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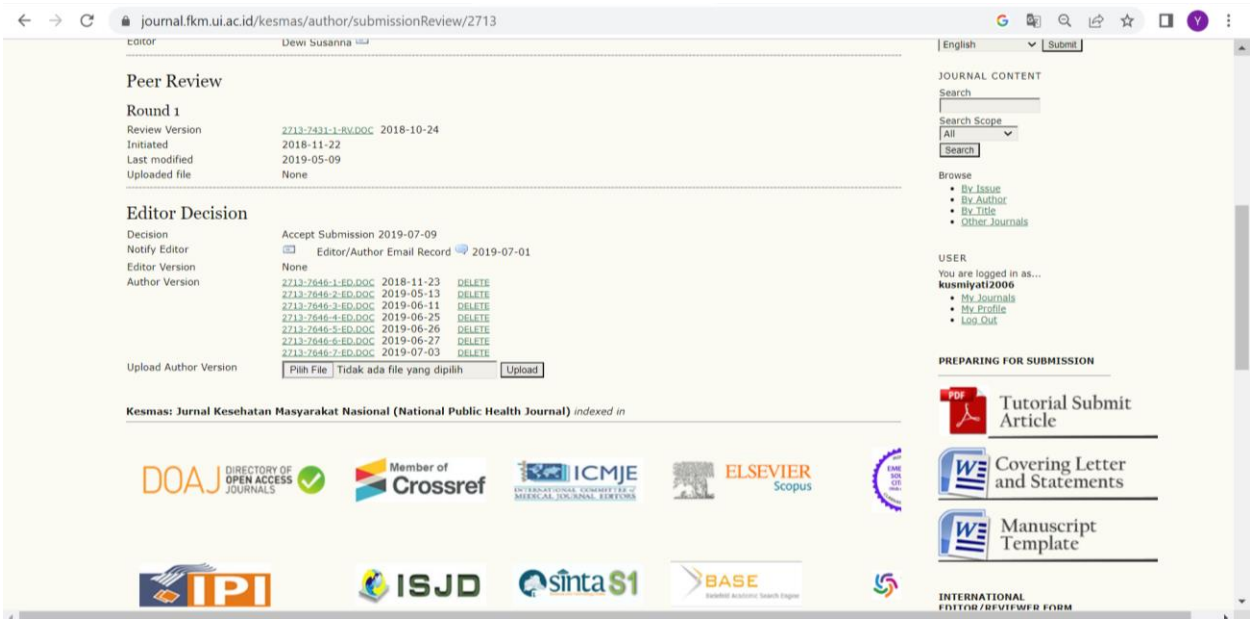
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# Duration of Hormonal Contraception and Risk of Cervical Cancer

## Lama Penggunaan Kontrasepsi Hormonal dan Kejadian Kanker Serviks

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**Abstract**

The use of long hormonal contraceptives can disrupt the balance of estrogen in the body, resulting in abnormal cell changes. This study aimed to determine a correlation between the duration of hormonal contraception and risk of cervical cancer. A case-control study was conducted on 190 in female patients in Dr. Sardjito Central General Hospital, Yogyakarta. Case samples were 95 women have cervical cancer diagnosis and control were 95 women with a negative pap smear. Data on cervical cancer and the duration of hormonal contraception are obtained from medical records. Cervical cancer is assessed by diagnosis. The length of hormonal contraception is categorized as long if more than 5 years. Data analysis used logistic regression. Results showed that 44,7% of samples used long-term hormonal contraception (over 5 years). Length of use of hormonal contraception had a significant correlation with the incidence of cervical cancer (p-value < 0.01). Hormonal contraceptive use more than 5 years have a risk 4.2 times (95% CI 1.01-5.69) of cervical cancer than using less than 5 years after being controlled with the first marriage age and parity.

**Keywords:** Cervical cancer, duration than 5 years, hormonal contraception

**Abstrak**

Penggunaan kontrasepsi hormonal yang lama dapat mengganggu keseimbangan estrogen dalam tubuh, sehingga menghasilkan perubahan sel yang tidak normal. Penelitian ini bertujuan untuk mengetahui hubungan antara lama penggunaan kontrasepsi hormonal dan risiko kanker serviks. Sebuah studi kasus kontrol dilakukan pada 190 perempuan yang dirawat di RSUP Dr. Sardjito, Yogyakarta. Sampel kasus adalah 95 wanita yang memiliki diagnosis kanker serviks dan kontrol adalah 95 wanita dengan hasil pap smear negatif. Data tentang kanker serviks dan lama penggunaan kontrasepsi diperoleh dari rekam medis. Kanker serviks dinilai berdasarkan diagnosis. Lama penggunaan kontrasepsi hormonal dikategorikan lama apabila lebih dari 5 tahun. Analisis data menggunakan regresi logistik. Hasil penelitian menunjukkan bahwa 44,7% sampel menggunakan kontrasepsi hormonal jangka panjang (lebih dari 5 tahun). Lama penggunaan kontrasepsi hormonal memiliki hubungan yang signifikan dengan kejadian kanker serviks (nilai p < 0,01). Penggunaan kontrasepsi hormonal lebih dari 5 tahun memiliki risiko 4.2 kali (95% CI 1.01-3.69) menderita kanker serviks daripada menggunakan kurang dari 5 tahun setelah dikontrol dengan faktor usia pernikahan pertama dan paritas.

Kata kunci: Kanker serviks, kontrasepsi hormonal, durasi lebih dari 5 tahun.

## Introduction

Cervical cancer is a cause of mortality among women in the world and Indonesia.[1] In the world, cervical cancer ranks third as the cause of death in women with an estimated death rate of 15 per 100.000 women.[2] Meanwhile, in developing countries including Indonesia, cervical cancer ranks highest as the most common cause of death among women, about 80% of total cases.[3] Cervical cancer patients in Indonesia estimated 90-100 among 100.000 inhabitants per year and ranked third (10,35%) as the cause of death of women after other (43,1%).[4,5,6] Yogyakarta is an area with the highest cancer incidence in Indonesia which has a prevalence of cervical cancer of 1.5 ‰. [7,8] Cervical cancer always ranks third of the 10 major cancers existing in Dr. Sardjito Central General Hospital. This data shows that there are still many cases of cervical cancer in Dr. Sardjito Central General Hospital.

Cervical cancer has a long journey from the precancerous stage, takes 10-20 years to develop into invasive cancer. Patients can complain of severe pain; pain can be felt during sexual intercourse, abnormal bleeding during sexual intercourse and when cancer has spread to the brain and lungs pulmonary (stage IVB), the life of the patient will be increasingly difficult to save. [9,10] Research conducted by Yvonne Nartey, Philip C. Hill, Kwabena Amo-Antwi, et al. in 2017, showed that of 821 women diagnosed with cervical cancer, 497 women (60,5%) died during follow-up. Having been diagnosed with cervical cancer can survive 1 year after diagnosis by 62%, 3 years after diagnosis by 39%, and 5 years of diagnosis 30% [10].

According to the results of research, showed that the factors that correlate with cervical cancer are early sexual intercourse is less than 20 years, parity is more than 3, and the use of hormonal contraception more than 5 years.[11] The risk factors of cervical cancer are low education, infections like trichomonas vaginalis, bacterial vaginosis, disorders on genitals, and contraceptive use. [11] How long the body's exposure to hormones in any hormonal contraception is still unknown, so the duration of each hormonal contraceptive usage still needs to be examined. [12].

Data of active family planning participants from 2014 to 2016 showed an increasing trend from year to year. Data of active family planning participants who used hormonal contraception was 81.58% to 81,97% (injected 47,54%, pills 23,58%, implants 10,46%).[13] The purpose of this study was to determine the relationship between the duration of hormonal contraception use and the incidence of cervical cancer and knowing other factors related to cervical cancer incidence.

## Methods

This study used a case-control design. Samples were patients who had examined at a cancer installation, and obstetrics-gynecology polyclinic Dr. Sardjito Hospital, Yogyakarta, Indonesia. Case samples were 95 women who were diagnosed with cervical cancer, while the control samples were 95 women who did not have cervical cancer (Pap smear tests were negative). Subjects were excluded if has never used hormonal contraception and medical record data is incomplete. The study was conducted in July 2018 with random assignment. Independent variable is duration of hormonal contraception, whereas the dependent variable is cervical cancer. Cervical cancer is assessed from diagnosis. The duration of hormonal contraception is length of use of hormonal contraception (injections, pills and implants). The duration of hormonal contraceptive use (injections, pills and implants) is categorized into two, namely more than 5 years and not long if the user is less than 5 years. The data were based on diagnosis recorded in the medical record. A possible confounders were marriage age less than 20 years, family history of cancer, active smoking, and parity more than 3. For statistical analysis, the bivariate analysis used chi-square tests, and the multivariate analysis used logistic regression. The p-value of the likelihood ratio to the chi-square was used as a guide to the model's goodness of fit. All p-values were two-tailed and statistical significance level was set as less than 0.05. Ethical approval granted from the Ethics Committee of the Faculty of Medicine, Gadjah Mada University No.KE/KF/0561/EC/2018.

## Results

This research was conducted at Dr. Sardjito. Total of subjects who participated in the study was 190 subjects (95 for case group/ women who were diagnosed with cervical cancer), and 95 for the control group (women who did not have cervical cancer or Pap smear tests were negative). The duration of hormonal contraceptive use (injections, pills and implants) is categorized into two, namely more than 5 years and not long if the user is less than 5 years. Table 1 presents the correlation of the duration of use hormonal contraception with cervical cancer and other affecting factors.

Tabel 1. Correlation of the duration of use hormonal contraception, age of marriage, parity, active smoking, family history of cancer with cervical cancer

| Variable | Case n (%) | Control n (%) | p-value | OR | 95% CI | |
|---|---|---|---|---|---|---|
| | | | | | Lower | Upper |
| **Hormonal contraception > 5 years** | 59 (62,1) | 26 (27,4) | 0,01 | 4,3 | 2,35 | 8,02 |
| " use of pills> 5 years | 16 (51,6) | 3 (13,0) | 0,01 | 7,1 | 1,74 | 28,9 |
| " use of injections > 5 years | 32 (66,7) | 13 (35,1) | 0,01 | 3,6 | 1,49 | 9,11 |
| " use of implants > 5 years | 11 (68,8) | 10 (28,6) | 0,01 | 5,5 | 1,51 | 19,9 |
| The first age of marriage < 20 years | 47 (49,5) | 28 (29,5) | 0,01 | 2,3 | 1,29 | 4,25 |
| Parity > 3 | 27 (28,4) | 13 (13,7) | 0,02 | 2,5 | 1,20 | 5,22 |
| Active Smoking | 2 (2,1) | 0 (0,0) | 0,49 | 2,0 | 1,75 | 2,33 |
| Family history of cancer | 2 (2,1) | 2 (2,1) | 1,00 | 1,00 | 0,13 | 7,24 |

n = Number of Sample; OR = Odds Ratio; CI= Convidence Interval

Table 1 performs the correlation between duration of use hormonal contraception, the first age of marriage, parity, active smoking, family history of cancer with cervical cancer. Duration of hormonal contraception had higher risk 4,3 times of cervical cancer than using less than 5 years. Duration of use of pills, injections and implant have a significant correlation with cervical cancer. Women who the first age of marriage <20 years had higher risk 2,3 times of cervical cancer. Parity > 3 had higher risk 2,5 times of cervical cancer. There is no significant correlation between active smoking and family history of cancer with cervical cancer.

Correlation between the duration of the use hormonal contraception, the first age of marriage, parity, active smoking, family history of cancer with cervical cancer was analyzed by logistic regression using the backward method. The first step regression analysis was performed by bivariate selection. The candidates entered in multivariate analysis are variables with p-value ≤ 0.250. The analysis showed that the first age of marriage and parity had p-value ≤ 0.250 while active smoking, family history of cancer had p-value > 0.250, so they were not included in the multivariable selection.

Table 2. Correlation of duration use hormonal contraception and cervical cancer after consideration of external variables

| Variable | β | p-value | OR | 95% CI | |
|---|---|---|---|---|---|
| | | | | Lower | Upper |
| Use of contraception hormonal >5 years | 1.435 | 0.000 | 4.2 | 1.011 | 5.692 |
| The first age of married<20 years | 0.659 | 0.046 | 1.9 | 0.993 | 4.847 |
| Parity >3 | 0.786 | 0.052 | 2.1 | 2.238 | 7.880 |

Notes: β= coefficient OR= Odds Ratio CI=Convidence Interval

Table 2 shows the correlation between the duration of the use hormonal contraception and cervical cancer after consideration of external variables (age of married <20 years and parity >3). Period of use of contraception hormonal had 4.2 times higher risk of cervical cancer after being controlled with the first marriage age and parity.

