

**BUKTI KORESPONDENSI**  
**ARTIKEL JURNAL KESEHATAN MASYARAKAT NASIONAL**

**Judul artikel** : *Durational of Hormonal Contraception and Risk of Cervical Cancer*

**Jurnal** : Jurnal Kesehatan Masyarakat Nasional (*National Public Health Journal*)

**Penulis** : Yuni Kusmiyati

<b>No</b>	<b>Perihal</b>	<b>Tanggal</b>
1	Submit melalui OJS	24 Oktober 2018
2	Hasil review naskah	23 November 2018
3	Hasil review naskah	13 Mei 2019
4	Hasil review naskah	11 Juni 2019
5	Hasil review naskah	25 Juni 2019
6	Hasil review naskah	26 Juni 2019
7	Naskah terbit	9 Juli 2019

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## #2713 Review

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### Submission

Authors	Yuni Kusmiyati, AnnisaPutri Prasistiyami, Heni Puji Wahyuningsih, Hesty Widyasih, Qorinah Estiningtyas Sakilah Adnani
Title	Duration of Hormonal Contraception and Risk of Cervical Cancer
Section	Articles
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Review Version	2713-7431-1-RV.DOC	2018-10-24
Initiated	2018-11-22	
Last modified	2019-05-09	
Uploaded file	None	

### Editor Decision

Decision	Accept Submission 2019-07-09																					
Notify Editor	Editor/Author Email Record 2019-07-01																					
Editor Version	None																					
Author Version	<table> <tr> <td>2713-7446-1-ED.DOC</td> <td>2018-11-23</td> <td>DELETE</td> </tr> <tr> <td>2713-7446-2-ED.DOC</td> <td>2019-05-13</td> <td>DELETE</td> </tr> <tr> <td>2713-7446-3-ED.DOC</td> <td>2019-06-11</td> <td>DELETE</td> </tr> <tr> <td>2713-7446-4-ED.DOC</td> <td>2019-06-25</td> <td>DELETE</td> </tr> <tr> <td>2713-7446-5-ED.DOC</td> <td>2019-06-26</td> <td>DELETE</td> </tr> <tr> <td>2713-7446-6-ED.DOC</td> <td>2019-06-27</td> <td>DELETE</td> </tr> <tr> <td>2713-7446-7-ED.DOC</td> <td>2019-07-03</td> <td>DELETE</td> </tr> </table>	2713-7446-1-ED.DOC	2018-11-23	DELETE	2713-7446-2-ED.DOC	2019-05-13	DELETE	2713-7446-3-ED.DOC	2019-06-11	DELETE	2713-7446-4-ED.DOC	2019-06-25	DELETE	2713-7446-5-ED.DOC	2019-06-26	DELETE	2713-7446-6-ED.DOC	2019-06-27	DELETE	2713-7446-7-ED.DOC	2019-07-03	DELETE
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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

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 (injection, 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 contraceptive, age of marriage, parity, active smoking, family history of cancer with cervical cancer									
Variable	Case n (%)	Control n (%)	p-value	Odds Ratio	95% CI	Lower Upper			
Hormonal contraception > 5 years	10 (88.3)	28 (27.6)	0.01	4.2	1.01	5.69			
Use of pills > 5 years	16 (31.6)	3 (13.0)	0.01	7.1	1.74	28.9			
Use of injection > 5 years	32 (86.7)	13 (35.1)	0.01	3.6	1.49	9.11			
Use of implant > 5 years	11 (88.0)	10 (38.6)	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 (38.4)	13 (13.7)	0.02	2.5	1.30	5.22			
Active Smoking	2 (2.1)	0 (0.0)	0.49	2.0	1.73	2.33			
Family history of cancer	2 (2.1)	2 (2.1)	1.00	1.00	0.13	7.24			

Table 1 performs the correlation between duration of use hormonal contraceptive, the first age of marriage, parity, active smoking, family history of cancer with cervical cancer. Duration of hormonal contraception had higher risk 4.2 times of cervical cancer than using less than 5 years. Duration of use of pills, injection 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.

that subjects. 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.<sup>10</sup> 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.<sup>11</sup>

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 promote for women hormonal or contraceptive accepters using hormonal up to 5 years.

