The Effect of Obesity, Oral Contraceptive and Passive Smoking on the Risk of Cervical Cancer

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ABSTRACT

Background: Studies have investigated the effects of obesity on cancer development. However, the relationship between obesity and cervical cancer risk is unclear. This study aimed to determine the effect of obesity, oral contraceptive and passive smoking on the risk of cervical cancer.
Subjects and Method: A case control study was conducted at Dr. Moewardi Hospital, from October to December 2018. A sample of 200 patients was selected by fixed disease sampling, consisting of 100 cervical cancer patients and 100 non cervical cancer patients. The dependent variable was cervical cancer. The independent variables were obesity, oral contraceptive use, smoking exposure, parity, age at first sexual intercourse, and family history. The data were obtained from medical record. The data were analyzed by a multiple logistic regression.
Results: The risk of cervical cancer increased with obesity (OR= 6.83; 95%CI= 2.44 to 19.17; p<0.001), cigarette smoke exposure (OR= 12.57; 95% CI= 4.59 to 34.41; p<0.001),oral contraceptive use (OR= 3.43; 95%CI= 1.27 to 9.25; p= 0.015), parity (OR= 3.94; 95%CI= 1.47 to 10.59; p= 0.006), and family history (OR= 5.63; 95%CI= 1.94 to 16.34; p= 0.001).The risk of cervical cancer decreased with delayed menarche (OR= 0.24; 95%CI= 0.09 to 0.68; p= 0.007) and delayed age at first sexual intercourse (OR= 0.21; 95%CI= 0.86 to 0.53; p= 0.001).
Conclusion: The risk of cervical cancer increases with obesity, oral contraceptive use, smoking exposure, parity, and family history.The risk of cervical cancer decreases with delayed menarche and delayed age at first sexual intercourse.

Keywords:obesity, oral contraception, smoking exposure, cervical cancer

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BACKGROUND

Cervical cancer is an important health problem throughout the world, becoming the second cancer in women and being ranked first in many developing countries, around 80% of the total cases (El-Moselhy et al, 2016). Human papillomavirus (HPV) is considered the most common sexually transmitted infection worldwide and more than 75% of sexually active adults have HPV infections for the rest of their lives (Raychaudhuri and Mandal, 2012; Assoumou et al, 2015). HPV 16 and 18 play an important role in the genesis of cervical carcinoma (Natphopsuk et al, 2012). Cervical cancer is 10% of all cases, taking into account all cancer diagnoses among female patients (Yoruk et al, 2016). In 2012, 528,000 new cases of cervical cancer were diagnosed, and 266,000 women died of this disease, almost 90% of whom were in low to middle income countries. Deaths from cervical cancer are estimated to increase by almost 25% over the next 10 years (WHO, 2014).

Based on Globocan estimates, the 2012 International Agency for Research on Cancer (IARC), the incidence of cervical cancer is 17 per 100,000 women. Data from the Indonesian Cancer Foundation Bulletin

(YKI) in 2017, cervical cancer ranks the highest number of cancer cases in Indonesia, nearly 15,000 cases every year. Half of sufferers die. This makes cervical cancer the number 1 female killer in Indonesia. The prevalence of cervical cancer in Indonesia in 2013 was 0.8%. Based on the 2013 Basic Health Research Data, the highest estimated number of people with cervical cancer in East Java province was 21,313 and Central Java as many as 19,990 (Ministry of Health Indonesia, 2015).

Adolescent cervical tissue is considered very vulnerable to HPV infection (Ruiz et al., 2012). Natphopsuk et al. (2012) showed that the interval between menarche and first sexual intercourse <6 years resulted in a significant increase in the risk of cervical cancer. Women who start having sex at an early age have a high risk of HPV infection and cervical cancer (American Cancer Society, 2017). Another factor associated with an increased risk of cervical cancer is multiparity with poor distance between birth, smoking, oral contraceptive use and family history (El-Moselhy et al., 2016).