## Discussion

This study found a correlation between duration of use hormonal contraception and cervical cancer. This strong association is marked by Odds ratio (OR) of 4.2. These results are in line with previous studies conducted. The results of this study support previous studies among others, a study who stated that long-term use of hormonal contraception could lead to cervical cancer. Hormonal contraceptives acted as a tool that controlled the growth of neoplasms. The acceptors who use hormonal contraception are often found in cervical dysplasia.[14] The use of hormonal contraceptives that are longer than 4 or 5 years can disrupt the balance of estrogen in the body resulting in abnormal cell changes. Estrogen is likely to be one of the factors that can make HPV DNA replication.[14] Likewise with the length of use of each hormonal contraception. Effect of hormonal contraception can cause hypersecretion and the proliferation of endocervical glands. In addition, causes metaplasia and portio epithelial dysplasia and mucous membranes of the endocervix. Hormonal contraception increases the risk of cervical cancer for women with HPV. It is suspected that gestagen triggers the carcinogenic effect of HPV.[7,14,15]

Use of hormonal contraception, causes mucus viscosity in the cervix due to oral hormonal contraceptive use or injection will support cervical cancer. This is because this mucus viscosity will prolong the existence of a carcinogenic agent (cancer-causing) in the cervix which is carried through sexual intercourse including the presence of the HPV virus which is the cause of cervical cancer. The duration of use of implant contraceptives can increase the incidence of cervical cancer considering the mechanism of hormones in the implant to thicken cervical mucus. The process of cervical mucus removal is the replacement of new cells and the addition of cells to the cervix to prevent the entry of sperm. If cervical mucus thickening occurs continuously and uncontrollably, the thickening will become abnormal which can lead to cervical cancer the immature will experience changes and can damage cells in the cervix.[16].

Sexual intercourse that is early can affect cervical epithelial tissue damage or the vagina cavity wall and can worsen leading to cell abnormalities that result in abnormal growth.[11] Women who begin sexual intercourse age <20 years is more at risk of developing cancer cervix. It is because in the young adult period the process of squamous cell metaplasia is substantially increased so the risk of atypical squamous transformation increases which then becomes cervical intraepithelial neoplasia (NIS).[17] The results of this study in accordance with previous studies showing women who had sexual intercourse for the first time at the age of <20 years were 2.41 times more likely to develop cervical cancer. The exposure of the uterus to the HPV will result in growth deviating into precancerous/cervical cancer.[18] Married age can be associated with age-related. At the age of the genital device that is not yet mature and has been used to connect it will damage the cervical epithelial tissue that can get worse on cell abnormalities and result in abnormal growth. Especially if the partner already has an HPV virus that is rapidly contracting.[18]

Women with high parity are associated with the occurrence of cervical column epithelium during pregnancy. This incidence causes new dynamics of immature metaplastic epithelium which can increase the risk of cell transformation especially in the cervix resulting in persistent HPV infection.[16] Sondang and Dian showed that women are often giving birth, it will affect the frequent occurrence of injury to a woman's reproductive organs, which in turn will make it easier for the HPV to cause cancer. In the case of women who gave birth frequently and at proximity, damage to the epithelial tissue develops towards the growth of abnormal cells that are potentially malignant. In labor that often has the opportunity to be contaminated by a virus that causes infection. The bacteria are present because of poorly maintained vaginal hygiene conditions that can develop into malignancy.[19]

According to American cancer, if a mother or sister has cervical cancer, it can increase the incidence of cervical cancer than those who do not have a family history of cervical cancer. This is due to the genetic tendency of the family to inherit the condition.[20] The results of this study indicate that women whose families have a history of cervical cancer do not influence cervical cancer. This study was different from the research which showed that family history of cervical cancer has a risk of 2.19 times affected by cervical cancer.[21] Respondents who have had cancer in their families cervix has a risk of 14.93 times for cervical cancer. Especially in the nuclear family (first) cervical cancer is a vulnerability that inherits. However, it is unclear whether the risks are related, with history of family cancer being due to genetic susceptibility or the influence of the environmental lifestyle.[11] At present there is a need for counseling on contraceptive use, especially hormonal contraception, because high levels of hormonal contraceptive use by acceptors are thought to be the effect of not providing extensive information about the advantages and disadvantages of contraception and quality contraceptive services [21]

## Conclusion

Duration of use of contraception hormonal >5 years has a strong correlation with cervical cancer after controlled by other factors. Method of contraception hormonal >5 years had 4.2 times higher (95% CI: 1.01-5.69) for cervical cancer than use of contraception hormonal < 5 years.

## Recommendations

For all women who do not want more children, to use non-hormonal long-term contraception. It is necessary to promotion for women or contraceptive acceptors using hormonal up to 5 years.

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## Lama Penggunaan Kontrasepsi Hormonal dan Kejadian Kanker Serviks


### Abstract

The use of long hormonal contraceptives can disrupt the balance of estrogen in the body, resulting in abnormal cell changes. This study aimed to determine a correlation between the duration of hormonal contraception and risk of cervical cancer. A case-control study was conducted on 190 in female patients in Dr. Sardjito Central General Hospital, Yogyakarta. Case samples were 95 women have cervical cancer diagnosis and control were 95 women with a negative pap smear. Data on cervical cancer and the duration of hormonal contraception are obtained from medical records. Cervical cancer is assessed by doctor's diagnosis. The length of hormonal contraception is categorized as long if more than 5 years. Data analysis used logistic regression. Results showed that 44,7% of samples used long-term hormonal contraception (over 5 years). Length of use of hormonal contraception had a significant correlation with the incidence of cervical cancer (p-value < 0.01). Hormonal contraceptive use more than 5 years have a risk 4.2 times (95% CI 1.01-5.69) of cervical cancer than using less than 5 years after being controlled with the first marriage age and parity.



**Keywords:** Cervical cancer, duration of using, age og marriage, parity, hormonal contraception



### Abstrak

Penggunaan kontrasepsi hormonal yang lama dapat mengganggu keseimbangan estrogen dalam tubuh, sehingga menghasilkan perubahan sel yang tidak normal. Penelitian ini bertujuan untuk mengetahui hubungan antara lama penggunaan kontrasepsi hormonal dan risiko kanker serviks. Sebuah studi kasus kontrol dilakukan pada 190 perempuan yang dirawat di RSUP Dr. Sardjito, Yogyakarta. Sampel kasus adalah 95 wanita yang memiliki diagnosa kanker serviks dan kontrol adalah 95 wanita dengan hasil pap smear negatif. Data tentang kanker serviks dan lama penggunaan kontrasepsi diperoleh dari rekam medis. Kanker serviks dinilai berdasarkan diagnosis. Lama penggunaan kontrasepsi hormonal dikategorikan lama apabila lebih dari 5 tahun. Analisis data menggunakan regresi logistik. Hasil penelitian menunjukkan bahwa 44,7% sampel menggunakan kontrasepsi hormonal jangka panjang (lebih dari 5 tahun). Lama penggunaan kontrasepsi hormonal memiliki hubungan yang signifikan dengan kejadian kanker serviks (nilai p < 0,01). Penggunaan kontrasepsi hormonal lebih dari 5 tahun memiliki risiko 4.2 kali (95% CI 1.01-3.69) menderita kanker serviks daripada menggunakan kurang dari 5 tahun setelah dikontrol dengan faktor usia pernikahan pertama dan paritas.



Kata kunci: Kanker serviks, kontrasepsi hormonal, lama penggunaan, usia kawin, paritas


### Introduction

Cervical cancer is a cause of mortality among women in the world and Indonesia.[1] In the world, cervical cancer ranks third as the cause of death in women with an estimated death rate of 15 per 100.000 women.[2] Meanwhile, in developing countries including Indonesia, cervical cancer ranks highest as the most common cause of death among women, about 80% of total cases.[3] Cervical cancer patients in Indonesia estimated 90-100 among 100.000 inhabitants per year [4,5,6] Yogyakarta is an area with the highest cancer incidence in Indonesia which has a prevalence of cervical cancer of 1.5 ‰. [7,8] Cervical cancer always ranks third of the 10 major cancers existing in Dr. Sardjito Central General Hospital.

Cervical cancer has a long journey from the precancerous stage, takes 10-20 years to develop into invasive cancer. Patients can complain of severe pain; pain can be felt during sexual intercourse, abnormal bleeding during sexual intercourse and when cancer has spread to the brain and lungs pulmonary (stage IVB), the life of the patient will be increasingly difficult to save. [9,10] Research conducted by Yvonne Nartey, Philip C. Hill, Kwabena Amo-Antwi, et al. in 2017, showed that of 821 women diagnosed with cervical cancer, 497 women (60,5%) died during follow-up. Having been diagnosed with cervical cancer can survive 1 year after diagnosis by 62%, 3 years after diagnosis by 39%, and 5 years of diagnosis 30% [10].

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### Methods

This study used a case-control design. Samples were patients who had examined at a cancer installation, and obstetrics-gynecology polyclinic Dr. Sardjito Hospital, Yogyakarta, Indonesia. Case samples were 95 women who were diagnosed with cervical cancer, while the control samples were 95 women who did not have cervical cancer (Pap smear tests were negative). Subjects were excluded if has never used hormonal contraception and medical record data is incomplete. The study was conducted in July 2018 with random assignment. Independent variable is duration of hormonal contraception, whereas the dependent variable is cervical cancer. Cervical cancer is assessed from diagnosis. The duration of hormonal contraception is length of use of hormonal contraception (injections, pills and implants). The duration of hormonal contraceptive use (injections, pills and implants) is categorized into two, namely more than 5 years and not long if the user is less than 5 years. The data were based on diagnosis recorded in the medical record. A possible confounders were marriage age less than 20 years, family history of cancer, active smoking, and parity more than 3. For statistical analysis, the bivariate analysis used chi-square tests, and the multivariate analysis used logistic regression. The p-value of the likelihood ratio to the chi-square was used as a guide to the model's goodness of fit. All p-values were two-tailed and statistical significance level was set as less than 0.05. Ethical approval granted from the Ethics Committee of the Faculty of Medicine, Gadjah Mada University No.KE/KF/0561/EC/2018.

### Results

This research was conducted at Dr. Sardjito. Total of subjects who participated in the study was 190 subjects (95 for case group/ women who were diagnosed with cervical cancer), and 95 for the control group (women who did not have cervical cancer or Pap smear tests were negative). The duration of hormonal contraceptive use (injections, pills and implants) is categorized into two, namely more than 5 years and not long if the user is less than 5 years. Table 1 presents the correlation of the duration of use hormonal contraception with cervical cancer and other affecting factors.

Tabel 1. Correlation of the duration of use hormonal contraception, age of marriage, parity, active smoking, family history of cancer with cervical cancer

| Variable | Case n (%) | Control n (%) | p-value | OR | 95% CI | |
|---|---|---|---|---|---|---|
| | | | | | Lower | Upper |
| Hormonal contraception > 5 years | 59 (62,1) | 26 (27,4) | 0,01 | 4,3 | 2,35 | 8,02 |
| - use of pills> 5 years | 16 (51,6) | 3 (13,0) | 0,01 | 7,1 | 1,74 | 28,9 |
| - use of injections > 5 years | 32 (66,7) | 13 (35,1) | 0,01 | 3,6 | 1,49 | 9.11 |
| - use of implants > 5 years | 11 (68,8) | 10 (28,6) | 0,01 | 5,5 | 1,51 | 19.9 |
| The first age of marriage < 20 years | 47 (49,5) | 28 (29,5) | 0,01 | 2,3 | 1,29 | 4,25 |
| Parity > 3 | 27 (28,4) | 13 (13,7) | 0,02 | 2,5 | 1,20 | 5,22 |
| Active Smoking | 2 (2,1) | 0 (0,0) | 0,49 | 2,0 | 1,75 | 2,33 |
| Family history of cancer | 2 (2,1) | 2 (2,1) | 1,00 | 1,00 | 0,13 | 7,24 |

n = Number of Sample; OR = Odds Ratio; CI= Convidence Interval

This study showed that the correlation between duration of use hormonal contraception, the first age of marriage, parity, active smoking, family history of cancer with cervical cancer. Duration of hormonal contraception had higher risk 4,3 times of cervical cancer than using less than 5 years. Duration of use of pills, injections and implant have a significant correlation with cervical cancer. Women who the first age of marriage <20 years had higher risk 2,3 times of cervical cancer. Parity > 3 had higher risk 2,5 times of cervical cancer There is no significant correlation between active smoking and family history of cancer with cervical cancer.

Correlation between the duration of the use hormonal contraception, the first age of marriage, parity, active smoking, family history of cancer with cervical cancer was analyzed by logistic regression using the backward method. The first step regression analysis was performed by bivariate selection. The candidates entered in multivariate analysis are variables with p-value ≤ 0.250. The analysis showed that the first age of marriage and parity had p-value ≤ 0.250 while active smoking, family history of cancer had p-value > 0.250, so they were not included in the multivariable selection.