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Abstract

Penggunaan kontrasepsi hormonal yang lama dapat mengganggu keseimbangan estrogen dalam tubuh, sehingga mengakibatkan 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 RSUD 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: 1,01-5,69) 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.<sup>10</sup> 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.<sup>11</sup> Meanwhile, in developing countries including Indonesia, cervical cancer ranks highest as the most common cause of death among women, about 80% of total cases.<sup>12</sup> Cervical cancer patients in Indonesia estimated 90-100 among 100,000 inhabitants per year and ranked third (10.5%) as the cause of death of women after other (43.1%).<sup>13,14</sup> Yogyakarta is no area with the highest cancer incidence in Indonesia which has a prevalence of cervical cancer of 5.4% to 5.6%.<sup>15</sup> Cervical cancer 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 is 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.<sup>16</sup> Research conducted by Yonnes Naray, Philip C. Hill, Kwabena Aamo-Antwi, et al. in 2017, showed that of 821 women diagnosed with cervical cancer, 497 women (60.7%) died during follow-up. Harma been diagnosed with cervical cancer can survive 1 year after

Correlation between the duration of the use hormonal contraceptive, 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 multivariate analysis are variables with  $p$ -value  $< 0.25$ . 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 contraceptive and cervical cancer after consideration of external variables

Consideration of external variables					
Variable	$\beta$	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

Note: p confidence OR= Odds Ratio CI= Confidence Interval

Table 2 shows the correlation between the duration of the use hormonal contraceptive and cervical cancer after consideration of external variables (age of married < 20 years and parity > 3). Period of use of contraceptive 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 contraceptive 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 report previous studies among others, a study who stated that long-term use of hormonal contraceptive could lead to cervical cancer. Hormonal contraceptive acted as a tool that controlled the growth of neoplasms. The acceptors who use hormonal contraceptive are often found in cervical squamous.<sup>17</sup> The use of long-term contraceptive that an 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.<sup>18</sup> Likewise with the length of use of each hormonal contraceptive. Effect of hormonal contraception can cause hyperproliferation and the proliferation of atypical squamous cells in addition, cause metaplasia and portio epithelial dysplasia and increase malignancies of the endocervix. Hormonal contraceptives increase the risk of cervical cancer for women with HPV. It is suspected that gestagen triggers the carcinogenic effect of HPV.<sup>19,20</sup>

Use of hormonal contraceptive, causes mucus viscosity in the cervix due to oral hormonal contraceptive use or injection will support cervical cancer. This is

diagnosis by 62%, 3 years after diagnosis by 39%, and 5 years of diagnosis 30%<sup>19</sup>

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 contraceptive more than 5 years.<sup>19</sup> The risk factors of cervical cancer are low education, infectious like trichomonas vaginalis, bacterial vaginosis, disorders on genital, and contraceptive use.<sup>21</sup> How long the body's exposure to hormones in any hormonal contraceptive is still unknown, so the duration of each hormonal contraceptive usage still needs to be examined.

Data of active family planning participant from 2014 to 2016 showed an increasing trend from year to year. Data of active family planning participants who used hormonal contraception was 81.38% to 81.87% (opened 47,54%, pills 23.58%, implants 10.46%).<sup>22</sup> The purpose of this study was to determine the relationship between the duration of hormonal contraceptive 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 institution, 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 contraceptives is length of use of hormonal contraceptives (injection, pills and implant). The duration of hormonal contraceptive use (injection, pills and implant) is categorized into two, namely more than 5 years and not long if the use is less than 5 years. The data were based on diagnosis recorded in the medical record. A possible confounder 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 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.KEK-F0561/EC-2018.

because this mucus viscosity will prolong the existence of a carcinogenic agent (cancer-causing) in the cervix which is caused 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.<sup>23</sup>

Sexual intercourse that is early can affect cervical epithelial tissue damage or the vagina cervix wall and can worsen leading to cell abnormalities that result in abnormal growth.<sup>24</sup> Women who begin sexual intercourse age < 20 years are more at risk of developing cervical cancer. It is because in the young adult period the process of squamous cell metaplasia is substantially increased to the risk of atypical squamous transformation increases which then becomes cervical metapathological neoplasia (NIS). 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.<sup>25</sup> 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 equally contagious.<sup>26</sup>

Women with high parity are associated with the occurrence of cervical column epithelium during pregnancy. This incidence causes new dynamics of immature neoplastic epithelium which can increase the risk of cell transformation especially in the cervix resulting in persistent HPV infection.<sup>14</sup> Sneland and Dan showed that women are often giving birth, it will affect the frequent occurrence of injury to a woman's reproductive organ, which in turn will make it easier for the HPV to cause cancer. In the case of women who gave birth frequently and at a young age, 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 cancer. The bacteria are present because of poorly maintained vaginal hygiene conditions that can develop into malignancy.<sup>27</sup>

