1.07 (0.32 - 3.60)	0.918
Passive vs Non-Smoker	25.04 (6.28 - 99.71)	0.000	24.77 (6.19 - 99.03)	0.000
Parity - ≥3	1.28 (0.52-3.13)	0.580	1.28 (0.52-3.12)	0.584
Blood pressure - Hypertension	0.86 (0.26-2.77)	0.801	0.83 (0.25-2.76)	0.767
Colposcopy - Low-High Grade	7.80 (2.23-27.20)	0.001	9.03 (2.49-32.77)	0.001

Note: BMI: body mass index; CIN: cervical-intraepithelial neoplasm; cOR: crude odd ratio; aOR: adjusted odd ratio; CI: confidence interval.

4. Discussion

Cervical cancer poses a significant health threat to women globally, particularly in developing nations, where approximately 80% of cases are reported. Various risk factors, including smoking, use of oral contraceptive pills, nutritional deficiencies, early marriage, sexual activity before the age of 18, multiple sexual partners, multiparity, HPV infection, and HIV infection, contribute to the development of cervical dysplasia and cancer.[13,14]

LSIL, or low-grade squamous intraepithelial lesion, is the result of a transient HPV infection known as koilocytosis and mild dysplasia or cervical intraepithelial neoplasia. The majority of women with LSIL test positive for HPV, and 90% of them experience spontaneous clearance within two years, especially adolescents and young women. LSIL is commonly detected during a colposcopy and is also referred to as mild dysplasia.[15] In our study, we observed that LSIL (Low-Grade Squamous Intraepithelial Lesion) did not exhibit any noticeable symptoms in the majority of cases. This prevalence could potentially be attributed to the composition of the patient cohort, with approximately 80% of participants being asymptomatic.

Our research findings indicate a significant association between smoking and the development of cervical dysplasia, in line with existing literature. Furthermore, the duration and intensity of smoking show a pronounced impact on the incidence of this condition.[15] There are several reasons why smoking can lead to cervical dysplasia in two ways. First, nicotine and cotinine can directly expose the DNA in cervical epithelial cells. Second, exposure to other metabolic products, such as polycyclic aromatic hydrocarbons and aromatic amines, can also contribute to cervical dysplasia.[16] However, a study by Poomtavorn and Spiryda produced different results.[17,18] A meta-analysis of 12,000 patients showed that smoking significantly increases the incidence of cervical dysplasia with an OR of 2.03.[19] According to Kjellberg et al.'s study,[20] smokers have a three times higher risk of CIN 2-3 than those who have never smoked. The current authors also found that smokers have a higher risk of CIN 2-3 and cervical carcinoma with an OR of 1.64. CIN 2-3 risk increases with a more extended smoking history and the number of daily cigarettes. In Matsumo et al.'s study[21], 516 patients with CIN 1 were monitored using cytology and colposcopy every four months. The probability of regression within two years was significantly lower for smokers compared to non-smokers (55% vs. 68.8%, $p = 0.004$), and the risk of persistence increased with the intensity and duration of smoking ($p=0.003$ and $p<0.001$, respectively). Furthermore, the study reported that individuals who smoke show a higher likelihood of prolonged infection with an odds ratio of 2.50, 95% CI (1.30-4.81), $p = 0.006$.[21] A study also found that smoking significantly increased the risk of developing CIN 2-3 and cervical cancer, with OR 2.3, 95% CI (1.3-4.3) $p<0.05$. This risk increases with a more extended smoking history and higher daily cigarette consumption. It has been found that smoking can impact the development of cervical lesions. A study revealed that quitting smoking resulted in a significant reduction in the size of these lesions. Among patients who quit smoking, 82% showed a 20% reduction in lesion size, compared to only 28% of those who continued smoking.[22,23]