Table 2. Correlation of duration use hormonal contraception and cervical cancer after consideration of external variables

| Variable | β | p-value | OR | 95% CI | |
|---|---|---|---|---|---|
| | | | | Lower | Upper |
| Use of contraception hormonal >5 years | 1.435 | 0.000 | 4.2 | 1.011 | 5.692 |
| The first age of married<20 years | 0.659 | 0.046 | 1.9 | 0.993 | 4.847 |
| Parity >3 | 0.786 | 0.052 | 2.1 | 2.238 | 7.880 |

Notes: β= coefficient OR= Odds Ratio CI=Convidence Interval

The result showed that the correlation between the duration of the use hormonal contraception and cervical cancer after consideration of external variables (age of married <20 years and parity >3). Period of use of contraception hormonal had 4.2 times higher risk of cervical cancer after being controlled with the first marriage age and parity.

### Discussion

This study found a correlation between duration of use hormonal contraception and cervical cancer. This strong association is marked by Odds ratio (OR) of 4.2. These results is same as or support the previous study that duration of use hormonal contraception associated with cervical cancer. The results of this study support previous studies among others, a study who stated that long-term use of hormonal contraception could lead to cervical cancer. Hormonal contraceptives acted as a tool that controlled the growth of neoplasms. The acceptors who use hormonal contraception are often found in cervical dysplasia.[14] The use of hormonal contraceptives that are longer than 4 or 5 years can disrupt the balance of estrogen in the body resulting in abnormal cell changes. Estrogen is likely to be one of the factors that can make HPV DNA replication.[14] Likewise with the length of use of each hormonal contraception. Effect of hormonal contraception can cause hyperexercition and the proliferation of endocervical glands. In addition, causes metaplasia and porto epithelial dysplasia and mucous membranes of the endocervix. Hormonal contraception increases the risk of cervical cancer for women with HPV. It is suspected that gestagen triggers the carcinogenic effect of HPV.[13,14,15]

Use of hormonal contraception, causes mucus viscosity in the cervix due to oral hormonal contraceptive use or injection will support cervical cancer. This is because this mucus viscosity will prolong the existence of a carcinogenic agent (cancer-causing) in the cervix which is carried through sexual intercourse including the presence of the HPV virus which is the cause of cervical cancer. The duration of use of implant contraceptives can increase the incidence of cervical cancer considering the mechanism of hormones in the implant to thicken cervical

and the addition of cells to the cervix to prevent the entry of sperm. If cervical mucus thickening occurs continuously and uncontrollably, the thickening will become abnormal which can lead to cervical cancer the immature will experience changes and can damage cells in the cervix.[16]

Sexual intercourse that is early can affect cervical epithelial tissue damage or the vagina cavity wall and can worsen leading to cell abnormalities that result in abnormal growth.[11] Women who begin sexual intercourse age <20 years is more at risk of developing cancer cervix. It is because in the young adult period the process of squamous cell metaplasia is substantially increased so the risk of atypical squamous transformation increases which then becomes cervical intraepithelial neoplasia (NIS).[17] The results of this study in accordance with previous studies showing women who had sexual intercourse for the first time at the age of <20 years were 2.41 times more likely to develop cervical cancer. The exposure of the uterus to the HPV will result in growth deviating into precancerous/cervical cancer.[17] Married age can be associated with age-related. At the age of the genital device that is not yet mature and has been used to connect it will damage the cervical epithelial tissue that can get worse on cell abnormalities and result in abnormal growth. Especially if the partner already has an HPV virus that is rapidly contracting.[18]

Women with high parity are associated with the occurrence of cervical column epithelium during pregnancy. This incidence causes new dynamics of immature metaplastic epithelium which can increase the risk of cell transformation especially in the cervix resulting in persistent HPV infection.[18] Sondang and Dian showed that women are often giving birth, it will affect the frequent occurrence of injury to a woman's reproductive organs, which in turn will make it easier for the HPV to cause cancer. In the case of women who gave birth frequently and at proximity, damage to the epithelial tissue develops towards the growth of abnormal cells that are potentially malignant. In labor that often has the opportunity to be contaminated by a virus that causes infection. The bacteria are present because of poorly maintained vaginal hygiene conditions that can develop into malignancy.[19]

According to American cancer, if a mother or sister has cervical cancer, it can increase the incidence of cervical cancer than those who do not have a family history of cervical cancer. This is due to the genetic tendency of the family to inherit the condition.[20] The results of this study indicate that women whose families have a history of cervical cancer do not influence cervical cancer. This study was different from the research which showed that family history of cervical cancer has a risk of 2.19 times affected by cervical cancer.[21] Respondents who have had cancer in their families cervix has a risk of 14.93 times for cervical cancer. Especially in the nuclear family (first) cervical cancer is a vulnerability that inherits. However, it is unclear whether the risks are related, with history of family cancer being due to genetic susceptibility or the influence of the environmental lifestyle.[18] At present there is a need for counseling on contraceptive use, especially hormonal contraception, because high levels of hormonal contraceptive use by acceptors are thought to be the effect of not providing extensive information about the advantages and disadvantages of contraception and quality contraceptive services [21]

### Conclusion

Duration of use of contraception hormonal >5 years has a strong correlation with cervical cancer after controlled by other factors. Method of contraception hormonal >5 years had 4.2 times higher (95% CI: 1.01-5.69) for cervical cancer than use of contraception hormonal <5 years.

### Recommendations

For all women who do not want more children, should use non-hormonal long-term contraception. It is necessary to promotion for women or contraceptive acceptors using hormonal up to 5 years.

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Korespondensi Tanggal 11 Juni 2019

# Duration of Hormonal Contraception and Risk of Cervical Cancer

# Lama Penggunaan Kontrasepsi Hormonal dan Kejadian Kanker Serviks


## Abstract

The use of long hormonal contraceptives can disrupt the balance of estrogen in the body, resulting in abnormal cell changes. This study aimed to determine a correlation between the duration of hormonal contraception and risk of cervical cancer. A case-control study was conducted on 190 in female patients in Dr. Sardjito Central General Hospital, Yogyakarta. Case samples were 95 women have cervical cancer diagnosis and control were 95 women with a negative pap smear. Data on cervical cancer and the duration of hormonal contraception are obtained from medical records. Cervical cancer is assessed by doctor's diagnosis. The length of hormonal contraception is categorized as long if more than 5 years. Data analysis used logistic regression. Results showed that 44,7% of samples used long-term hormonal contraception (over 5 years). Length of use of hormonal contraception had a significant correlation with the incidence of cervical cancer (p-value < 0.01). Hormonal contraceptive use more than 5 years have a risk 4.2 times (95% CI 1.01-5.69) of cervical cancer than using less than 5 years after being controlled with the first marriage age and parity.



**Keywords:** Cervical cancer, duration of using, age og marriage, parity, hormonal contraception



## Abstrak

Penggunaan kontrasepsi hormonal yang lama dapat mengganggu keseimbangan estrogen dalam tubuh, sehingga menghasilkan perubahan sel yang tidak normal. Penelitian ini bertujuan untuk mengetahui hubungan antara lama penggunaan kontrasepsi hormonal dan risiko kanker serviks. Sebuah studi kasus kontrol dilakukan pada 190 perempuan yang dirawat di RSUP Dr. Sardjito, Yogyakarta. Sampel kasus adalah 95 wanita yang memiliki diagnosa kanker serviks dan kontrol adalah 95 wanita dengan hasil pap smear negatif. Data tentang kanker serviks dan lama penggunaan kontrasepsi diperoleh dari rekam medis. Kanker serviks dinilai berdasarkan diagnosis. Lama penggunaan kontrasepsi hormonal dikategorikan lama apabila lebih dari 5 tahun. Analisis data menggunakan regresi logistik. Hasil penelitian menunjukkan bahwa 44,7% sampel menggunakan kontrasepsi hormonal jangka panjang (lebih dari 5 tahun). Lama penggunaan kontrasepsi hormonal memiliki hubungan yang signifikan dengan kejadian kanker serviks (nilai p < 0,01). Penggunaan kontrasepsi hormonal lebih dari 5 tahun memiliki risiko 4.2 kali (95% CI 1.01-3.69) menderita kanker serviks daripada menggunakan kurang dari 5 tahun setelah dikontrol dengan faktor usia pernikahan pertama dan paritas.



Kata kunci: Kanker serviks, kontrasepsi hormonal, lama penggunaan, usia kawin, paritas


## Introduction

Cervical cancer is a cause of mortality among women in the world and Indonesia.[1] In the world, cervical cancer ranks third as the cause of death in women with an estimated death rate of 15 per 100.000 women.[2] Meanwhile, in developing countries including Indonesia, cervical cancer ranks highest as the most common cause of death among women, about 80% of total cases.[3] Cervical cancer patients in Indonesia estimated 90-100 among 100.000 inhabitants per year [4,5,6] Yogyakarta is an area with the highest cancer incidence in Indonesia which has a prevalence of cervical cancer of 1.5 ‰. [7,8] Cervical cancer always ranks third of the 10 major cancers existing in Dr. Sardjito Central General Hospital.

Cervical cancer has a long journey from the precancerous stage, takes 10-20 years to develop into invasive cancer. Patients can complain of severe pain; pain can be felt during sexual intercourse, abnormal bleeding during sexual intercourse and when cancer has spread to the brain and lungs pulmonary (stage IVB), the life of the patient will be increasingly difficult to save. [9,10] Research conducted by Yvonne Nartey, Philip C. Hill, Kwabena Amo-Antwi, et al. in 2017, showed that of 821 women diagnosed with cervical cancer, 497 women (60,5%) died during follow-up. Having been diagnosed with cervical cancer can survive 1 year after diagnosis by 62%, 3 years after diagnosis by 39%, and 5 years of diagnosis 30% [10].

According to the results of research, showed that the factors that correlate with cervical cancer are early sexual intercourse is less than 20 years, parity is more than 3, and the use of hormonal contraception more than 5 years.[11] The risk factors of cervical cancer are low education, infections like trichomonas vaginalis, bacterial vaginosis, disorders on genitals, and contraceptive use. [11] How long the body's exposure to hormones in any hormonal contraception is still unknown, so the duration of each hormonal contraceptive usage still needs to be examined. [12]

Data of active family planning participants from 2014 to 2016 showed an increasing trend from year to year. Data of active family planning participants who used hormonal contraception was 81.58% to 81,97% (injected 47,54%, pills 23,58%, implants 10,46%).[13] The purpose of this study was to determine the relationship between the duration of hormonal contraception use and the incidence of cervical cancer and knowing other factors related to cervical cancer incidence.

## Methods

This study used a case-control design. Samples were patients who had examined at a cancer installation, and obstetrics-gynecology polyclinic Dr. Sardjito Hospital, Yogyakarta, Indonesia. Case samples were 95 women who were diagnosed with cervical cancer, while the control samples were 95 women who did not have cervical cancer (Pap smear tests were negative). Subjects were excluded if has never used hormonal contraception and medical record data is incomplete. The study was conducted in July 2018 with random assignment. Independent variable is duration of hormonal contraception, whereas the dependent variable is cervical cancer. Cervical cancer is assessed from diagnosis. The duration of hormonal contraception is length of use of hormonal contraception (injections, pills and implants). The duration of hormonal contraceptive use (injections, pills and implants) is categorized into two, namely more than 5 years and not long if the user is less than 5 years. The data were based on diagnosis recorded in the medical record. A possible confounders were marriage age less than 20 years, family history of cancer, active smoking, and parity more than 3. For statistical analysis, the bivariate analysis used chi-square tests, and the multivariate analysis used logistic regression. The p-value of the likelihood ratio to the chi-square was used as a guide to the model's goodness of fit. All p-values were two-tailed and statistical significance level was set as less than 0.05. Ethical approval granted from the Ethics Committee of the Faculty of Medicine, Gadjah Mada University No.KE/KF/0561/EC/2018.

## Results

This research was conducted at Dr. Sardjito. Total of subjects who participated in the study was 190 subjects (95 for case group/ women who were diagnosed with cervical cancer), and 95 for the control group (women who did not have cervical cancer or Pap smear tests were negative). The duration of hormonal contraceptive use (injections, pills and implants) is categorized into two, namely more than 5 years and not long if the user is less than 5 years. Table 1 presents the correlation of the duration of use hormonal contraception with cervical cancer and other affecting factors.

Tabel 1. Correlation of the duration of use hormonal contraception, age of marriage, parity, active smoking, family history of cancer with cervical cancer

| Variable | Case n (%) | Control n (%) | p-value | OR | 95% CI | |
|---|---|---|---|---|---|---|
| | | | | | Lower | Upper |
| Hormonal contraception > 5 years | 59 (62,1) | 26 (27,4) | 0,01 | 4,3 | 2,35 | 8,02 |
| - use of pills> 5 years | 16 (51,6) | 3 (13,0) | 0,01 | 7,1 | 1,74 | 28,9 |
| - use of injections > 5 years | 32 (66,7) | 13 (35,1) | 0,01 | 3,6 | 1,49 | 9.11 |
| - use of implants > 5 years | 11 (68,8) | 10 (28,6) | 0,01 | 5,5 | 1,51 | 19.9 |
| The first age of marriage < 20 years | 47 (49,5) | 28 (29,5) | 0,01 | 2,3 | 1,29 | 4,25 |
| Parity > 3 | 27 (28,4) | 13 (13,7) | 0,02 | 2,5 | 1,20 | 5,22 |
| Active Smoking | 2 (2,1) | 0 (0,0) | 0,49 | 2,0 | 1,75 | 2,33 |
| Family history of cancer | 2 (2,1) | 2 (2,1) | 1,00 | 1,00 | 0,13 | 7,24 |

n = Number of Sample; OR = Odds Ratio; CI= Convidence Interval

This study showed that the correlation between duration of use hormonal contraception, the first age of marriage, parity, active smoking, family history of cancer with cervical cancer. Duration of hormonal contraception had higher risk 4,3 times of cervical cancer than using less than 5 years. Duration of use of pills, injections and implant have a significant correlation with cervical cancer. Women who the first age of marriage <20 years had higher risk 2,3 times of cervical cancer. Parity > 3 had higher risk 2,5 times of cervical cancer There is no significant correlation between active smoking and family history of cancer with cervical cancer.