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.<sup>28</sup> 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.<sup>29</sup> 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

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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. A case-control study was conducted on 190 in female patients in Dr. Sardjito Central General Hospital, Yogyakarta. Case samples were 95 women who had 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 of marriage, parity, hormonal contraception

Abstrak

Penggunaan kontrasepsi hormonal yang lama dapat mengganggu keseimbangan estrogen dalam tubuh, sehingga mengakibatkan 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

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=95)	Control (n=95)	p-value	OR	95% CI
Hormonal contraception > 5 years	39 (41.0)	35 (37.0)	0.01	4.2	1.01-5.69
- use of pills > 5 years	14 (15.0)	3 (3.0)	0.01	7.1	1.74-28.9
- use of injections > 5 years	22 (26.7)	12 (15.1)	0.01	3.6	1.49-9.11
- use of implants > 5 years	11 (18.0)	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)	19 (13.7)	0.02	2.5	1.20-5.22
Active Smoking	2 (2.1)	0 (0.0)	0.49	2.0	1.73-2.33
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= Confidence 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 4.2 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 calculation entered in subsequent 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.

providing extensive information about the advantages and disadvantages of contraception and quality contraceptive services<sup>11</sup>

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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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 1,01-5,69) 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.<sup>(1)</sup> In the world, cervical cancer ranks third as the cause of death in women with an estimated death rate of 13 per 100,000 women.<sup>(2)</sup> Meanwhile, in developing countries including Indonesia, cervical cancer ranks highest as the most common cause of death among women, about 80% of total cases.<sup>(3)</sup> Cervical cancer patients in Indonesia estimated 90,100 among 100,000 inhabitants per year.<sup>(4)</sup> Yogyakarta is an area with the highest cancer incidence in Indonesia which has a prevalence of cervical cancer of 1.3%.<sup>(5-6)</sup> Cervical cancer always ranks third of the 10 major cancers existing in Dr. Sardjito Central General Hospital.

Cervical cancer is 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.<sup>(7-8)</sup> Research conducted by Yvonne Nartey, Philip C. Hill, Kwame Amo-Ameyi, 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%.<sup>(9)</sup>

According to the results of research, showed that the factors that correlate with cervical cancer are early sexual intercourse in less than 20 years, parity is more than 3, and the use of hormonal contraception more than 5 years.<sup>(10)</sup> The risk factors of cervical cancer are low education, infectious like chlamydia, bacterial vaginosis, disorders on genital, and contraceptive use.<sup>(11)</sup> 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.<sup>(12)</sup>

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

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

Variable	$\beta$	p-value	OR	95% CI
Use of contraception hormonal > 5 years	1.433	0.000	4.2	1.011-28.905
The first age of married < 20 years	0.659	0.046	1.9	0.993-4.947
Parity > 3	0.788	0.052	2.1	1.238-3.600

Notes:  $\beta$  = coefficient OR = Odds Ratio CI= Confidence 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 neoplasia. The acceptors who use hormonal contraception are often found in cervical neoplasia.<sup>(13)</sup> 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.<sup>(14)</sup> Likewise with the length of use of each hormonal contraception. Effect of hormonal contraception can cause hyperproliferation and the proliferation of endocervical glands.<sup>(15)</sup> In addition, causes metaplasia and porta epithelial dysplasia and mucosa metaplasia of the endocervix. Hormonal contraceptives increases the risk of cervical cancer for women with HPV. It is suspected that estrogen triggers the carcinogenic effect of HPV.<sup>(16-18)</sup>

Use of hormonal contraception, cause 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.<sup>(19)</sup>

23.58%, implants 10.46%).<sup>(19)</sup> 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 institution, 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 confounder 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.KEP/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.

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 miniature will experience changes and can damage cells in the cervix.<sup>(20)</sup>

Sexual intercourse that is early can affect cervical epithelial tissue damage or the vagina cavity wall and can women leading to cell abnormalities that result in abnormal growth.<sup>(21)</sup> Women who began 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 become cervical intraepithelial neoplasia (NIS).<sup>(22)</sup> 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.<sup>(23)</sup> Married age can be associated with age-related. At the age of the genital device that is not yet matured 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.<sup>(24)</sup>

Women with high parity are associated with the occurrence of cervical column epithelium during pregnancy. This incidence causes new dynamics of numerous metaplastic epithelium which can increase the risk of cell transformation especially in the cervix resulting in persistent HPV infection.<sup>(25)</sup> Sundberg and Diaz 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 premature, 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.<sup>(26)</sup>

