*Poltekita: Jurnal Ilmu Kesehatan*
*http://jurnal.poltekkespalu.ac.id/index.php/JIK*

*Vol.16 No.4 February 2023: Hal. 497-504*
*p-ISSN: 1907-459X e-ISSN: 2527-7170*

**Article Review**

# *Correlation between Oral Contraceptive Use and the Incidence of Cervical Cancer*

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***ABSTRACT***

*Cervical cancer is a malignant tumor that develops in the cervix and is the second most common type of cancer experienced by women in the world. Causes of cervical cancer include HPV infection, use of oral contraceptives, age of marriage, parity and exposure to cigarette smoke. This study aims to determine the correlation between oral contraceptive use and the incidence of cervical cancer. This literature study research involved secondary data derived from the Google Scholar, Research Gate and Science Direct databases. The keywords applied in the study were oral contraceptives, birth control pills AND cervical cancer. The journals involved were searched for similarities, dissimilarities and compared to one another. As mentioned in 11 journals, long-term use of oral contraceptives of ≥5 years could increase the risk of cervical cancer. Furthermore, three journals stated the grade of cervical precancerous lesions of CIN 2/3 as the risk factor of cervical cancer, and two journals stated the grade of cervical cancer of stage 2/2+ as the risk factor of cervical cancer. Based on the chi-square test results, 4 journals presented a significance value (p-value) of <0.05, which indicated a correlation between oral contraceptives and the incidence of cervical cancer. 9 other journals found the highest OR value = 9.11 and the lowest OR = 1.50 which meant that women who used Oral contraceptives were 9 times more at risk of developing cervical cancer. Oral contraceptive use was associated with cervical cancer based on the duration of use of more than 5 years and led to a risk of causing CIN 2/3 among women. There were other factors that could affect the incidence of cervical cancer, namely age of marriage, parity and exposure to cigarette smoke.*

***Keywords : Oral Contraceptive, Birth Control Pills, Cervical Cancer.***

https://doi.org/10.33860/jik.v16i4.1285



## INTRODUCTION

Congenital Rubella Syndrome (CRS) is a Cervical cancer malignant tumor that develops in the cervix (the lowest part of the uterus near the top of the vagina). Cervical cancer is the second most common type of cancer experienced by women in the world. This cancer often affects women aged 35 to 55 years, but some research evidence explains that cervical cancer can also affect women in the age range of 20 to 30 years. Causes of cervical cancer include low socio-economic factors, use of oral contraceptives (with negative or positive HPV), family history of cervical cancer, impaired immunity, and several other risk factors [1].

Based on the exposure to information and health data reported in Indonesia's Health Profile in 2016, there were 36,306,662 active contraceptive users (74.80%), and 8,280,823 were oral contraceptive users (22.81%)[2]. Based on population and family planning information in 2017, there were 12.2% of oral contraceptive users[3]. Oral contraceptives have several advantages, namely easy to use, don't need a visit to a health facility, and they are almost 100% effective if consumed regularly at the same time. In addition, fertility can also return soon after the use of oral contraceptives is stopped[4].

The basis of combined oral contraceptives is to mimic natural processes in the body. Estrogen and progesterone which are

normally produced by the ovaries will be replaced by oral contraceptives. Ovarian hormone production will be suppressed by oral contraceptives so that releasing factor in the brain is also suppressed which ultimately prevent ovulation to occur [5].

There are two types of oral contraceptives, some contain progestin and some contain a combination of estrogen and progestin[6]. Mucus viscosity tends to activate carcinogenic agents and also HPV which is the dominant factor in the incidence of cervical cancer in women[7].

Of the 3636 respondents, 27% were current users of hormonal contraception for 10 years or more. Among 886 cases and 3636 controls, 94% and 92% had used the combined pills or the mini pills, respectively[8]. Hormonal steroids (such as those in Oral Contraceptives) have been shown to activate the genomic elements of the HPV type 16 virus and the virus can cause cervical cancer. Another study revealed that the majority of 35 women (80%) used oral contraceptives which had been shown to increase the cumulative incidence of invasive cervical cancer at the age of 50 years from 7.3 to 8.3 per 1000 in developing countries[9].

There were 159,800 deaths in Asia due to cervical cancer. Cervical cancer can attack women aged 20-29 years, but the peak of cervical cancer cases occurs when women are aged 55-64 years, and will decrease in women aged over 65 years. One study explained that one in five women in India was diagnosed with cervical cancer. India is one of the countries with the most cervical cancer patients [10].