Correlation between the duration of the use hormonal contraception, the first age of marriage, parity, active smoking, family history of cancer with cervical cancer was analyzed by logistic regression using the backward method. The first step regression analysis was performed by bivariate selection. The candidates entered in multivariate analysis are variables with p-value ≤ 0.250. The analysis showed that the first age of marriage and parity had p-value ≤ 0.250 while active smoking, family history of cancer had p-value > 0.250, so they were not included in the multivariable selection.

Table 2. Correlation of duration use hormonal contraception and cervical cancer after consideration of external variables

| Variable | β | p-value | OR | 95% CI | |
|---|---|---|---|---|---|
| | | | | Lower | Upper |
| Use of contraception hormonal >5 years | 1.435 | 0.000 | 4.2 | 1.011 | 5.692 |
| The first age of married<20 years | 0.659 | 0.046 | 1.9 | 0.993 | 4.847 |
| Parity >3 | 0.786 | 0.052 | 2.1 | 2.238 | 7.880 |

Notes: β= coefficient OR= Odds Ratio CI=Convidence Interval

The result showed that the correlation between the duration of the use hormonal contraception and cervical cancer after consideration of external variables (age of married <20 years and parity >3). Period of use of contraception hormonal had 4.2 times higher risk of cervical cancer after being controlled with the first marriage age and parity.

## Discussion

This study found a correlation between duration of use hormonal contraception and cervical cancer. This strong association is marked by Odds ratio (OR) of 4.2. These results is same as or support the previous study that duration of use hormonal contraception associated with cervical cancer. The results of this study support previous studies among others, a study who stated that long-term use of hormonal contraception could lead to cervical cancer. Hormonal contraceptives acted as a tool that controlled the growth of neoplasms. The acceptors who use hormonal contraception are often found in cervical dysplasia.[14] The use of hormonal contraceptives that are longer than 4 or 5 years can disrupt the balance of estrogen in the body resulting in abnormal cell changes. Estrogen is likely to be one of the factors that can make HPV DNA replication.[14] Likewise with the length of use of each hormonal contraception. Effect of hormonal contraception can cause hyperexcretion and the proliferation of endocervical glands. In addition, causes metaplasia and porto epithelial dysplasia and mucous membranes of the endocervix. Hormonal contraception increases the risk of cervical cancer for women with HPV. It is suspected that gestagen triggers the carcinogenic effect of HPV.[13,14,15]

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and the addition of cells to the cervix to prevent the entry of sperm. If cervical mucus thickening occurs continuously and uncontrollably, the thickening will become abnormal which can lead to cervical cancer the immature will experience changes and can damage cells in the cervix.[16]

Sexual intercourse that is early can affect cervical epithelial tissue damage or the vagina cavity wall and can worsen leading to cell abnormalities that result in abnormal growth.[13] Women who begin sexual intercourse age <20 years is more at risk of developing cancer cervix. It is because in the young adult period the process of squamous cell metaplasia is substantially increased so the risk of atypical squamous transformation increases which then becomes cervical intraepithelial neoplasia (NIS).[17] The results of this study in accordance with previous studies showing women who had sexual intercourse for the first time at the age of <20 years were 2.41 times more likely to develop cervical cancer. The exposure of the uterus to the HPV will result in growth deviating into precancerous/cervical cancer.[13] Married age can be associated with age-related. At the age of the genital device that is not yet mature and has been used to connect it will damage the cervical epithelial tissue that can get worse on cell abnormalities and result in abnormal growth. Especially if the partner already has an HPV virus that is rapidly contracting.[18]

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According to American cancer, if a mother or sister has cervical cancer, it can increase the incidence of cervical cancer than those who do not have a family history of cervical cancer. This is due to the genetic tendency of the family to inherit the condition.[20] The results of this study indicate that women whose families have a history of cervical cancer do not influence cervical cancer. This study was different from the research which showed that family history of cervical cancer has a risk of 2.19 times affected by cervical cancer.[21] Respondents who have had cancer in their families cervix has a risk of 14.93 times for cervical cancer. Especially in the nuclear family (first) cervical cancer is a vulnerability that inherits. However, it is unclear whether the risks are related, with history of family cancer being due to genetic susceptibility or the influence of the environmental lifestyle.[13] At present there is a need for counseling on contraceptive use, especially hormonal contraception, because high levels of hormonal contraceptive use by acceptors are thought to be the effect of not providing extensive information about the advantages and disadvantages of contraception and quality contraceptive services [21]

## Conclusion

Duration of use of contraception hormonal >5 years has a strong correlation with cervical cancer after controlled by other factors. Method of contraception hormonal >5 years had 4.2 times higher (95% CI: 1.01-5.69) for cervical cancer than use of contraception hormonal <5 years.

## Recommendations

For all women who do not want more children, should use non-hormonal long-term contraception. It is necessary to promotion for women or contraceptive acceptors using hormonal up to 5 years.

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Korespondensi Tanggal 25 Juni 2019

# Duration of Hormonal Contraception and Risk of Cervical Cancer

## Lama Penggunaan Kontrasepsi Hormonal dan Kejadian Kanker Serviks


### Abstract

The use of long hormonal contraceptives can disrupt the balance of estrogen in the body, resulting in abnormal cell changes. This study aimed to determine a correlation between the duration of hormonal contraception and risk of cervical cancer. This study used a case-control design. The Population were patients who had examined at a cancer installation and obstetrics-gynecology polyclinic Dr. Sardjito Hospital in 2018. Case samples were 95 women have cervical cancer diagnosis and control samples were 95 woman with a negative cervical cancer. Subjects were excluded if has never used hormonal contraception and medical record data is incomplete. Sampling with random sampling. The study was conducted in July 2018. Independent variable is duration of hormonal contraception, whereas the dependent variable is cervical cancer. Cervical cancer is assessed by doctor's diagnosis. The duration of hormonal contraception is length of use of hormonal contraception (injections, pills and implants). The length of hormonal contraception is categorized as long if more than 5 years. A possible confounders were marriage age less than 20 years, family history of cancer, active smoking, and parity more than 3. The data were based on diagnosis recorded in the medical record. Data analysis used logistic regression. Results showed that 44,7% of samples used long-term hormonal contraception (over 5 years). Length of use of hormonal contraception had a significant correlation with the incidence of cervical cancer (p-value < 0.01). Hormonal contraceptive use more than 5 years have a risk 4,2 times (95% CI 1,01-5,69) of cervical cancer than using less than 5 years after being controlled with the first marriage age and parity.



**Keywords:** Cervical cancer, duration of using, age of marriage, parity, hormonal contraception



### Abstrak

Penggunaan kontrasepsi hormonal yang lama dapat mengganggu keseimbangan estrogen dalam tubuh, sehingga menghasilkan perubahan sel yang tidak normal. Penelitian ini bertujuan untuk mengetahui hubungan antara lama penggunaan kontrasepsi hormonal dan risiko kanker serviks. Penelitian ini menggunakan desain kasus-kontrol. Populasi adalah pasien yang pernah diperiksa di instalasi kanker dan poliklinik obstetri-ginekologi Rumah Sakit Dr. Sardjito Tahun 2018. Sampel kasus adalah 95 wanita yang didiagnosis kanker serviks dan kontrol adalah 95 wanita dengan kanker serviks negatif. Subjek dieksklusi apabila tidak pernah menggunakan kontrasepsi hormonal dan data rekam media tidak lengkap. Pengambilan sampel dengan random sampling.Variabel independen adalah lama penggunaan kontrasepsi hormonal, sedangkan variabel dependen adalah kanker serviks. Kanker serviks dinilai berdasarkan diagnosis dokter. Lama penggunaan kontrasepsi hormonal dikategorikan panjang jika lebih dari 5 tahun. Variabel luar yang juga dinilai adalah usia pernikahan kurang dari 20 tahun, riwayat keluarga menderita kanker, merokok aktif, dan paritas lebih dari 3. Data berasal dari catatan medis. Analisis data menggunakan regresi logistik. Hasil penelitian menunjukkan bahwa 44,2% sampel menggunakan kontrasepsi hormonal jangka panjang (lebih dari 5 tahun). Lama penggunaan kontrasepsi hormonal memiliki korelasi yang signifikan dengan kejadian kanker serviks (nilai-p <0,01). Penggunaan kontrasepsi hormonal lebih dari 5 tahun memiliki risiko 4,2 kali (95% CI 1,01-5,69) mendapat kanker serviks dibandingkan penggunaan kurang dari 5 tahun setelah dikendalikan faktor paritas dan usia pernikahan pertama.



Kata kunci: Kanker serviks, lama penggunaan, usia menikah, paritas, kontrasepsi hormonal


### Introduction

Cervical cancer is a cause of mortality among women in the world and Indonesia.[1,2] In the world, cervical cancer ranks third as the cause of death in women with an estimated death rate of 15 per 100.000 women.[1,2] Meanwhile, in developing countries including Indonesia, cervical cancer ranks highest as the most cause of death among women, about 80% of total cases.[1,2] Cervical cancer patients in Indonesia estimated 90-100 among 100.000 inhabitants per year [3,4,5]. Yogyakarta is an area with the highest cancer incidence in Indonesia which has a prevalence of cervical cancer of 1.5 ‰. [3,5] Cervical cancer always ranks third of the 10 major cancer existing in Dr. Sardjito Central General Hospital.

Cervical cancer has a long journey from the precancerous stage, takes 10-20 years to develop into invasive cancer. Patients can complain of severe pain; pain can be felt during sexual intercourse, abnormal bleeding during sexual intercourse and when cancer has spread to the brain and lungs pulmonary (stage IVB), the life of the patient will be increasingly difficult to save. [6,7] Research conducted by Yvonne Nartey, Philip C. Hill, Kwabena Amo-Antwi, et al. in 2017, showed that of 821 women diagnosed with cervical cancer, 497 women (60,5%) died during follow-up. Having been diagnosed with cervical cancer can survive 1 year after diagnosis by 62%, 3 years after diagnosis by 39%, and 5 years of diagnosis 30% [7,8].

According to the results of research, showed that the factors that correlate with cervical cancer are early sexual intercourse is less than 20 years, parity is more than 3, and the use of hormonal contraception more than 5 years.[9] The risk factors of cervical cancer are low education, infections like trichomonas vaginalis, bacterial vaginosis, disorders on genitals, and contraceptive use. [10] How long the body's exposure to hormones in any hormonal contraception is still unknown, so the duration of each hormonal contraceptive usage still needs to be examined. [11,12]

Data of active family planning participants from 2014 to 2016 showed an increasing trend from year to year. Data of active family planning participants who used hormonal contraception was 81.58% to 81,97% (injected 47,54%, pills 23,58%, implants 10,46%).[13] The purpose of this study was to determine the relationship between the duration of hormonal contraception use and the incidence of cervical cancer and knowing other factors related to cervical cancer incidence.

### Methods

This study used a case-control design. The Population were patients who had examined at a cancer installation and obstetrics-gynecology polyclinic Dr. Sardjito Hospital Yogyakarta, Indonesia in 2018. The study was conducted in July 2018. Sampling with random sampling. Case samples were 95 women who were diagnosed with cervical cancer, while the control samples were 95 women who did not have cervical cancer (Pap smear tests were negative). Subjects were excluded if has never used hormonal contraception and medical record data is incomplete. Independent variable is duration of hormonal contraception, whereas the dependent variable is cervical cancer. Cervical cancer is assessed by doctor's diagnosis. The duration of hormonal contraception is length of use of hormonal contraception (injections, pills and implants). The duration of hormonal contraceptive use (injections, pills and implants) is categorized into two, namely more than 5 years and not long if the user is less than 5 years. The data were based on diagnosis recorded in the medical record. A possible confounders were marriage age less than 20 years, family history of cancer, active smoking, and parity more than 3. For statistical analysis, the bivariate analysis used chi-square tests, and the multivariate analysis used logistic regression. The p-value of the likelihood ratio to the chi-square was used as a guide to the model's goodness of fit. All p-values was two-tailed and statistical significance level was set as less than 0.05. Ethical approval granted from the Ethics Committee of the Faculty of Medicine, Gadjah Mada University No.KE/KF/0561/EC/2018.