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.<sup>(27)</sup> 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.<sup>(28)</sup> Respondents who have had cancer in their families cervical 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.<sup>(29)</sup> 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 sex

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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. A case-control study was conducted on 190 in female patients in Dr. Sardjito Central General Hospital, Yogyakarta. Case samples were 95 women who had 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 of marriage, parity, hormonal contraception

Abstrak

Penggunaan kontrasepsi hormonal yang lama dapat mengganggu keseimbangan estrogen dalam tubuh, sehingga mengakibatkan 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 1,01-5,69) menderita kanker serviks daripada menggunakan kurang dari 5 tahun setelah dikontrol dengan faktor usia pernikahan pertama dan paritas.

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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=95)	Control (n=95)	p-value	OR	95% CI
Hormonal contraception > 5 years	39 (41.1)	25 (26.3)	0.01	4.3	2.37 - 8.02
- use of pills > 5 years	14 (15.0)	3 (3.0)	0.01	7.1	1.74 - 28.9
- use of injections > 5 years	22 (26.7)	12 (15.1)	0.01	3.6	1.49 - 9.11
- use of implants > 5 years	11 (18.0)	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)	19 (13.7)	0.02	2.5	1.20 - 5.22
Active Smoking	2 (2.1)	0 (0.0)	0.49	2.0	1.73 - 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= Confidence 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 calculation entered in subsequent analysis are variables with p-value < 0.250. The analysis showed that the first age of marriage <20 years 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.

providing extensive information about the advantages and disadvantages of contraception and quality contraceptive services.<sup>(24)</sup>

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

Variable	β	p-value	OR	95% CI
Use of contraception hormonal > 5 years	1.433	0.000	4.2	1.811 - 9.892
The first age of married <20 years	0.659	0.046	1.9	0.993 - 4.947
Parity > 3	0.788	0.052	2.1	2.216 - 1.800

Notes: β= coefficient OR= Odds Ratio CI= Confidence 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 neoplasia. The acceptors who use hormonal contraception are often found in cervical neoplasia.<sup>(25)</sup> 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.<sup>(26)</sup> Likewise with the length of use of each hormonal contraceptive. Effect of hormonal contraception can cause hyperproliferation and the proliferation of endocervical glands. In addition, causes metaplasia and porta epithelial dysplasia and mucosa metaplasia of the endocervix. Hormonal contraceptives increases the risk of cervical cancer for women with HPV. It is suspected that estrogen triggers the carcinogenic effect of HPV.<sup>(27-28)</sup>

Use of hormonal contraception, cause 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.<sup>(29)</sup>

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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 was patients who had been diagnosed with cervical cancer at Sardjito General Hospital in 2018. Case samples were 95 women with cervical cancer diagnosed and confirmed by histology. Controls were 95 women with a negative cervical cancer diagnosis and confirmed by histology. Subjects were excluded if they were using hormonal contraceptives and medical record data is incomplete. Sampling with random sampling. The study was conducted in July 2018. Independent variable is duration of hormonal contraceptive, whereas the dependent variable is cervical cancer. Cervical cancer is caused by doctor's diagnosis. The duration of hormonal contraceptive is length of use of hormonal contraceptive (injection, pills and implants). The length of hormonal contraceptive is categorized as long if more than 5 years. A possible confounder was family history of cervical cancer. Family history of cancer, active smoking and parity more than 3. The data were bivariate and logistic regression. Results showed that 44.7% of samples used long-term hormonal contraceptive (over 5 years). Length of use of hormonal contraceptive had a significant correlation with the incidence of cervical cancer ( $p$ -value < 0.01). Hormonal contraceptive use more than 5 years have a risk 2.5 times (OR=2.5 (1.1-5.4)) 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 at marriage, parity, hormonal contraceptive

Result

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. Of the sample group, the duration of hormonal contraceptive use (injection, pills and implants) is categorized into two, namely more than 5 years and not long (the use is less than 5 years). Table 1 presents the correlation of the duration of use hormonal contraceptive with cervical cancer and other affecting factors.