Interestingly, this study found that patients who are frequently exposed to secondhand smoke or generally called passive smokers, also had a significant risk of having cervical dysplasia (cOR 25.04, 95% CI [6.28 – 99.71] and aOR 24.77, 95% CI [6.19 – 99.03]). A previous meta-analysis of 4 cohort studies and 10 case-control studies involving 384,995 patients showed a positive correlation between passive smoking and cervical cancer with OR 1.70, 95% CI (1.40 – 2.07) $p <0.01$.[24] A multicentric case-control study involving 1,919 couples investigated the potential link between male smokers and the development of CIN 3 / cervical carcinoma in situ (CIS) and invasive cervical cancer (ICC) in women. The study found no association between passive smoking and CIS but did find a significant

association with ICC. This suggests that exposure to passive cigarette smoke may be a late-stage carcinogen in transitioning from preinvasive lesions to invasive cervical cancer.[25] According to a study in Korea, non-smokers who are exposed to secondhand smoke are at a higher risk of developing CIN 1. This risk is particularly elevated in women who don't smoke and are exposed to secondhand smoke for two or more hours each day with multivariate OR 2.34, 95% CI (1.41–3.90) had a higher risk of CIN 1.[26] The connection between passive smoking and cervical neoplasm is not well understood. However, several mechanisms are thought to play a significant role. Firstly, continuous smoking can weaken the immune system, increasing the risk of HPV infection. HPV is known to be the leading cause of cervical cancer. Secondly, nicotine has been shown to promote the development of tumors. Lastly, interactions with smoke can significantly affect the effectiveness and toxicity of anticancer drugs.[24,26]

This study also found that an earlier age at first intercourse significantly increases the risk of cervical dysplasia. This finding is in line with a study conducted in Brazil, and this study showed that age at first sexual intercourse under 17 years is a risk factor for HSIL regardless of the age of the woman.[27] Biological immaturity and hormonal influences are thought to cause the association between early age after first intercourse and cervical dysplasia.[28, 29] However, a study from Adhikari reported that cervical atypia was not associated with the early start of sexual activity after menarche.[30,31]

Our study found that cervical dysplasia was significantly associated with their first sexual intercourse at a younger age, under 20 years, with cOR 2.39, 95% CI (1.04 - 5.48) and aOR 2.44, 95% CI (1.04 - 5.69). This aligns with the findings of similar studies by Okwi[32], and Utoo et al.[33], which also reported a higher prevalence of precancerous lesions in those who had their first sexual intercourse before 20 years old. This increased risk can be attributed to a vulnerable period during puberty when metaplastic changes occur. Factors like infection during this time can trigger dysplasia and subsequent carcinogenesis. Additionally, the squamocolumnar junction (SCJ) in young women is located outside the external uterine ostium, making it susceptible to external factors such as mutagens that can trigger dysplastic changes in the epithelium.[34,35] In a study conducted by Mhaske et al. regarding cervical cancer risk, it was found that 86.4% of women were married before the age of 17. This study also revealed that early marriage was positively linked to cervical cancer, consistent with the findings of a case-control study on awareness of cervical carcinoma conducted by Capalash and Sobit. The study results showed that cervical cancer was associated with marrying at a young age, having low socioeconomic status, and higher parity.[36] Similarly, a study by Khalaf et al. explored the connection between early marriage, socio-medical characteristics, and cervical Pap smear results. The findings demonstrated that abnormal Pap smears were more likely to be detected in women married at or before 18 years old and marriage at an early age was significantly linked to abnormal colposcopy results.[37]

This study serves as a fundamental basis for future research. We utilized total sampling to ensure that the total number of participants in the study was similar to the entire population at BaliMed Hospital Denpasar, where data was collected. Our findings revealed a significant correlation between age at first sexual intercourse and smoking. Additionally, we examined the impact of smoking not only on active smokers but also on patients who are exposed to secondhand smoke. It is important to note that certain limitations need to be addressed concerning this study, which is that the same gynecologist conducted all of the colposcopies, which made it challenging to evaluate interobserver reliability. Since the accuracy of colposcopic findings can vary depending on the skill of the person performing the procedure, the results may be less applicable across different practitioners. However, this approach did provide a consistent and standardized examination for all participants. Another one is that the sample

size was relatively small and uncontrolled. Conducting a more extensive and diverse cohort study across multiple centers to obtain more definitive evidence would be advisable. This would enable researchers to ascertain with greater certainty whether or not smoking and the age at which individuals first engage in sexual intercourse truly represent significant risk factors for cervical dysplasia.

5. Conclusion

Overall, this study found a correlation between the age at which an individual first engages in sexual activity and their likelihood of developing cervical dysplasia. Specifically, those who engage in sexual activity at a young age are more susceptible to experiencing this condition. Furthermore, the study highlights the significant impact of smoking on cervical dysplasia, including passive exposure to smoke. It is essential to consider these factors when assessing one's risk for cervical dysplasia and taking preventative measures.

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