### Results

This research was conducted at Dr. Sardjito. Total of subjects who participated in the study was 190 subjects (95 for case group/ women who was diagnosed with cervical cancer), and 95 for the control group (women who did not have cervical cancer or Pap smear tests were negative). The duration of hormonal contraceptive use (injections, pills and implants) is categorized into two, namely more than 5 years and not long if the user is less than 5 years. Table 1 presents the correlation of the duration of use hormonal contraception with cervical cancer and other affecting factors.

Tabel 1. Correlation of the duration of use hormonal contraception, age of marriage, parity, active smoking, family history of cancer with cervical cancer

| Variable | Case n (%) | Control n (%) | p-value | OR | 95% CI | |
|---|---|---|---|---|---|---|
| | | | | | Lower | Upper |
| **Hormonal contraception** > 5 years | 59 (62,1) | 20 (21,4) | 0,01 | 4,3 | 2,35 | 8,02 |
| use of pills> 5 years | 16 (51,6) | 3 (13,0) | 0,01 | 7,1 | 1,74 | 28,9 |
| use of injections > 5 years | 32 (66,7) | 13 (35,1) | 0,01 | 3,6 | 1,49 | 9,11 |
| use of implants > 5 years | 11 (68,8) | 10 (28,6) | 0,01 | 5,5 | 1,51 | 19,9 |
| The first age of marriage < 20 years | 47 (49,5) | 28 (29,5) | 0,01 | 2,3 | 1,29 | 4,25 |
| Parity > 3 | 27 (28,4) | 13 (13,7) | 0,02 | 2,5 | 1,20 | 5,22 |
| Active Smoking | 2 (2,1) | 0 (0,0) | 0,49 | 2,0 | 1,75 | 2,33 |
| Family history of cancer | 2 (2,1) | 2 (2,1) | 1,00 | 1,00 | 0,13 | 7,24 |

n = Number of Sample; OR = Odds Ratio; CI= Convidence Interval

This study showed that the correlation between duration of use hormonal contraception, the first age of marriage, parity, active smoking, , family history of cancer with cervical cancer. Duration of hormonal contraception had higher risk 4,3 times of cervical cancer than using less than 5 years. Duration of use of pills, injections and implant have a significant correlation with cervical cancer. Women who the first age of marriage <20 years had higher risk 2,3 times of cervical cancer. Parity > 3 had higher risk 2,5 times of cervical cancer There is no significant correlation between active smoking and family history of cancer with cervical cancer.

Correlation between the duration of the use hormonal contraception, the first age of marriage, parity, active smoking, family history of cancer with cervical cancer was analyzed by logistic regression using the backward method. The first step regression analysis was performed by bivariate selection. The candidates entered in multivariate analysis are variables with p-value ≤ 0.250. The analysis showed that the first age of marriage and parity had p-value ≤ 0.250 while active smoking, family history of cancer had p-value > 0.250, so they were not included in the multivariable selection.

Table 2. Correlation of duration use hormonal contraception and cervical cancer after consideration of external variables

| Variable | β | p-value | OR | 95% CI | |
|---|---|---|---|---|---|
| | | | | Lower | Upper |
| Use of contraception hormonal >5 years | 1.435 | 0.000 | 4.2 | 1.001 | 5.692 |
| The first age of married<20 years | 0.659 | 0.046 | 1.9 | 0.993 | 4.847 |
| Parity >3 | 0.786 | 0.052 | 2.1 | 2.238 | 7.880 |

Notes: β= coefficient OR= Odds Ratio CI=Convidence Interval

The result showed that the correlation between the duration of the use hormonal contraception and cervical cancer after consideration of external variables (age of married <20 years and parity >3). Period of use of contraception hormonal had 4.2 times higher risk of cervical cancer after being controlled with the first marriage age and parity.

### Discussion

This study found a correlation between duration of use hormonal contraception and cervical cancer. This strong association is marked by Odds ratio (OR) of 4.2. These results is same as or support the previous study that duration of use hormonal contraception associated with cervical cancer. The results of this study support previous studies among others, a study who stated that long-term use of hormonal contraception could lead to cervical cancer. A biologically plausible mechanism for this relationship is hormonal contraceptive acted as a tool that controlled the growth of neoplasms. The acceptors who use hormonal contraception are often found in cervical dysplasia.[14] The use of hormonal contraceptives that are longer than 4 or 5 years can disrupt the balance of estrogen in the body resulting in abnormal cell changes. Estrogen is likely to be one of the factors that can make HPV DNA replication.[15] Likewise with the length of use of such hormonal contraception.

Effect of hormonal contraception can cause hypersecretion and the proliferation of endocervical glands. In addition, causes metaplasia and portio epithelial dysplasia and mucous membranes of the endocervix. Hormonal contraception increases the risk of cervical cancer for women with HPV. It is suspected that gestagen triggers the carcinogenic effect of HPV.[15,16]

Use of hormonal contraception, causes mucus viscosity in the cervix due to oral hormonal contraceptive use or injection will support cervical cancer. This is because this mucus viscosity will prolong the existence of a carcinogenic agent (cancer-causing) in the cervix which is carried through sexual intercourse including the presence of the HPV virus which is the cause of cervical cancer. The duration of use of implant contraceptives can increase the incidence of cervical cancer considering the mechanism of hormones in the implant to thicken cervical mucus. The process of cervical mucus removal is the replacement of new cells and the addition of cells to the cervix to prevent the entry of sperm. If cervical mucus thickening occurs continuously and uncontrollably, the thickening will become abnormal which can lead to cervical cancer the immature will experience changes and can damage cells in the cervix.[17]

Other factors such as age at first marriage and parity were statistically related to cervical cancer incidence. Sexual intercourse that is early can affect cervical epithelial tissue damage or the vagina cavity wall and can worsen leading to cell abnormalities that result in abnormal growth.[17] Women who begin sexual intercourse age <20 years is more at risk of developing cancer cervix. It is because in the young adult period the process of squamous cell metaplasia is substantially increased so the risk of atypical squamous transformation increases which then becomes cervical intraepithelial neoplasia (VIS).[17] The results of this study in accordance with previous studies showing women who had sexual intercourse for the first time at the age of <20 years were 2.41 times more likely to develop cervical cancer. The exposure of the uterus to the HPV will result in growth deviating into precancerous cervical cancer.[17] Married age can be associated with age-related. At the age of the genital device that is not yet mature and has been used to connect it will damage the cervical epithelial tissue that can get worse on cell abnormalities and result in abnormal growth. Especially if the partner already has an HPV virus that is rapidly contracting.[18]

Women with high parity are associated with the occurrence of cervical column epithelium during pregnancy. This incidence causes new dynamics of immature metaplastic epithelium which can increase the risk of cell transformation especially in the cervix resulting in persistent HPV infection.[19] Sonday and Dias showed that women are often giving birth, it will affect the frequent occurrence of injury to a woman's reproductive organs, which in turn will make it easier for the HPV to cause cancer. In the case of women who gave birth frequently and at proximity, damage to the epithelial tissue develops towards the growth of abnormal cells that are potentially malignant. In labor that often has the opportunity to be contaminated by a virus that causes infection. The bacteria are present because of poorly maintained vaginal hygiene conditions that can develop into malignancy.[19]

### Conclusion

Duration of use of contraception hormonal >5 years has a strong correlation with cervical cancer. Method of contraception hormonal >5 years had 4.2 times higher for cervical cancer than use of contraception hormonal < 5 years. Other factors such as age at first marriage and parity were statistically related to cervical cancer incidence while smoking and family history there is no relationship statistically with the incidence of cervical cancer.

### Recommendation:

For all women who do not want more children, should use non-hormonal long-term contraception. It is necessary to promotion for woman or contraceptive acceptors using hormonal up to 5 years.

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Korespondensi Tanggal 26 Juni 2019

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## Lama Penggunaan Kontrasepsi Hormonal dan Kejadian Kanker Serviks


### Abstract

The use of long hormonal contraceptives can disrupt the balance of estrogen in the body, resulting in abnormal cell changes. This study aimed to determine a correlation between the duration of hormonal contraception and risk of cervical cancer. This study used a case-control design. The population were patients who had examined at a cancer installation and obstetrics-gynecology polyclinic Dr. Sardjito Hospital in 2018. Case samples were 95 women have cervical cancer diagnosis and control were 95 women with a negative pap smear. Sampling with random sampling. Dependent variable cervical cancer and independent variable the duration of hormonal contraception are obtained from medical records. Cervical cancer is assessed by doctor's diagnosis. Data analysis used logistic regression. Results showed that 44,7% of samples used long-term hormonal contraception (over 5 years). Length of use of hormonal contraception had a significant correlation with the incidence of cervical cancer (p-value < 0.01). Hormonal contraceptive use more than 5 years have a risk 4.2 times (95% CI 1.01-5.69) of cervical cancer than using less than 5 years after being controlled with the first marriage age and parity.


**Keywords:** Cervical cancer, duration of using, age of marriage, parity, hormonal contraception



### Abstrak

Penggunaan kontrasepsi hormonal yang lama dapat mengganggu keseimbangan estrogen dalam tubuh, sehingga menghasilkan perubahan sel yang tidak normal. Penelitian ini bertujuan untuk mengetahui hubungan antara lama penggunaan kontrasepsi hormonal dengan risiko kanker serviks. Penelitian ini menggunakan desain case-control. Populasi adalah pasien yang diperiksa di instalasi kanker dan poliklinik obstetri-ginekologi Rumah Sakit Dr. Sardjito tahun 2018. Sampel kasus adalah 95 wanita yang didiagnosis kanker serviks dan kontrol adalah 95 wanita dengan pap smear negatif. Pengambilan sampel dengan random sampling. Variabel dependen kanker serviks dan variabel independen lama penggunaan kontrasepsi hormonal diperoleh dari catatan medis. Kanker serviks dinilai berdasarkan diagnosis dokter. Analisis data menggunakan regresi logistik. Hasil penelitian menunjukkan bahwa 44,7% sampel menggunakan kontrasepsi hormon jangka panjang (lebih dari 5 tahun). Lama penggunaan kontrasepsi hormonal memiliki hubungan yang signifikan dengan kejadian kanker serviks (nilai-p <0,01). Penggunaan kontrasepsi hormonal lebih dari 5 tahun memiliki risiko 4,2 kali (95% CI 1,01-5,69) kanker serviks dibandingkan menggunakan kurang dari 5 tahun setelah dikendalikan dengan usia dan paritas pernikahan pertama.



**Kata kunci:** Kanker serviks, lama penggunaan, usia menikah, paritas, kontrasepsi hormonal


### Introduction

Cervical cancer is a cause of mortality among women in the world and Indonesia.[1] In the world, cervical cancer ranks third as the cause of death in women with an estimated death rate of 15 per 100.000 women.[2] Meanwhile, in developing countries including Indonesia, cervical cancer ranks highest as the most common cause of death among women, about 80% of total cases.[3] Cervical cancer patients in Indonesia estimated 90-100 among 100.000 inhabitants per year.[4,5] Yogyakarta is an area with the highest cancer incidence in Indonesia which has a prevalence of cervical cancer of 1.5 ‰.[5,6] Cervical cancer always ranks third of the 10 major cancers existing in Dr. Sardjito Central General Hospital.

Cervical cancer has a long journey from the precancerous stage, takes 10-20 years to develop into invasive cancer. Patients can complain of severe pain; pain can be felt during sexual intercourse, abnormal bleeding during sexual intercourse and when cancer has spread to the brain and lungs pulmonary (stage IVB), the life of the patient will be increasingly difficult to save.[5,1] Research conducted by Yvonne Nartey, Philip C. Hill, Kwabena Amo-Antwi, et al. in 2017, showed that of 821 women diagnosed with cervical cancer, 497 women (60,5%) died during follow-up. Having been diagnosed with cervical cancer can survive 1 year after diagnosis by 62%, 3 years after diagnosis by 39%, and 5 years of diagnosis 30%. [16]

According to the results of research, showed that the factors that correlate with cervical cancer are early sexual intercourse is less than 20 years, parity is more than 3, and the use of hormonal contraception more than 5 years.[7] The risk factors of cervical cancer are low education, infections like trichomonas vaginalis, bacterial vaginosis, disorders on genitals, and contraceptive use.[17] How long the body's exposure to hormones in any hormonal contraception is still unknown, so the duration of each hormonal contraceptive usage still needs to be examined.[12]

Data of active family planning participants from 2014 to 2016 showed an increasing trend from year to year. Data of active family planning participants who used hormonal contraception was 81.58% to 81,97% (injected 47,54%, pills 23,58%, implants 10,46%).[18] The purpose of this study was to determine the relationship between the duration of hormonal contraception use and the incidence of cervical cancer and knowing other factors related to cervical cancer incidence.