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

Variable	Case (n=95)	Control (n=95)	OR	95% CI	P-Value
<b>Hormonal contraceptive</b> P value	70 (73.7)	20 (21.1)	0.01	4.1	0.001
use of pills > 5 years	16 (16.8)	1 (1.1)	0.01	7.3	0.001
use of injection > 5 years	32 (33.7)	1 (1.1)	0.01	3.6	0.001
use of implants > 5 years	11 (11.6)	1 (1.1)	0.01	5.5	0.001
<b>Age at marriage</b> P value > 5	47 (49.5)	28 (29.5)	0.01	2.3	0.001
Age < 5	27 (28.4)	11 (11.7)	0.02	2.5	0.001
<b>Active smoking</b>	2 (2.1)	0 (0.0)	0.49	0.20	0.529
<b>Family history of cancer</b>	2 (2.1)	2 (2.1)	1.00	1.00	0.515

OR = Odds Ratio; CI = Confidence Interval

This study showed that the correlation between duration of use hormonal contraceptive, the duration of use hormonal contraceptive, age at marriage, parity, active smoking and family history of disease with cervical cancer. Duration of hormonal contraceptive had higher risk 4.1 times of cervical cancer than using less than 5 years. Duration of use of pills, injections and implants had a significant correlation with cervical cancer. Women who the first age at 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.

Abstract

**Penggunaan kontrasepsi hormonal yang lama dapat mengganggu keseimbangan estrogen dalam tubuh, sehingga mengakibatkan 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 didiagnosis di Sardjito General Hospital pada tahun 2018. Sampel kasus adalah 95 wanita yang didiagnosis kanker serviks dengan hasil histologi. Sampel kontrol adalah 95 wanita yang didiagnosis kanker serviks negatif dengan hasil histologi. Subjek dikecualikan jika mereka menggunakan kontrasepsi hormonal dan data rekam medis tidak lengkap. Pengambilan sampel dengan random sampling. Penelitian dilakukan pada bulan Juli 2018. Variabel independen adalah durasi kontrasepsi hormonal, sedangkan variabel dependen adalah kanker serviks. Durasi kontrasepsi hormonal adalah lamanya penggunaan kontrasepsi hormonal (injection, pills and implants). Durasi kontrasepsi hormonal dikategorikan sebagai lama jika lebih dari 5 tahun. Variabel lain yang mungkin mengganggu adalah riwayat kanker serviks. Riwayat kanker serviks dikategorikan sebagai lama jika lebih dari 5 tahun. Data bivariate dan regresi logistik menunjukkan bahwa 44,7% sampel menggunakan kontrasepsi hormonal jangka panjang (lebih dari 5 tahun). Lama penggunaan kontrasepsi hormonal memiliki korelasi yang signifikan dengan kejadian kanker serviks ( $p$ -value < 0,01). Penggunaan kontrasepsi hormonal lebih dari 5 tahun memiliki risiko 2,5 kali (OR CI 1,1-5,4) insidensi kanker serviks dibandingkan penggunaan kontrasepsi yang kurang dari 5 tahun setelah dikendalikan faktor pertama dan usia pernikahan pertama.**

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

Introduction

Cervical cancer is a cause of mortality among women in the world and Indonesia. 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. Meanwhile, in developing countries including Indonesia, cervical cancer ranks highest as the most common cause of death among women, about 80% of total cases. Cervical cancer patients in Indonesia estimated 80-100 among 100,000 individuals per year [1-3]. Cervical cancer is an area with the highest cancer incidence in Indonesia which has a prevalence of cervical cancer of 1.5 % [4]. Cervical cancer always ranks third of the 10 major cancer existing in Dr. Sardjito Central General Hospital. Cervical cancer has a long course from pre-invasive stage, then 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 large pulmonary (stage IVB), the life of the patient will be increasingly difficult to live [5]. Research results by Yoonas-Narany, Philip C. Hill, Khrisana-Arso-Arri, et al. in 2011, showed that of 121 women diagnosed with cervical cancer, 497 women (60.3%) died during

Correlation between the duration of the use hormonal contraceptive, the first age at 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 the backward method. The results of the multivariate analysis are variable with  $p$ -value < 0.050. The analysis showed that the first age at marriage and parity had a value < 0.050 with active smoking, family history of cancer had  $p$ -value > 0.500, so they were not included in the multivariate selection.