Regions considered to have high risk according to Age Standardized Rate (ASRs) with more than 30 cases per 100,000 population are East Africa (42.7%), Melanesia (33.3%), South Africa (31.5%) and Africa Middle (30.6%)[11]. Ethinylestradiol of 30-35 micrograms plus levonorgestrel are thought to increase the risk of the incidence of cervical cancer [12].

Every year, there is an increase cases of cervical cancer in Indonesia. In 2021, 41 new cases and 20 deaths due to cervical cancer were found [13]. A study conducted by Musfirah (2019) found that as many as 49 respondents (71.1%) used oral contraceptives for >5 years and suffered from cervical cancer, of which 37 respondents (54.4%) were not diagnosed with cervical cancer[14]. On the other hand, 19 respondents (27.9%) used oral contraceptives for <5 years and suffered from cervical cancer, of which 31 respondents were not diagnosed with cervical cancer (45.6%).

Family planning acceptors must be equipped with knowledge about efficiency and effectiveness, consumption rules, benefits, side effects and duration of contraceptive use to minimize complications in the future, such as the incidence of cervical cancer when consuming oral contraceptive pills for a long time. In addition, there is a need for intervention and support from the government to reduce the prevalence or prevent the incidence of cervical cancer, such as maturing the age of marriage. Another way that is expected to reduce the incidence of cervical cancer in women is the provision of socialization by healthcare workers regarding the prevalence of cervical cancer both in Indonesia and the world, risk factors, causes and prevention of cervical cancer as well as specific recommendation for married women to take VIA examinations at least once every 3 years to support government programs in efforts to reduce the prevalence of cervical cancer among women.

This study aims to determine the correlation between oral contraceptive use and the incidence of cervical cancer.

## METHOD

The study currently conducted was a literature or literature review study with a traditional review design. This study involved secondary data selected through predetermined criteria so that the journals obtained were aligned with the topic to be studied. The literature used consisted of articles and journals published in the last 5 years with a minimum number of 5 national journals and 10 international journals. The journals were accessed through the Google Scholar, Research Gate and Science Direct databases. The researchers further summarize the articles in accordance with the established criteria. Researchers looked for similarities, dissimilarities, and compared the journals regarding the characteristics of oral contraceptive users based on the duration of oral contraceptive use; age of marriage; parity; exposure to cigarette smoke, and the level of cervical cancer started from the normal cervix (non-cancer); precancerous lesions/atypia/dysplasia and cervical cancer, year of publication, population, sample,

variables, study design, study results and database. Furthermore, an analysis was carried out according to the inclusion criteria that had been set by the researchers using the exposition method, so that there was a suitability with the topic of "Correlation between Oral Contraceptive Use and Incidence of Cervical Cancer".

The keywords applied in searching national journals were oral contraceptives, birth control pills AND cervical cancer. Meanwhile, keywords in searching international journals are oral contraceptives, contraceptive pills AND cervical cancer.

## RESULTS

Researchers found 15 journals from several databases that met the inclusion criteria for this literature study. All journals involved in this literature study used original research with several study designs. Most journals had a sample size of >100 respondents. National journals obtained by researchers were conducted in several sites such as Surakarta, Medan, Riau, Jakarta and Makassar. Meanwhile, international journals selected by researchers were conducted in Australia, Bangladesh, Egypt, Turkey, Ethiopia, the Netherlands, Denmark and Cameroon. Of all journals that met the inclusion criteria, there were 7 journals with the same objective as set by the researchers.

**Table 1. Study Characteristics.**

| No | Study Design | n | (%) |
|---|---|---|---|
| 1 | Retrospective Cohort | 5 | 33.3 |
| 2 | Descriptive Qualitative | 1 | 6.7 |
| 3 | Cross sectional | 3 | 20 |
| 4 | Case control | 6 | 40 |
| | **Total** | 15 | 100 |
| **No** | **Year** | **n** | **(%)** |
| 1 | 2018 | 3 | 20 |
| 2 | 2019 | 1 | 6.7 |
| 3 | 2020 | 7 | 46.7 |
| 4 | 2021 | 4 | 26.7 |
| | **Total** | 15 | 100 |

Based on table 1, the most widely used study design in both national and international journals was case control in 6 journals (40%). Regarding the year of journal publication, both national journals and international journals were most widely published in 2020 so that out of the 15 journals obtained, 7 journals (46.7%) were published in 2020.