Tobacco use is a risk factor for death in cancer in general (20%) (Dewi, 2017). Tobacco in cigarettes can reduce the body's immune system and affect the body's ability to fight HPV infection in the cervix. Women who do not smoke but are exposed to cigarettes experience a 73% increase in the risk of cervical cancer compared to women who are not exposed (Zeng et al., 2012). Obesity increases the risk of cervical carcinoma and is important in the incidence of cervical adenocarcinoma associated with hormonal risk factors (Momenimovahed and Salehiniya, 2017; Lee et al., 2013; Poorolajal and Jenabi, 2016).

Every 2 minutes, there is one woman who dies of cervical cancer in the world, whereas in Indonesia, every 1 hour there is one woman who dies of this malignant cancer (Ministry of Health, 2015). The cervical cancer mortality rate in Indonesia is relatively high because it is mostly caused by delays in diagnosis. When checking the condition, usually the cancer has spread to other organs in the body. This causes the treatment to be made more difficult. However, it is known that cervical cancer can be prevented through screening and vaccination (Savitri, 2015).

The results of early detection of cervical cancer in Central Java for women aged 30-50 years stated 111 women suspected cervical cancer from 20,548 women with positive VIA until 2016 (Indonesian Ministry of Health, 2017). Based on the educational records of Dr. Moewardi Surakarta, the number of visits to cervical cancer patients in 2016 was 6,515 patients. The number of inpatients and outpatients in 2017 was 2,461 and 7,033 patients respectively. In 2018 cervical cancer patients were hospitalized and outpatient at Dr. Moewardi hospital were 1,540 and 8,589 patients respectively. Cervical cancer is included in the 3 biggest diseases inpatient care and the top 10 most outpatient diseases in Dr. Moewardi hospital. Cervical cancer is also the top 10 disease causing death in Dr. Hospital Moewardi.

Based on this background and the high number of patients suffering from cervical cancer, the researchers are interested in examining further about the factors that influence the incidence of cervical cancer in Dr. MoewardiHospital Surakarta.

SUBJECTS AND METHOD
1. Study Design
The research conducted is an epidemiological study that is analytic observation with a case control study design and based on its type according to chronological timings using a retrospective study. The

study was conducted at DrMoewardi Hospital Surakarta, Indonesia in October 2018 until December 2018.

2. Population and Samples

The source population used in this study was cervical cancer patients who underwent treatment at Dr. Moewardi Surakarta. The case population was cervical cancer patients undergoing treatment at Dr. Moewardi hospital was both outpatient and inpatient for 100 subjects. While the control population is patients other than cervical cancer who are undergoing treatment at Dr. Moewardi amounting to 100 subjects. The sampling was done using a fixed disease sampling technique.

3. Research Variables

The dependent variable is the incidence of cervical cancer. The independent variables include obesity, oral contraceptive use, exposure to cigarette smoke, the distance between the age of menarche and the age at first sexual intercourse, parity, age at first sexual intercourse and family history.

4. Operational Definition of Variables

Cervical cancer was defined as a cancer of the cervix suffered by patients who have been diagnosed based on histopathological tissue biopsy. Obesity is an increase in body weight beyond the limits of physical and skeletal needs, due to excessive accumulation of body fat. The use of oral contraception is a history of oral contraceptive use (pills) in less than 5 years. Exposure to cigarette smoke is smokers and non-smokers who are exposed to all chemicals derived from burning cigarettes, at least 30 minutes/ day exposure, both exposed at home, workplace or public places. The distance between the age of menarche and the age of the first time sexual intercourse is the time interval between the age of first menstruation and the age of the first time having sexual intercourse. Parity is the number of pregnancies that produce a fetus

that is able to live outside the womb / born alive. The first age of sexual intercourse is the age of first sexual intercourse both before and after marriage. Family history is a family history of a mother or sister who has cervical cancer.

5. Data Analysis

Univariate analysis was performed to see the frequency distribution and the percentage of the characteristics of the study subjects. Bivariate analysis was conducted to study the relationship between cervical cancer incidence and independent variables using the chi-square statistical test. Multivariate analysis was performed using multiple logistic regression analysis with the Stata 13 program to measure the influence of more than one predictor variable or independent variable on the dependent variable.