Table 2. Correlation of duration use hormonal contraceptive and cervical cancer after consideration of certain variables

	P value	OR	95% CI
Age at marriage < 20 years	0.001	2.3	1.1-5.4
Parity > 3	0.001	2.5	1.1-5.4

The result showed that the correlation between the duration of the use hormonal contraceptive and cervical cancer after consideration of certain variables (age at marriage < 20 years and parity > 3). Period of use of hormonal contraceptive had 2.5 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 contraceptive and cervical cancer. This strong association is marked by Odds ratio 4.1. This result is similar to or support the previous study that duration of use hormonal contraceptive associated with cervical cancer. The results of this study were consistent with the previous study that duration of use hormonal contraceptive could lead to cervical cancer. A histological examination showed that the duration of use hormonal contraceptive was a risk factor that caused the growth of neoplasia. The acceptance who use hormonal contraceptive are often found in cervical dysplasia. The use of hormonal contraceptive that are longer than 4 or 7 years on during the balance of estrogen in the body resulting in abnormal cell changes. Estrogen is likely to be one of the factors that can cause HPV DNA replication. Likewise with the length of use of each hormonal contraceptive.

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% [6].

According to the results of research, showed that the factors that correlates with cervical cancer are early sexual intercourse is less than 20 years, parity is more than 3, and the use of hormonal contraceptive more than 5 years [7]. The risk factors of cervical cancer are low education, infectious like neisseria vaginalis, bacterial vaginosis, dysplasia on genital, and contraceptive use [8]. How long the body's exposure to hormones in any hormonal contraceptive is still unknown, so the duration of each hormonal contraceptive usage will need to be estimated.

Data of active family planning participants from 2014 to 2018 showed an increasing trend from year to year. Data of active family planning participants who used hormonal contraceptive was 11.57% in 2014, increased to 17.4%, pills 23.18%, implants 10.46% [9]. The purpose of this study was to determine the relationship between the duration of hormonal contraceptive 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 obstetric-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 had been diagnosed with cervical cancer, while the control sample were 95 women who did not have cervical cancer (Pap smear tests were negative). Subjects were excluded if they were using hormonal contraceptive and medical record data is incomplete. Independent variable is duration of hormonal contraceptive, whereas the dependent variable is cervical cancer. Cervical cancer is caused by doctor's diagnosis. The duration of hormonal contraceptive is length of use of hormonal contraceptive (injection, pills and implants). The duration of hormonal contraceptive use is categorized as long if more than 5 years, namely more than 5 years and not long if the use is less than 5 years. Data sampling was based on diagnosis recorded in the medical record. A possible confounder was family history of cancer. Family history of cancer, active smoking, and parity more than 3. For statistical analysis, the bivariate analysis used chi-square test, and the multivariate analysis used logistic regression. The  $p$ -value of the likelihood ratio test to the chi-square was used as a guide to the  $p$ -value of the test. All  $p$ -values were two-tailed and statistical significance level was set as less than 0.05. Ethical approval passed from the Ethics Committee of the Faculty of Medicine, Oidjah Mada University No.KEP/051/EC/2018.

Effect of hormonal contraceptive can cause hyperandrogenism and the proliferation of endocervical glands. In addition, cause atypical and point epithelial dysplasia and mucous membranes of the endocervix. Hormonal contraceptive can increase the risk of cervical cancer with HPV. It is suspected that paragon triggers the carcinogenic effect of HPV [10]. Use of hormonal contraceptive will increase the exposure of a carcinogen agent (cancer-causing) in the cervix which is caused through sexual intercourse including exposure of the HPV virus which is the cause of cervical cancer. The duration of use of hormonal contraceptive can increase the incidence of cervical cancer by increasing the penetration of hormones in the implant to thicken cervical mucus. The growth of cervical mucus results in 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 incoherently, the thickening will become abnormal which can lead to cervical cancer the immature cell experience changes and can damage cells in the cervix [11].

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 cervix wall and can women leading to cell abnormalities that result in abnormal growth. Women who begin sexual intercourse age < 20 years is more at risk of developing cervical cancer. 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 (CIN). The results of this study is accordance with previous studies showing women who had sexual intercourse for the first time at the age of < 20 years were 3-4 times more likely to develop cervical cancer. The exposure of the uterus to the HPV will result in growth during into precancerous cervical cancer [12]. Married age can be associated with age-related. At the age of the genital device that is not yet matured and has been used to connect it will damage the cervix epithelial tissue that can get worse as cell abnormalities and result in abnormal growth. Especially if the partner directly has an HPV virus that is highly contagious.

Women with high parity are associated with the occurrence of cervical cancer, especially during pregnancy. This incidence causes few dynamics of cellular neoplastic epithelium which can increase the risk of cell transformation especially in the cervix resulting in persistent HPV infection. Findings and Data showed that women are often giving birth, it will affect the frequent occurrence of injury to a woman's reproductive organ, which is then will make cancer for the cervix. In the use of women who give birth frequently and a pregnancy, damage the epithelial tissue develops towards the growth of abnormal cells that are potentially malignant. It takes 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 [13].