**Table 2. Cervical Cancer Grades.**

| No | Cervical Cancer Grade | | n | (%) |
|---|---|---|---|---|
| 1 | Normal Cervix | | - | |
| 2 | Precancerous Lesion | CIN 1 | 1 | 6.7 |
| | | CIN 2/3 | 3 | 20 |
| | | Not explained | 3 | 20 |
| 3 | Cervical Cancer | Stage1 | - | |
| | | Stage 2/2+ | 2 | 13.3 |
| | | Not explained | 7 | 46.7 |

Based on table 2 regarding the level of cervical cancer, as many as 1 journal (6.7%) stated that oral contraceptives could increase the risk of cervical precancerous lesion of CIN 1, 3 journals (20%) stated that oral contraceptives could increase the risk of cervical precancerous lesion of CIN 2/3, and 3 journals (20) %) did not describe the level of precancerous lesion. In addition, as many as 2 journals (13.3%) stated the grade of cervical cancer of stage 2/2+ and 7 journals (46.7%) did not state the grade of cervical cancer.

**Table 3. Characteristics of Oral Contraceptive Users.**

| No | Characteristic of User | | n | (%) |
|---|---|---|---|---|
| 1 | Length of Use of Oral Contraceptive | < 4 years | - | |
| | | ≥4 years | 1 | 6.7 |
| | | <5 years | 3 | 20 |
| | | ≥5 years | 11 | 73.3 |
| 2 | Age of Marriage | <20 years | 7 | 46.7 |
| | | ≥ 20 years | - | |
| 3 | Parity | < 3 | - | |
| | | ≥ 3 | 7 | 46.7 |
| 4 | Cigarette Smoke Exposure | Exposed | 4 | 26.7 |
| | | Not Exposed | 2 | 13.3 |

Based on table 3 regarding, the characteristics of oral contraceptive users, the duration of oral contraceptive use of ≥5 years was stated in 11 national and international journals (73.3%). In addition, a total of 7 journals (46.7%) stated the age of marriage of <20 years, 7 other journals stated a parity of ≥3, and 4 journals (26.7%) stated that oral contraceptive users were exposed to cigarette smoke.

## DISCUSSION

Characteristics of Oral Contraceptive Users as Risk Factors for Cervical Cancer**.** Cervical cancer is a type of cancer that often affects women started with the development of precancerous lesions on the cervix [14]. The dominant factor for cervical cancer is HPV (Human Papilloma Virus) infection, followed by other risk factors and the exact etiology of cervical cancer is unknown. Oral contraceptive use for a long time is considered a risk factor for cervical cancer among women.

A study conducted by Khatun et al. (2018) proved that the users of oral contraceptives for >5 years had a higher risk for developing cervical cancer than non-users. Each contraceptive method definitely has side effects for the body[15], Therefore, it is not recommended to use any type of contraception for a long time. In this study, the relative risk value of oral contraceptives did not explain the increased risk of cervical cancer. Based on WHO report, the use of oral contraceptives had a relative risk of 1.19 times higher than normal and would increase in line with the duration of use [15].

In a study conducted by Musfirah (2019), it was explained that by including combined oral contraceptives in the body, the levels of estrogen and progesterone hormones in the body will be higher. Progesterone in the body will make cervical mucus thicker which makes it difficult for sperm to enter through the cervix. This way of working makes women sensitive to HPV, causing inflammation of the genitalia and this can cause cervical cancer. The balance of estrogen in the body will be disrupted if a woman uses long-term hormonal contraception so that abnormal cells can develop rapidly[14].

Besides the duration of oral contraceptive use, the risk factors for increasing the incidence of cervical cancer can be determined from the age of marriage. A woman who who has been married before the age of 20 is considered at risk. A such age, cervical mucosal cells are still immature and sensitive with stimuli/foreign substances, including chemicals contained in sperm cells. If there is continuous stimulation, cervical mucous cells can develop into malignant cancer cells.

The similar finding was expressed in the study conducted by in Arfailasufandi et al. (2019), which showed that women who engaged in sexual activity at the age of <20 years had a 5.44 times higher risk of experiencing cervical cancer (OR=5.44, p<0.001)[16]. Likewise a study conducted by Santoso (2021), it was explained that of 43 mothers with cancer with the age of marriage of ≤20 years, a total of 29 people (67.4%) had cervical cancer. Meanwhile, out of 21 women with an age of marriage of >20 years, 8 (38.1%) had cervical[17].