### Methods

This study used a case-control design. The Population were patients who had examined at a cancer installation and obstetrics-gynecology polyclinic Dr. Sardjito Hospital Yogyakarta, Indonesia in 2018. The study was conducted in July 2018. Sampling with random sampling. Case samples were 95 women who were diagnosed with cervical cancer, while the control samples were 95 women who did not have cervical cancer (Pap smear tests were negative). Subjects were excluded if has never used hormonal contraception and medical record data is incomplete. Independent variable is duration of hormonal contraception, whereas the dependent variable is cervical cancer. Cervical cancer is assessed by doctor's diagnosis. The duration of hormonal contraception is length of use of hormonal contraception (injections, pills and implants). The duration of hormonal contraceptive use (injections, pills and implants) is categorized into two, namely more than 5 years and not long if the user is less than 5 years. The data were based on diagnosis recorded in the medical record. A possible confounders were marriage age less than 20 years, family history of cancer, active smoking, and parity more than 3. For statistical analysis, the bivariate analysis used chi-square tests, and the multivariate analysis used logistic regression. The p-value of the likelihood ratio to the chi-square was used as a guide to the model's goodness of fit. All p-values were two-tailed and statistical significance level was set as less than 0.05. Ethical approval granted from the Ethics Committee of the Faculty of Medicine, Gadjah Mada University No.KE/KF/0561/EC/2018.

### Results

This research was conducted at Dr. Sardjito. Total of subjects who participated in the study was 190 subjects (95 for case group/women who were diagnosed with cervical cancer), and 95 for the control group (women who did not have cervical cancer or Pap smear tests were negative). The duration of hormonal contraceptive use (injections, pills and implants) is categorized into two, namely more than 5 years and not long if the user is less than 5 years. Table 1 presents the correlation of the duration of use hormonal contraception with cervical cancer and other affecting factors.

Tabel 1. Correlation of the duration of use hormonal contraception, age of marriage, parity, active smoking, family history of cancer with cervical cancer

| Variable | Case n (%) | Control n (%) | p-value | OR | 95% CI | |
|---|---|---|---|---|---|---|
| | | | | | Lower | Upper |
| Hormonal contraception > 5 years | 59 (62.1) | 26 (27.4) | 0.01 | 4.3 | 2.35 | 8.02 |
| " use of pills> 5 years | 16 (51.6) | 3 (13.0) | 0.01 | 7.1 | 1.74 | 28.9 |
| " use of injections > 5 years | 32 (66.7) | 13 (35.1) | 0.01 | 3.6 | 1.49 | 9.11 |
| " use of implants > 5 years | 11 (68.8) | 10 (28.6) | 0.01 | 5.5 | 1.51 | 19.9 |
| The first age of marriage < 20 years | 47 (49.5) | 28 (29.5) | 0.01 | 2.3 | 1.29 | 4.25 |
| Parity > 3 | 27 (28.4) | 13 (13.7) | 0.02 | 2.5 | 1.20 | 5.22 |
| Active Smoking | 2 (2.1) | 0 (0.0) | 0.49 | 2.0 | 1.75 | 2.33 |
| Family history of cancer | 2 (2.1) | 2 (2.1) | 1.00 | 1.00 | 0.13 | 7.24 |

n = Number of Sample; OR = Odds Ratio; CI= Convidence Interval

This study showed that the correlation between duration of use hormonal contraception, the first age of marriage, parity, active smoking, family history of cancer with cervical cancer. Duration of hormonal contraception had higher risk 4,3 times of cervical cancer than using less than 5 years. Duration of use of pills, injections and implant have a significant correlation with cervical cancer. Women who the first age of marriage <20 years had higher risk 2,3 times of cervical cancer. Parity > 3 had higher risk 2,5 times of cervical cancer. There is no significant correlation between active smoking and family history of cancer with cervical cancer.

Correlation between the duration of the use hormonal contraception, the first age of marriage, parity, active smoking, family history of cancer with cervical cancer was analyzed by logistic regression using the backward method. The first step regression analysis was performed by bivariate selection. The candidates entered in multivariate analysis are variables with p-value ≤ 0.250. The analysis showed that the first age of marriage and parity had p-value ≤ 0.250 while active smoking, family history of cancer had p-value > 0.250, so they were not included in the multivariable selection.

Table 2. Correlation of duration use hormonal contraception and cervical cancer after consideration of external variables

| Variable | β | p-value | OR | 95% CI | |
|---|---|---|---|---|---|
| | | | | Lower | Upper |
| Use of contraception hormonal >5 years | 1.435 | 0.000 | 4.2 | 1.011 | 5.692 |
| The first age of married<20 years | 0.659 | 0.046 | 1.9 | 0.993 | 4.847 |
| Parity >3 | 0.786 | 0.052 | 2.1 | 2.238 | 7.880 |

Notes: β= coefficient OR= Odds Ratio CI=Convidence Interval

The result showed that the correlation between the duration of the use hormonal contraception and cervical cancer after consideration of external variables (age of married <20 years and parity >3). Period of use of contraception hormonal had 4.2 times higher risk of cervical cancer after being controlled with the first marriage age and parity.

### Discussion

This study found a correlation between duration of use hormonal contraception and cervical cancer. This strong association is marked by Odds ratio (OR) of 4.2. These results is same as or support the previous study that duration of use hormonal contraception associated with cervical cancer. The results of this study support previous studies among others, a study who stated that long-term use of hormonal contraception could lead to cervical cancer. A biologically plausible mechanism for this relationship is hormonal contraceptives acted as a tool that controlled the growth of neoplasms. The acceptors who use hormonal contraception are often found in cervical dysplasia.[19] The use of hormonal contraceptives that are longer than 4 or 5 years can disrupt the balance of estrogen in the body resulting in abnormal cell changes. Estrogen is likely to be one of the factors that can make HPV DNA replication.[4] Likewise with the length of use of each hormonal contraception.

Effect of hormonal contraception can cause hypersecretion and the proliferation of endocervical glands. In addition, causes metaplasia and portio epithelial dysplasia and mucous membranes of the endocervix. Hormonal contraception increases the risk of cervical cancer for women with HPV. It is suspected that gestagen triggers the carcinogenic effect of HPV.[7,14]

Use of hormonal contraception, causes mucus viscosity in the cervix due to oral hormonal contraceptive use or injection will support cervical cancer. This is because this mucus viscosity will prolong the existence of a carcinogenic agent (cancer-causing) in the cervix which is carried through sexual intercourse including the presence of the HPV virus which is the cause of cervical cancer. The duration of use of implant contraceptives can increase the incidence of cervical cancer considering the mechanism of hormones in the implant to thicken cervical mucus. The process of cervical mucus removal is the replacement of new cells and the addition of cells to the cervix to prevent the entry of sperm. If cervical mucus thickening occurs continuously and uncontrollably, the thickening will become abnormal which can lead to cervical cancer the immature will experience changes and can damage cells in the cervix.[19]

Other factors such as age at first marriage and parity were statistically related to cervical cancer incidence. Sexual intercourse that is early can affect cervical epithelial tissue damage or the vagina cavity wall and can worsen leading to cell abnormalities that result in abnormal growth.[1] Women who begin sexual intercourse age <20 years is more at risk of developing cancer cervix, it is because in the young adult period the process of squamous cell metaplasia is substantially increased so the risk of atypical squamous transformation increases which then becomes cervical intraepithelial neoplasia (NIS).[20] The results of this study in accordance with previous studies showing women who had sexual intercourse for the first time at the age of <20 years were 2.41 times more likely to develop cervical cancer. The exposure of the uterus to the HPV will result in growth deviating into precancerous/cervical cancer.[7] Married age can be associated with age-related. At the age of the genital device that is not yet mature and has been used to connect it will damage the cervical epithelial tissue that can get worse on cell abnormalities and result in abnormal growth. Especially if the partner already has an HPV virus that is rapidly contracting.[1]

Women with high parity are associated with the occurrence of cervical column epithelium during pregnancy. This incidence causes new dynamics of immature metaplastic epithelium which can increase the risk of cell transformation especially in the cervix resulting in persistent HPV infection.[17] Sondang and Dian showed that women are often giving birth, it will affect the frequent occurrence of injury to a woman's reproductive organs, which in turn will make it easier for the HPV to cause cancer. In the case of women who gave birth frequently and at proximity, damage to the epithelial tissue develops towards the growth of abnormal cells that are potentially malignant. In labor that often has the opportunity to be contaminated by a virus that causes infection. The bacteria are present because of poorly maintained vaginal hygiene conditions that can develop into malignancy.[18]

According to American cancer, if a mother or sister has cervical cancer, it can increase the incidence of cervical cancer than those who do not have a family history of cervical cancer. This is due to the genetic tendency of the family to inherit the condition.[19] The results of this study indicate that women whose families have a history of cervical cancer do not influence cervical cancer. This study was different from the research which showed that family history of cervical cancer has a risk of 2.19 times affected by cervical cancer.[7] Respondents who have had cancer in their families cervix has a risk of 14.93 times for cervical cancer. Especially in the nuclear family (first) cervical cancer is a vulnerability that inherits. However, it is unclear whether the risks are related, with history of family cancer being due to genetic susceptibility or the influence of the environmental lifestyle.[4] At present there is a need for counseling on contraceptive use, especially hormonal contraception, because high levels of hormonal contraceptive use by acceptors are thought to be the effect of not providing extensive information about the advantages and disadvantages of contraception and quality contraceptive services. [20]

### Conclusion

Duration of use of contraception hormonal >5 years has a strong correlation with cervical cancer. Method of contraception hormonal >5 years had 4.2 times higher for cervical cancer than use of contraception hormonal < 5 years. Other factors such as age at first marriage and parity were statistically related to cervical cancer incidence while smoking and family history there is no relationship statistically with the incidence of cervical cancer.

### Recommendations

For all women who do not want more children, should use non-hormonal long-term contraception. It is necessary to promotion for women or contraceptive acceptors using hormonal up to 5 years.

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# Duration of Hormonal Contraception and Risk of Cervical Cancer

# Lama Penggunaan Kontrasepsi Hormonal dan Kejadian Kanker Serviks


## Abstract

The use of long hormonal contraceptives can disrupt the balance of estrogen in the body, resulting in abnormal cell changes. This study aimed to determine a correlation between the duration of hormonal contraception and risk of cervical cancer. This study used a case-control design. The population were patients who had examined at a cancer installation and obstetrics-gynecology polyclinic Dr. Sardjito Hospital in 2018. Case samples were 95 women have cervical cancer diagnosis and control were 95 women with a negative pap smear. Sampling with random sampling. Dependent variable cervical cancer and independent variable the duration of hormonal contraception are obtained from medical records. Cervical cancer is assessed by doctor's diagnosis. Data analysis used logistic regression. Results showed that 44.7% of samples used long-term hormonal contraception (over 5 years). Length of use of hormonal contraception had a significant correlation with the incidence of cervical cancer (p-value < 0.01). Hormonal contraceptive use more than 5 years have a risk 4.2 times (95% CI 1.01-5.69) of cervical cancer than using less than 5 years after being controlled with the first marriage age and parity.


**Keywords:** Cervical cancer, duration of using, age og marriage, parity, hormonal contraception



## Abstrak

Penggunaan kontrasepsi hormonal yang lama dapat mengganggu keseimbangan estrogen dalam tubuh, sehingga menghasilkan perubahan sel yang tidak normal. Penelitian ini bertujuan untuk mengetahui hubungan antara lama penggunaan kontrasepsi hormonal dengan risiko kanker serviks. Penelitian ini menggunakan desain case-control. Populasi adalah pasien yang diperiksa di instalasi kanker dan poliklinik obstetri-ginekologi Rumah Sakit Dr. Sardjito tahun 2018. Sampel kasus adalah 95 wanita yang didiagnosis kanker serviks dan kontrol adalah 95 wanita dengan pap smear negatif. Pengambilan sampel dengan random sampling. Variabel dependen kanker serviks dan variabel independen lama penggunaan kontrasepsi hormonal diperoleh dari catatan medis. Kanker serviks dinilai berdasarkan diagnosis dokter. Analisis data menggunakan regresi logistik. Hasil penelitian menunjukkan bahwa 44.7% sampel menggunakan kontrasepsi hormon jangka panjang (lebih dari 5 tahun). Lama penggunaan kontrasepsi hormonal memiliki hubungan yang signifikan dengan kejadian kanker serviks (nilai-p <0.01). Penggunaan kontrasepsi hormonal lebih dari 5 tahun memiliki risiko 4.2 kali (95% CI 1.01-5.69) kanker serviks dibandingkan menggunakan kurang dari 5 tahun setelah dikendalikan dengan usia dan paritas pernikahan pertama.



**Kata kunci:** Kanker serviks, lama penggunaan, usia menikah, paritas, kontrasepsi hormonal


## Introduction

Cervical cancer is a cause of mortality among women in the world and Indonesia.[1] In the world, cervical cancer ranks third as the cause of death in women with an estimated death rate of 15 per 100.000 women.[2] Meanwhile, in developing countries including Indonesia, cervical cancer ranks highest as the most common cause of death among women, about 80% of total cases.[3] Cervical cancer patients in Indonesia estimated 90-100 among 100.000 inhabitants per year.[4,5,6] Yogyakarta is an area with the highest cancer incidence in Indonesia which has a prevalence of cervical cancer of 1.5 ‰.[7,8] Cervical cancer always ranks third of the 10 major cancers existing in Dr. Sardjito Central General Hospital.