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. 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. Respondents who have had cancer in their family (first) cervical cancer is a vulnerability that inherits. However, it is unclear whether the risk is related, with history of family cancer being due to genetic susceptibility or the influence of the environment. Likewise, As proven there is a need for consulting on contraceptive use, especially hormonal contraceptive, because high levels of hormonal contraceptive use by accepted as thought to be the effect of not providing extensive information about the advantages and disadvantages of contraception and quality contraceptive services [14].

**Conclusion**  
Duration of use of hormonal contraceptive > 5 years had a risk 4.1 times higher of cervical cancer. Method of contraceptive hormonal > 5 years had 4.2 times higher for cervical cancer than use of contraceptive 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 contraceptive. It is necessary to promote the women or contraceptive acceptance using hormonal up to 5 years.

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Correlation (OR) between duration of use hormonal contraceptive and cervical cancer after consideration of certain variables

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 surveillance and cytogenetics-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 contraceptives (over 5 years). Length of use of hormonal contraceptives had a significant correlation with the incidence of cervical cancer ( $p$ -value  $< 0.01$ ). Hormonal contraceptive use more than 5 years have risk 4.2 times (95% CI 1.01-17.58) 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 at marriage, parity, hormonal contraceptives

Abstrak

Penggunaan kontrasepsi hormonal yang lama dapat mengganggu keseimbangan estrogen dalam tubuh, sehingga mengakibatkan 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 poliambul kanker dan poliambul sitologi-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. Penentuan sampel dengan cara acak sederhana. Variabel dependen kanker serviks dan variabel independen lama penggunaan kontrasepsi hormonal diperoleh dari catatan medis. Analisis 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 1,01-17,58) 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<sup>1</sup>. 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<sup>2</sup>. Meanwhile, in developing countries including Indonesia, cervical cancer ranks highest as the most common cause of death among women, about 10% of total cases<sup>3</sup>. Cervical cancer patients in Indonesia estimated 90-100 among 100,000 inhabitants per year<sup>4,5</sup>. Yogyakarta is an area with the highest cancer incidence in Indonesia which has a prevalence of cervical cancer of 1.3 %<sup>6</sup>. 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<sup>7</sup>. Research conducted by Yousaf Narey, Philip C Hill, Kristiana 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 42%, 3 years after diagnosis by 39%, and 5 years of diagnosis 30%<sup>8</sup>.

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<sup>9</sup>. The risk factors of cervical cancer are low education, early sexual intercourse, bacterial vaginosis, disorders on genital, and contraceptive use<sup>10</sup>. 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<sup>11</sup>.

Data of active family planning participants from 2014 to 2016 showed an increasing trend year to year. Data of active family planning participants who used hormonal contraception was 51.58% to 81.77% (depend  $< 17.24\%$ ), pill 23.58%, implants 10.46%<sup>12</sup>. 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 surveillance and cytogenetics-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 in length of use of hormonal contraceptives (injection, pills and implants). The duration of hormonal contraceptive use (injection, 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 confounder 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.KEPK/051/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 (injection, 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 relationship of the duration of use hormonal contraceptives 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
Hormonal contraception > 5 years	58 (62.1)	28 (29.5)	0.01	4.3	1.01-17.58
- use of pills > 5 years	16 (51.6)	7 (33.0)	0.01	7.1	1.74-28.9
- use of injections > 5 years	32 (66.7)	12 (55.1)	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)	12 (13.7)	0.02	2.5	1.20-5.22
Active smoking	2 (2.1)	6 (6.6)	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= Confidence 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  $\leq 0.250$ . The analysis showed that the first age of marriage and parity had  $p$ -value  $\leq 0.250$  while active smoking, family history of cancer had  $p$ -value  $> 0.250$ , so they were not included in the multivariable selection.

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.<sup>20</sup>

Conclusion

Duration of use of contraception hormonal > 5 years has a strong correlation with cervical cancer. Method of contraception hormonal > 5 years had 4.3 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 women or contraceptive acceptors using hormonal up to 5 years.