Age of marriage of <20 years is also considered a trigger factor for cervical cancer. Marriage when the age is not ideal can have an adverse effect on both the mother and the baby. In addition, sexual intercourse when the anatomical cells are still immature can increase the chances of the development of cervical cancer. The age recommended by the BKKBN as the ideal age to marry is at least 21 years for women and at least 25 years for men.

The younger the age of marriage, the higher the parity. Parity is a woman's ability to give birth normally. Too frequent parity can lead to health problems for a woman. Reproductive health problems will increase along with high parity. This is also explained through the study conducted by Arfailasufandi et al. (2019) that women who had given birth to 3 or more children were 3.94 times more likely to experience cervical cancer[16]. Trauma associated with vaginal delivery can increase the likelihood of HPV infection[18].The baby passes through the cervix in normal delivery and allows a little damage to the cervical epithelial tissue so that it can cause abnormal cell changes[19]. This indicates that the risk of cervical cancer increases with the increasing number of children born. Repeated spontaneous births increase the risk of trauma to the birth canal and make it easier for HPV to infect the cervix.

In addition to the three factors mentioned above, high exposure to cigarette smoke is also associated with a higher risk of HPV infection. One of the risk factors that cause cervical intraepithelial neoplasia (CIN) is active smoking with one pack of cigarettes or more per day. Meanwhile, passive smokers with lifetime exposure of more than 20 packs of cigarettes per year had a 7.2 times higher risk of HPV infection (OR=7.2). Nicotine contained in cigarettes is suspected as an ingredient that activates carcinogenic agents. The nicotine in cigarettes will enter the cervical mucus and then stimulate cervical mucous cells by covering the cervix so that the immune system decreases and

further triggers the development of abnormal cells.

Healthcare workers can provide education to the public so that they consider the benefits or advantages of using oral contraceptives more than the risks. It must be clarified that cervical cancer is multifactorial (it can be caused by several risk factors). It is not only caused by one factor, one of which is the use of oral contraceptives. To minimize the prevalence of cervical cancer, healthcare workers should suggest women to replace the use of oral contraceptives if they have been using oral contraceptives for ≥ 5 years.

Cervical Cancer Grades**.** In a study conducted by Attya et al. (2020), 117 patients (86%) had negative results for intra-epithelial lesions, while 19 patients (14%) had positive results for intraepithelial lesions[20]. Ten of them (7.4%) were diagnosed with ASCUS, 5 (3.7%) were diagnosed with LSIL, 3 (2.2%) were diagnosed with HSIL and only 1 person (0.7%) was diagnosed with SCC. 10 people were in the atypia stage, which meant that there were changes in uterine cells which could be due to inflammation or a viral infection and a PAP smear examination must be repeated to diagnose whether these abnormal cells were the beginning of cervical cancer. The next diagnosis showed that 5 people were diagnosed with LSIL/CIN level 1, 3 people were diagnosed with HSIL (CIN 2/3) and 1 person was diagnosed with SCC or invasive cervical cancer.

The high-risk HPV infection was more common among COC users, and that COCs altered the susceptibility or immune response to HPV infection which would potentially improve the diagnosis of CIN 2+ after long-term use of COC. In a recent study conducted by Xu et al. (2018), COC use was shown to increase the risk of CIN II and III [7]. Results of a study conducted by Loopik et al. (2020) showed an increase in CIN III increases among COC users. CIN2 and CIN3 are the high-grade cancer precursors that are more likely to develop into invasive cancer.

Generally, only a small proportion of HPV infections develop into grade 2CIN after 3 years of invasion. A small proportion of grade 3 CIN can turn into invasive cervical cancer after 5 years of invasion and only a small proportion of grade 3 CIN can turn into invasive cancer after 30 years of invasion.

If a precancerous lesion turns into invasive cancer, the division of the grades is different from the precancerous lesions grades. The stages of cervical cancer are aligned with the classification of The International Federation of Gynecology and Obstetrics (FIGO), namely stage 0 which is called carcinoma in situ, stage 1 where the carcinoma develops in the cervical area only, stage 2 where tumor expands outside the uterus but do not affect pelvic wall or reach the lower 1/3 of the vagina, stage 3 where tumor expands to the pelvic wall or reaches the lower 1/3 of the vagina and stage 4 where tumor expands to the bladder or rectum mucosa and/or beyond the small pelvis[21].