Cervical cancer has a long journey from the precancerous stage, takes 10-20 years to develop into invasive cancer. Patients can complain of severe pain; pain can be felt during sexual intercourse, abnormal bleeding during sexual intercourse and when cancer has spread to the brain and lungs pulmonary (stage IVB), the life of the patient will be increasingly difficult to save.[9,1] Research conducted by Yvonne Nartey, Philip C. Hill, Kwabena Amo-Antwi, et al. in 2017, showed that of 821 women diagnosed with cervical cancer, 497 women (60.5%) died during follow-up. Having been diagnosed with cervical cancer can survive 1 year after diagnosis by 62%, 3 years after diagnosis by 39%, and 5 years of diagnosis 30%. [10]

According to the results of research, showed that the factors that correlate with cervical cancer are early sexual intercourse is less than 20 years, parity is more than 3, and the use of hormonal contraception more than 5 years.[3] The risk factors of cervical cancer are low education, infections like trichomonas vaginalis, bacterial vaginosis, disorders on genitals, and contraceptive use.[11] How long the body's exposure to hormones in any hormonal contraception is still unknown, so the duration of each hormonal contraceptive usage still needs to be examined.[12]

Data of active family planning participants from 2014 to 2016 showed an increasing trend from year to year. Data of active family planning participants who used hormonal contraception was 81.58% to 81.97% (injected 47.54%, pills 23.58%, implants 10.46%).[13] The purpose of this study was to determine the relationship between the duration of hormonal contraception use and the incidence of cervical cancer and knowing other factors related to cervical cancer incidence.

## Methods

This study used a case-control design. The Population were patients who had examined at a cancer installation and obstetrics-gynecology polyclinic Dr. Sardjito Hospital Yogyakarta, Indonesia in 2018. The study was conducted in July 2018. Sampling with random sampling. Case samples were 95 women who were diagnosed with cervical cancer, while the control samples were 95 women who did not have cervical cancer (Pap smear tests were negative). Subjects were excluded if has never used hormonal contraception and medical record data is incomplete. Independent variable is duration of hormonal contraception, whereas the dependent variable is cervical cancer. Cervical cancer is assessed by doctor's diagnosis. The duration of hormonal contraception is length of use of hormonal contraception (injections, pills and implants). The duration of hormonal contraceptive use (injections, pills and implants) is categorized into two, namely more than 5 years and not long if the user is less than 5 years. The data were based on diagnosis recorded in the medical record. A possible confounders were marriage age less than 20 years, family history of cancer, active smoking, and parity more than 3. For statistical analysis, the bivariate analysis used chi-square tests, and the multivariate analysis used logistic regression. The p-value of the likelihood ratio to the chi-square was used as a guide to the model's goodness of fit. All p-values were two-tailed and statistical significance level was set as less than 0.05. Ethical approval granted from the Ethics Committee of the Faculty of Medicine, Gadjah Mada University No.KE/KF/0561/EC/2018.

## Results

This research was conducted at Dr. Sardjito. Total of subjects who participated in the study was 190 subjects (95 for case group/women who were diagnosed with cervical cancer), and 95 for the control group (women who did not have cervical cancer or Pap smear tests were negative). The duration of hormonal contraceptive use (injections, pills and implants) is categorized into two, namely more than 5 years and not long if the user is less than 5 years. Table 1 presents the correlation of the duration of use hormonal contraception with cervical cancer and other affecting factors.

**Table 1. Correlation of the duration of use hormonal contraception, age of marriage, parity, active smoking, family history of cancer with cervical cancer**

| Variable | Case n (%) | Control n (%) | p-value | OR | 95% CI | |
|---|---|---|---|---|---|---|
| | | | | | Lower | Upper |
| **Hormonal contraception > 5 years** | 59 (62.1) | 26 (27.4) | 0.01 | 4.3 | 2.35 | 8.02 |
| - use of pills> 5 years | 16 (51.6) | 3 (13.0) | 0.01 | 7.1 | 1.74 | 28.9 |
| - use of injections > 5 years | 32 (66.7) | 13 (35.1) | 0.01 | 3.6 | 1.49 | 9.11 |
| - use of implants > 5 years | 11 (68.8) | 10 (28.6) | 0.01 | 5.5 | 1.51 | 19.9 |
| The first age of marriage < 20 years | 47 (49.5) | 28 (29.5) | 0.01 | 2.3 | 1.29 | 4.25 |
| Parity > 3 | 27 (28.4) | 13 (13.7) | 0.02 | 2.5 | 1.20 | 5.22 |
| Active Smoking | 2 (2.1) | 0 (0.0) | 0.49 | 2.0 | 1.75 | 2.33 |
| Family history of cancer | 2 (2.1) | 2 (2.1) | 1.00 | 1.00 | 0.13 | 7.24 |

n = Number of Sample; OR = Odds Ratio; CI= Convidence Interval

This study showed that the correlation between duration of use hormonal contraception, the first age of marriage, parity, active smoking, family history of cancer with cervical cancer. Duration of hormonal contraception had higher risk 4.3 times of cervical cancer than using less than 5 years. Duration of use of pills, injections and implant have a significant correlation with cervical cancer. Women who the first age of marriage <20 years had higher risk 2.3 times of cervical cancer. Parity > 3 had higher risk 2.5 times of cervical cancer There is no significant correlation between active smoking and family history of cancer with cervical cancer.

Correlation between the duration of the use hormonal contraception, the first age of marriage, parity, active smoking, family history of cancer with cervical cancer was analyzed by logistic regression using the backward method. The first step regression analysis was performed by bivariate selection. The candidates entered in multivariate analysis are variables with p-value ≤ 0.250. The analysis showed that the first age of marriage and parity had p-value ≤ 0.250 while active smoking, family history of cancer had p-value > 0.250, so they were not included in the multivariable selection.

**Table 2. Correlation of duration use hormonal contraception and cervical cancer after consideration of external variables**

| Variable | β | p-value | OR | 95% CI | |
|---|---|---|---|---|---|
| | | | | Lower | Upper |
| Use of contraception hormonal >5 years | 1.435 | 0.000 | 4.2 | 1.011 | 5.692 |
| The first age of married<20 years | 0.659 | 0.046 | 1.9 | 0.993 | 4.847 |
| Parity >3 | 0.786 | 0.052 | 2.1 | 2.238 | 7.880 |

Notes: β= coefficient OR= Odds Ratio CI=Convidence Interval

The result showed that the correlation between the duration of the use hormonal contraception and cervical cancer after consideration of external variables (age of married <20 years and parity >3). Period of use of contraception hormonal had 4.2 times higher risk of cervical cancer after being controlled with the first marriage age and parity.

## Discussion

This study found a correlation between duration of use hormonal contraception and cervical cancer. This strong association is marked by Odds ratio (OR) of 4.2. These results is same as or support the previous study that duration of use hormonal contraception associated with cervical cancer. The results of this study support previous studies among others, a study who stated that long-term use of hormonal contraception could lead to cervical cancer. A biologically plausible mechanism for this relationship is hormonal contraceptives acted as a tool that controlled the growth of neoplasms. The acceptors who use hormonal contraception are often found in cervical dysplasia.[14] The use of hormonal contraceptives that are longer than 4 or 5 years can disrupt the balance of estrogen in the body resulting in abnormal cell changes. Estrogen is likely to be one of the factors that can make HPV DNA replication.[4] Likewise with the length of use of each hormonal contraception.

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Other factors such as age at first marriage and parity were statistically related to cervical cancer incidence. Sexual intercourse that is early can affect cervical epithelial tissue damage or the vagina cavity wall and can worsen leading to cell abnormalities that result in abnormal growth.[1] Women who begin sexual intercourse age <20 years is more at risk of developing cancer cervix. It is because in the young adult period the process of squamous cell metaplasia is substantially increased so the risk of atypical squamous transformation increases which then becomes cervical intraepithelial neoplasia (NIS).[16] The results of this study in accordance with previous studies showing women who had sexual intercourse for the first time at the age of <20 years were 2.41 times more likely to develop cervical cancer. The exposure of the uterus to the HPV will result in growth deviating into precancerous/cervical cancer.[3] Married age can be associated with age-related. At the age of the genital device that is not yet mature and has been used to connect it will damage the cervical epithelial tissue that can get worse on cell abnormalities and result in abnormal growth. Especially if the partner already has an HPV virus that is rapidly contracting.[1]

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**Conclusion**

Duration of use of contraception hormonal >5 years has a strong correlation with cervical cancer. Method of contraception hormonal >5 years had 4.2 times higher for cervical cancer than use of contraception hormonal < 5 years. Other factors such as age at first marriage and parity were statistically related to cervical cancer incidence while smoking and family history there is no relationship statistically with the incidence of cervical cancer.

**Recommendations**

For all women who do not want more children, should use non-hormonal long-term contraception. It is necessary to promotion for women or contraceptive acceptors using hormonal up to 5 years.

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Comment [M1]: sudah diacobaiki.

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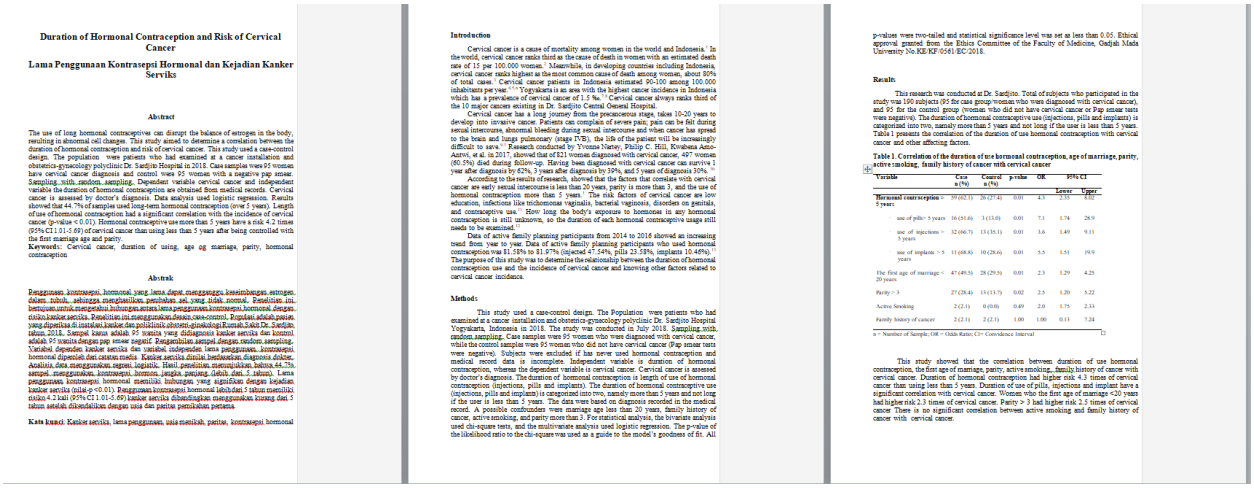
Korespondensi 3 Juli 2019



**Duration of Hormonal Contraception and Risk of Cervical Cancer**

**Lama Penggunaan Kontrasepsi Hormonal dan Kejadian Kanker Serviks**


**Abstract**

The use of long hormonal contraceptives can disrupt the balance of estrogen in the body, resulting in abnormal cell changes. This study aimed to determine a correlation between the duration of hormonal contraception and risk of cervical cancer. This study used a case-control design. The population were patients who had examined at a cancer installation and obstetrics-gynaecology polyclinic Dr. Sardjito Hospital in 2018. Case samples were 95 women have cervical cancer diagnosis and control were 95 woman with a negative pap smear. Sampling with random sampling. Dependent variable cervical cancer and independent variable the duration of hormonal contraception are obtained from medical records. Cervical cancer is assessed by doctor's diagnosis. Data analysis used logistic regression. Results showed that 44.7% of samples used long-term hormonal contraception (over 5 years). Length of use of hormonal contraception had a significant correlation with the incidence of cervical cancer (p-value < 0.01). Hormonal contraceptive use more than 5 years have a risk 4.2 times (95% CI 1.01-5.69) of cervical cancer than using less than 5 years after being controlled with the first marriage age and parity.

**Keyword:** Cervical cancer, duration of using, age ag marriage, parity, hormonal contraception

**Abstrak**

Penggunaan kontrasepsi hormonal yang lama dapat mengganggu keseimbangan estrogen dalam tubuh, sehingga menyebabkan perubahan sel yang tidak normal. Penelitian ini bertujuan untuk mengetahui hubungan antara lama penggunaan kontrasepsi hormonal dengan risiko kanker serviks. Penelitian ini menggunakan desain case-control. Populasi adalah pasien yang dipelitsa di instalasi kanker dan poliklinik obstetri-ginekologi Rumah Sakit Dr. Sardjito, tahun 2018. Sampel kasus adalah 95 wanita yang didiagnosis kanker serviks dan kontrol adalah 95 wanita dengan pap smear negatif. Pengambilan sampel dengan random sampling. Variabel dependen kanker serviks dan variabel independen lama penggunaan kontrasepsi hormonal diperoleh dari catatan medis. Kanker serviks dinilai berdasarkan diagnosis dokter. Analisis data menggunakan regresi logistik. Hasil penelitian menunjukkan bahwa 44.7% sampel menggunakan kontrasepsi hormon jangka panjang (lebih dari 5 tahun). Lama penggunaan kontrasepsi hormonal memiliki hubungan yang signifikan dengan kejadian kanker serviks (nilai-p <0.01). Penggunaan kontrasepsi hormonal lebih dari 5 tahun memiliki risiko 4.2 kali (95% CI 1.01-5.69) kanker serviks dibandingkan menggunakan kurang dari 5 tahun setelah dikendalikan dengan usia dan paritas pernikahan pertama.