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

Variable	p	p-value	OR	Lower	Upper
Use of contraception hormonal > 5 years	1.435	0.000	4.3	1.011	18.62
The first age of marriage < 20 years	0.059	0.046	1.9	0.993	4.847
Parity > 3	0.786	0.052	2.1	1.238	3.490

Note: p= coefficient OR= Odds Ratio CI= Confidence 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 4.3. These results is same as to 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 neoplasia. The acceptors who use hormonal contraceptives are often found in cervical dysplasia<sup>14</sup>. 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<sup>15</sup>. 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 porto epithelial dysplasia and mucous membranes of the endocervix. Hormonal contraceptives increase the risk of cervical cancer for women with HPV. It is suspected that gestagen triggers the carcinogenic effect of HPV<sup>16</sup>.

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 stimulate 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 becomes sticky occurs continuously and uncontrollably, the thickening will become abnormal which can lead to cervical cancer the mucus will experience changes and can damage cells in the cervix<sup>17</sup>.

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 cervix wall and can worsen leading to cell abnormalities that result in abnormal growth. Women who begin sexual intercourse age < 20 years is more at risk of developing cervical cancer. 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 (CIN)<sup>18</sup>. The results of this study is 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. 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 consent 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<sup>19</sup>.

Women with high parity are associated with the occurrence of cervical column epithelium during pregnancy. This incidence causes new dynamic of mature neoplastic epithelium which can increase the risk of cell transformation especially in the cervix resulting in persistent HPV infection<sup>20</sup>. Soedjadi 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 give 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<sup>21</sup>.

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<sup>22</sup>. 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. Respondents who have had cancer in their families cover a risk of 14.93 times for cervical cancer. Especially in the nuclear family (first) nuclear family is a vulnerability that inherits. However, it is unclear whether the risks are related, with history of family cancer long due to genetic susceptibility or the influence of the environmental lifestyle. At present there is a need for counseling on contraceptive use, especially hormonal contraception, because high levels of hormonal

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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 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 1,01-5,69) 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

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/061/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 (38.6)	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 (0.1)	1.00	1.00	0.13	7.24

n = Number of Sample, OR = Odds Ratio, CI= Confidence 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.

Introduction

Cervical cancer is a cause of mortality among women in the world and Indonesia.<sup>1</sup> 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.<sup>2</sup> Meanwhile, in developing countries including Indonesia, cervical cancer ranks highest as the most common cause of death among women, about 80% of total cases.<sup>3</sup> Cervical cancer patients in Indonesia estimated 90-100 among 100,000 inhabitants per year.<sup>1,12</sup> Yogyakarta is an area with the highest cancer incidence in Indonesia which has a prevalence of cervical cancer of 1.5 %.<sup>14</sup> 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.<sup>15</sup> Research conducted by Yvonne Narley, 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%.<sup>16</sup>

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.<sup>1</sup> The risk factors of cervical cancer are low education, infections like trichomonas vaginalis, bacterial vaginosis, disorders on genital, and contraceptive use.<sup>11</sup> 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.<sup>17</sup>

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 25.58%, implants 10.46%).<sup>18</sup> 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 use 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

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=Confidence 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.<sup>19</sup> 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.<sup>4</sup> 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.<sup>1,14</sup>

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.<sup>13</sup>

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.<sup>1</sup> 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).<sup>14</sup> 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.<sup>1</sup> 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.<sup>15</sup>

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.<sup>11</sup> 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.<sup>16</sup>

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.<sup>17</sup> 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.<sup>2</sup> 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. 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.<sup>18</sup>

#### 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 [M2]: sudah dicek.



Kesmas : National Public Health Journal (ACCEPT SUBMISSION)

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Dari: Jurnal Kesmas (jurnalkesmas.ui@gmail.com)

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Tanggal: Kamis, 18 Juli 2019 pukul 08.33 WIB

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Yth. Yuni Kusmiyati

Terima kasih telah mengirimkan artikel kepada Kesmas : National Public Health Journal. Artikel berjudul "Duration of Hormonal Contraception and Risk of Cervical Cancer" akan diterbitkan di jurnal kami pada edisi 14 (1) bulan Agustus mendatang. Saat ini artikel sedang dalam persiapan proses terbit, yakni edit bahasa dan proofreading. Kami mohon kerjasama penulis untuk melakukan perbaikan sesuai dengan kurun waktu yang kami berikan apabila hasil edit bahasa dan proofreading telah selesai. Selain itu, mohon mengirimkan no. hp yang bisa dihubungi untuk proses penerbitan jurnal nanti.

Terima kasih.

Dewi Susanna  
Editor in Chief  
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## Dummy Artikel dan Surat Persetujuan Cetak

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Tanggal: Rabu, 7 Agustus 2019 pukul 16.08 WIB

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Yth. Ibu Yuni Kusmiyati

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