6. Research Ethics

Research ethics include informed consent, anonymity, confidentiality, and ethical clearance. Ethical clearance in this study was obtained from Faculty of Medicine, Sebelas Maret University with protocol number 01/18/10/335 issued on October 24, 2018.

RESULTS

1. Sample Characteristics

The characteristics of the research subjects in the case group were 100 subjects and the control group as many as 100 research subjects. The frequency distribution of the characteristics of the research subject will be described in Table 1.

2. Bivariate Analysis

Table 2 showed the results of bivariate analysis. Table 2 showed that the risk of cervical cancer increased with obesity (OR= 5.20; 95% CI= 2.78 to 9.70; p<0.001), oral contraception (OR= 3.41; 95% CI= 1.89 to 6.15; p<0.001), exposure to cigarette smoke (OR= 10.02; 95% CI= 5.01 to 20.07; p

<0.001), distance between age of menarche and first sexual activity (OR= 0.29; 95% CI= 0.16 to 0.54; p<0.001), parity (OR= 4.14; 95% CI= 2.27 to 7.57; p<0.001), and family history of cervical cancer (OR= 6.14;

95% CI= 3.09 to 12.22; p<0.001). The risk of cervical cancer decreased with age at first sexual activity (OR= 0.08; 95% CI= 0.04 to 0.16; p<0.001).

Table 1. Sample Characteristics

Variable	n	%
Cervical Cancer		
Yes	100	50
No	100	50
Obesity		
Normal (IMT 18.7 – 23.8)	79	39.5
Obesity (IMT 23.9 - > 27.0)	121	60.5
The use of oral contraception		
< 5 years	85	42.5
≥ 5 years	115	57.5
Exposure to smoke		
Exposed (≥ 30 minutes)	76	38
Not exposed (<30 minutes)	124	62
Time between the age of menarche and the first sexual intercourse		
< 6 years	69	34.5
≥ 6 years	131	65.5
Parity		
< 3 children	117	58.5
≥ 3 children	83	41.5
Age at first sexual relationship		
< 18 years	97	48.5
≥ 18 years	103	51.5
Family history		
Yes	64	32
No	136	68

3. Multivariate Analysis

Table 3 showed the results of a multiple logistic regression. Table 3 showed that the risk of cervical cancer increased with obesity (OR= 6.83; CI 95%= 2.44 to 19.17; p <0.001), oral contraceptive use (OR= 3.43; CI95%= 1.27 to 9.25; p= 0.015), exposure to cigarette smoke (OR= 12.57; CI 95%= 4.59 to 34.41; p<0.001), parity (OR= 3.94; CI 95%= 1.47 to 10.59; p= 0.006), and family

history (OR= 5.63; CI 95%= 1.94 to 16.34; p= 0.001).

The reduced risk of cervical cancer was influenced by the distance between the age of menarche and the age at first sexual activity (OR= 0.24; CI 95%= 0.09 to 0.68; p= 0.007) and age at first sexual activity (OR= 0.21; CI 95%= 0.09 to 0.53; p= 0.001).

Table 2. Bivariate Analysis

Independent Variables	Cervical Cancer		No		OR	95% CI		p
	n	%	n	%		Lower Limit	Upper Limit	
Obesity								
Normal (BMI 18.7 – 23.8)	42	34.7	79	65.3	5.20	2.78	9.70	<0.001
Obesity (BMI 23.9 - > 27.0)	58	73.4	21	26.6				
The Use of Oral Contraceptive								
< 5 years	28	32.9	57	67.1	3.41	1.89	6.15	<0.001
≥ 5 years	72	62.6	43	37.4				
Cigarette smoke exposure								
Exposed (≥ 30 menit)	62	81.6	14	18.4	10.02	5.01	20.07	<0.001
Not exposed (< 30 menit)	38	30.6	86	69.4				
Distance between age of menarche and the first sexual activity								
< 6 years	48	69.6	21	30.4	0.29	0.16	0.54	<0.001
≥ 6 years	52	39.7	79	60.3				
Parity								
< 3 children	42	35.9	75	64.1	4.14	2.27	7.57	<0.001
≥ 3 children	58	69.9	25	30.1				
The age of first sexual activity								
< 18 years	76	78.4	21	21.6	0.08	0.04	0.16	<0.001
≥ 18 years	24	23.3	79	76.7				
Family history								
Yes	50	78.1	14	21.9	6.14	3.09	12.22	<0.001
No	50	36.8	86	63.2				