**Kata kunci:** Kanker serviks, lama penggunaan, usia menikah, paritas, kontrasepsi hormonal


**Introduction**

Cervical cancer is a cause of mortality among women in the world and Indonesia.[1] In the world, cervical cancer ranks third as the cause of death in women with an estimated death rate of 15 per 100.000 women.[2] Meanwhile, in developing countries including Indonesia, cervical cancer ranks highest as the most common cause of death among women, about 85% of total cases. Cervical cancer patients in Indonesia estimated 90-100 among 100.000 inhabitants per year.[3,4] Yogyakarta is an area with the highest cancer incidence in Indonesia which has a prevalence of cervical cancer of 1.5 ‰.[5] Cervical cancer always ranks third of the 10 major cancers existing in Dr. Sardjito Central General Hospital.

Cervical cancer has a long journey from the precancerous stage, takes 10-20 years to develop into invasive cancer. Patients can complain of severe pain; pain can be felt during sexual intercourse, abnormal bleeding during sexual intercourse and when cancer has spread to the brain and lungs pulmonary (stage IVB), the life of the patient will be increasingly difficult to save.[6] Research conducted by Yvonne Nartey, Philip C. Hill, Rivaldesa Amo-Antwi, et al. in 2017, showed that of 821 women diagnosed with cervical cancer, 497 women (60.5%) died during follow-up. Having been diagnosed with cervical cancer can survive 1 year after diagnosis by 62%, 3 years after diagnosis by 39%, and 5 years of diagnosis 30%. [7]

According to the results of research, showed that the factors that correlate with cervical cancer are early sexual intercourse is less than 20 years, parity is more than 3, and the use of hormonal contraception more than 5 years.[1] The risk factors of cervical cancer are low education, infectious like trichomonas vaginalis, bacterial vaginosis, disorders on genitals, and contraceptive use.[8] How long the body's exposure to hormones in any hormonal contraception is still unknown, so the duration of such hormonal contraceptive usage still needs to be examined.[9]

Data of active family planning participants from 2014 to 2016 showed an increasing trend from year to year. Data active family planning participants who used hormonal contraception was 81.58% to 81.97% (injected 47.54%, pills 23.58%, implants 10.46%).[5] The purpose of this study was to determine the relationship between the duration of hormonal contraception use and the incidence of cervical cancer and knowing other factors related to cervical cancer incidence.

**Methods**

This study used a case-control design. The Population were patients who had examined at a cancer installation and obstetrics-gynecology polyclinic Dr. Sardjito Hospital Yogyakarta, Indonesia in 2018. The study was conducted in July 2018. Sampling with random sampling. Case samples were 95 women who were diagnosed with cervical cancer, while the control samples were 95 women who did not have cervical cancer (Pap smear tests were negative). Subjects were excluded if has never used hormonal contraception and medical record data is incomplete. Independent variable is duration of hormonal contraception, whereas the dependent variable is cervical cancer. Cervical cancer is assessed by doctor's diagnosis. The duration of hormonal contraception is length of use of hormonal contraception (injections, pills and implants). The duration of hormonal contraceptive use (injections, pills and implants) is categorized into two, namely more than 5 years and not long if the user is less than 5 years. The data were based on diagnosis recorded in the medical record. A possible confounders were marriage age less than 20 years, family history of cancer, active smoking, and parity more than 3. For statistical analysis, the bivariate analysis used chi-square tests, and the multivariate analysis used logistic regression. The p-value of the likelihood ratio to the chi-square was used as a guide to the model's goodness of fit. All p-values were two-tailed and statistical significance level was set as less than 0.05. Ethical approval granted from the Ethics Committee of the Faculty of Medicine, Gadjah Mada University No.KE/FK/0561/EC/2018.

**Results**

This research was conducted at Dr. Sardjito. Total of subjects who participated in the study was 190 subjects (95 for care group/women who were diagnosed with cervical cancer), and 95 for the control group (woman who did not have cervical cancer or Pap smear tests were negative). The duration of hormonal contraceptive use (injections, pills and implants) is categorized into two, namely more than 5 years and not long if the user is less than 5 years. Table1 presents the correlation of the duration of use hormonal contraception with cervical cancer and other affecting factors.

**Table 1. Correlation of the duration of use hormonal contraception, age of marriage, parity, active smoking, family history of cancer with cervical cancer**

| Variable | Case n (%) | Control n (%) | p-value | OR | 95% CI | |
|---|---|---|---|---|---|---|
| | | | | | Lower | Upper |
| **Hormonal contraception > 5 years:** | 59 (62.1) | 26 (27.4) | 0.01 | 4.5 | 2.35 | 8.62 |
| use of pills> 5 years | 16 (51.6) | 3 (13.0) | 0.01 | 7.1 | 1.74 | 28.9 |
| use of injections > 5 years | 32 (66.7) | 13 (35.1) | 0.01 | 3.6 | 1.49 | 9.11 |
| use of implants > 5 years | 11 (68.8) | 10 (28.6) | 0.01 | 5.5 | 1.51 | 19.9 |
| The first age of marriage < 20 years | 47 (49.5) | 28 (29.5) | 0.01 | 2.3 | 1.29 | 4.25 |
| Parity > 3 | 27 (28.4) | 13 (13.7) | 0.02 | 2.5 | 1.20 | 5.22 |
| Active Smoking | 2 (2.1) | 0 (0.0) | 0.49 | 2.0 | 1.75 | 2.33 |
| Family history of cancer | 2 (2.1) | 2 (2.1) | 1.00 | 1.00 | 0.13 | 7.24 |

n = Number of Sample; OR = Odds Ratio; CI= Convidence Interval

This study showed that the correlation between duration of use hormonal contraception, the first age of marriage, parity, active smoking,, family history of cancer with cervical cancer. Duration of hormonal contraception had higher risk 4.3 times of cervical cancer than using less than 5 years. Duration of use of pills, injections and implant have a significant correlation with cervical cancer. Women who the first age of marriage <20 years had higher risk 2.3 times of cervical cancer. Parity > 3 had higher risk 2.5 times of cervical cancer There is no significant correlation between active smoking and family history of cancer with cervical cancer.

Correlation between the duration of the use hormonal contraception, the first age of marriage, parity, active smoking, family history of cancer with cervical cancer was analyzed by logistic regression using the backward method. The first step regression analysis was performed by bivariate selection. The candidates entered in multivariate analysis are variables with p-value ≤ 0.250. The analysis showed that the first age of marriage and parity had p-value ≤ 0.250 while active smoking, family history of cancer had p-value > 0.250, so they were not included in the multivariable selection.

**Table 2. Correlation of duration use hormonal contraception and cervical cancer after consideration of external variables**

| Variable | β | p-value | OR | 95% CI | |
|---|---|---|---|---|---|
| | | | | Lower | Upper |
| Use of contraception hormonal >5 years | 1.455 | 0.000 | 4.2 | 1.011 | 5.692 |
| The first age of married<20 years | 0.659 | 0.046 | 1.9 | 0.993 | 4.847 |
| Parity >3 | 0.786 | 0.052 | 2.1 | 2.238 | 7.880 |

Notes: β= coefficient OR= Odds Ratio CI=Convidence Interval

The result showed that the correlation between the duration of the use hormonal contraception and cervical cancer after consideration of external variables (age of married <20 years and parity >3). Period of use of contraception hormonal had 4.2 times higher risk of cervical cancer after being controlled with the first marriage age and parity.

**Discussion**

This study found a correlation between duration of use hormonal contraception and cervical cancer. This strong association is marked by Odds ratio (OR) of 4.2. These results is same as or support the previous study that duration of use hormonal contraception associated with cervical cancer. The results of this study support previous research conducted, a study who stated that long-term use of hormonal contraception could lead to cervical cancer. A biologically plausible mechanism for this relationship is hormonal contraceptives acted as a tool that controlled the growth of neoplasms. The receptors who use hormonal contraceptives are often found in cervical dysplasia.[7] The use of hormonal contraceptives that are longer than 4 or 5 years can disrupt the balance of estrogen in the body, resulting in abnormal cell changes. Estrogen is likely to be one of the factors that can make HPV DNA replication.[8] Lifetimes with the length of use of each hormonal contraception.

Effect of hormonal contraception can cause hyperexcretion and the proliferation of endocervical glands. In addition, causes metaplasia and portio epithelial dysplasia and mucosa membranes of the endocervix. Hormonal contraception increases the risk of cervical cancer for women with HPV. It is suspected that gestagen triggers the carcinogenic effect of HPV.[7,9]

Use of hormonal contraception, causes mucus viscosity in the cervix due to oral hormonal contraceptive use or injection will support cervical cancer. This is because this mucus viscosity will prolong the existence of a carcinogenic agent (cancer-causing) in the cervix which is carried through sexual intercourse including the presence of the HPV virus which is the cause of cervical cancer. The duration of use of implant contraceptives can increase the incidence of cervical cancer considering the mechanism of hormones in the implant to thicken cervical mucus. The process of cervical mucus removal is the replacement of new cells and the addition of cells to the cervix to prevent the entry of sperm. If cervical mucus thickening occurs continuously and uncontrollably, the thickening will become abnormal which can lead to cervical cancer the immature will experience changes and can damage cells in the cervix.[1,3]

Other factors such as age at first marriage and parity were statistically related to cervical cancer incidence. Sexual intercourse that is early can affect cervical epithelial tissue damage or the vagina cavity wall and can worsen leading to cell abnormalities that result in abnormal growth.[1] Women who begin sexual intercourse age <20 years is more at risk of developing cancer cervix. It is because in the young adult period the process of squamous cell metaplasia is substantially increased so the risk of atypical squamous transformation increases which then becomes cervical intraepithelial neoplasia (NIS).[10] The results of this study in accordance with previous studies showing women who had sexual intercourse for the first time at the age of <20 years were 2.41 times more likely to develop cervical cancer. The exposure of the uterus to the HPV will result in growth deviating into precancerous/cervical cancer.[7] Married age can be associated with age-related. At the age of the genital device that is not yet mature and has been used to connect it will damage the cervical epithelial tissue that can get worse on cell abnormalities and result in abnormal growth. Especially if the partner already has an HPV virus that is rapidly contracting.[1]

Women with high parity are associated with the occurrence of cervical column epithelium during pregnancy. This incidence causes new dynamics of immature metaplastic epithelium which can increase the risk of cell transformation especially in the cervix resulting in persistent HPV infection.[11] Sondang and Dian showed that women are often giving birth, it will affect the frequent occurrence of injury to a woman's reproductive organs, which in turn will make it easier for the HPV to cause cancer. In the case of women who gave birth frequently and at proximity, damage to the epithelial tissue develops towards the growth of abnormal cells that are potentially malignant. In labor that often has the opportunity to be contaminated by a virus that causes infection. The bacteria are present because of poorly maintained vaginal hygiene conditions that can develop into malignancy.[12]

According to American cancer, if a mother or sister has cervical cancer, it can increase the incidence of cervical cancer than those who do not have a family history of cervical cancer. This is due to the genetic tendency of the family to inherit the condition.[13] The results of this study indicate that women whose families have a history of cervical cancer do not influence cervical cancer. This study was different from the research which showed that family history of cervical cancer has a risk of 2.19 times affected by cervical cancer.[2] Respondents who have had cancer in their families cervix has a risk of 14.93 times for cervical cancer. Especially in the nuclear family (first) cervical cancer is a vulnerability that inherits. However, it is unclear whether the risks are related, with history of family cancer being due to genetic susceptibility or the influence of the environmental lifestyle.[3] At present there is a need for counseling on contraceptive use, especially hormonal contraception, because high levels of hormonal contraceptive use by acceptors are thought to be the effect of not providing extensive information about the advantages and disadvantages of contraception and quality contraceptive services. [20]

**Conclusion**

Duration of use of contraception hormonal >5 years has a strong correlation with cervical cancer. Method of contraception hormonal >5 years had 4.2 times higher for cervical cancer than use of contraception hormonal < 5 years. Other factors such as age at first marriage and parity were statistically related to cervical cancer incidence while smoking and family history there is no relationship statistically with the incidence of cervical cancer.

**Recommendations**

For all women who do not want more children, should use non-hormonal long-term contraception. It is necessary to promotion for women or contraceptive acceptors using hormonal up to 5 years.

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