Based on the FIGO classification, 22.8% of women were in stage IIIB followed by 18.4% in stage IVA at the time of diagnosis. In line with this, a study conducted by Zidi et al in Utomo et al. (2020) found that the use of oral contraceptives was 1.86 times more likely to increase the risk of suffering from stage III or IV cervical cancer[21].

Prevention efforts that can be made by healthcare workers are conducting counseling regarding risk factors, causes and preventive efforts of cervical cancer and also providing assistance to women, especially married women, to carry out early detection of cervical cancer on a regular basis through Acetic Acid Visual Inspection (IVA), pap smears or biopsies and colposcopy as necessary.

Correlation between Oral Contraceptives and the Incidence of Cervical Cancer. Oral contraceptives make women more sensitive to HPV and this may disrupt the balance of estrogen in the body. When persistent inflammation occurs in the genitalia due to estrogen imbalance caused by long-term use of oral contraceptives, normal cells will develop into abnormal ones[14]. Long-term use of oral contraceptives for more than 5 years is believed to increase a woman's risk of developing cervical cancer by 1.5-2.5 times. Natural hormone secretion in the body will be disturbed when oral contraceptives enter the body. The progesterone content in oral contraceptives will thicken cervical mucus, making it difficult for sperm to enter through the cervix[22].

Correlation between the use of oral contraceptives and the incidence of cervical cancer since oral contraceptives were believed to make the body experience a deficiency of folic acid, making it easier for mutagens to entry

and estrogen is thought to be one of the factors that accelerate HPV DNA duplication. The use of hormonal contraceptives including oral contraceptives could reduce levels of nutrients in the body (Vitamins C, B12, B6, B2, folic acid and zinc) which play a role in the immune system. It was reported that as many as 67% of cervical cancer patients had at least one abnormal vitamin level, while the other 33% experienced multiple abnormal nutrition levels.

According to Arfailasufandi et al. (2019), intraepithelial lesions that occur in oral contraceptive acceptors can be caused by HPV due to consumption of oral contraceptives[16]. The high-risk HPV infection was more common in COC users, and it was shown that COCs altered the susceptibility or immune response to HPV infection. Women with CIN3 and women with CIN2 who lost fertility function in Denmark were always treated with conisation to prevent the development of the lesions[23]. WHO does not recommend stopping the use of oral contraceptives even though several studies have mentioned oral contraceptives as a risk factor for cervical cancer because the effectiveness of their use is more beneficial than the risks.

The speed of development of cancer invasion is different from one case to another. Even though the tumor has spread to one organ, there is still a possibility that a patient has no symptoms. There are no definite symptoms in early stage cancer. The symptoms that often occur are characterized by quite a lot of vaginal discharge and sometimes accompanied by blood spots. Symptoms are increasingly evident as the cancer cells develop, such as bleeding that is more frequent, more volume and lasts a long time. Sometimes, vaginal mucus that smells bad is also found due to infection and tissue necrosis. If cervical cancer reaches an advanced stage, other symptoms may be found, such as pain in the hips or legs[24].

Cervical cancer certainly has an impact on the lives of patients and their families, and also affects the government's health budget because the government must provide adequate facilities for the treatment of cervical cancer patients. Counseling efforts to prevent and screen cervical cancer must be increased and considered by every authorized party. Cervical cancer screening is needed to recognize the symptoms that occur, to prevent it from progressing to an advanced stage and to treat it quickly and precisely. VIA examination is the program that has been introduced by the government as an effort to early detect cervical cancer. Such examination needs to be performed at least once every 3 years.

## CONCLUSION

Based on the characteristics of oral contraceptive users, most of them had duration of oral contraceptive use of ≥5 years, age of marriage of <20 years, parity of ≥3, and exposure to cigarette smoke. The grade of precancerous lesions that might arise due to long-term use of oral contraceptives was CIN 2/3. If not treated immediately, precancerous lesions will develop into cervical cancer. The majority of women diagnosed with stage 2/2+ cervical cancer was due to lack of knowledge about cervical cancer screening. Oral contraceptives were correlated with cervical cancer based on the length of use of more than 5 years, the risk of CIN 2/3 among women. Furthermore, there were other factors that could affect the incidence of cervical cancer, namely age of marriage, parity and exposure to cigarette smoke. The study findings can be used as a reference for the public to encourage them to consult with healthcare workers before using contraceptives, especially oral contraceptives to reduce side effects that can be caused. Future researchers are recommended to evaluate the most risky factors of cervical cancer.

## CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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