Table 3. Multiple Logistic Regression Analysis

Independent Variables	OR	CI95%		p
		Lower Limit	Upper Limit	
Obesity	6.83	2.44	19.17	<0.001
The Use of Oral Contraception	3.43	1.27	9.25	0.015
Exposure to Cigarette Smoke	12.57	4.59	34.41	<0.001
Distance between age of menarche and first sexual activity	0.24	0.09	0.68	0.007
Parity	3.94	1.47	10.59	0.006
Age at First Sexual Activity	0.21	0.09	0.53	0.001
Family History	5.63	1.94	16.34	0.001

DISCUSSION

1. The relationship between obesity and the incidence of cervical cancer

The results of multiple logistic regression analysis in this study indicated that there was a relationship between obesity and the incidence of cervical cancer. There was a positive and significant relationship between obesity and the incidence of cervical cancer. This study showed that obese women were 6.83 times more likely to have cervical cancer. The results of this study were in line with the research conducted by Seng et al. (2018) which showed that there was a significant relationship between obesity and the incidence of cervical cancer. The average BMI in cervical

cancer patients was higher than non-cervical cancer.

A study of El-Moselhy et al. (2016) showed that obese women have a risk by 5.42 times higher for cervical cancer compared to women with normal weight (OR = 5.42; CI95% 3.03-9.74). Obesity played a role in the pathogenesis of cervical adeno-carcinoma through hormonal activity, in addition, obese women tend to not do screening for cervical cancer (Momenimovahed and Salehiniya, 2017). Obesity was not only a risk factor, but can also affect prognosis through a variety of pathways including related features of adverse diseases, comorbidities that can interfere with treatment, hormonal influences, and other mechanisms (Irimie *et al.*, 2011).

2. The relationship between oral contraceptive use and the incidence of cervical cancer

The results of the analysis showed that there was a positive relationship between oral contraceptive use and the incidence of cervical cancer and it was statistically significant. This study showed that women who used oral contraceptives more than 5 years have a risk of 3.43 times for cervical cancer. This study was in line with Chelimo et al. (2013) which stated that oral contraceptive users for 5 years or more were 4 times more likely to have invasive cervical cancer and more than 3 times had insitu carcinoma.

Hormonal receptors were present in human cervical tissue. In women who use oral contraception histological, the changes occurred in the cervical epithelium, immunological changes that increased sensitivity to viral factors, and oral contraception caused secretion of mucus which facilitated the entry of mutagens (Ardahan, 2016).

3. The relationship between cigarette smoke exposure and the incidence of cervical cancer

The results of the analysis showed a positive relationship between exposure to cigarette smoke and the incidence of cervical cancer and it was statistically significant. Women who were exposed to cigarette smoke were 12.57 times more likely to have cervical cancer. The results of this study were in line with Zeng et al. (2012) which showed that women who were exposed to cigarette smoke had a 73% increased risk of cervical cancer compared to women who were not exposed.

Meta-analysis study done by Feng et al. (2017) stated that high exposure to the smoking environment was slightly associated with a higher risk of HPV infection. Passive smoker with a lifetime exposure of more than 20 packs of cigarettes per year has a 7.2 times higher risk of HPV infection (OR= 7.2; CI 95%= 2.5-20.6). Many studies have focused on carcinogens related to tobacco including nicotine, cotinin, benzo (a) pyrene, 4- (methylnitrosamino) -1- (3-pyridyl) -1-butanone.

4. The relationship between the distance between age of menarche and age at first sexual activity and the incidence of cervical cancer

The results of the analysis showed that there was a negative relationship between the distance between the age of menarche and the age at first sexual activity with the incidence of cervical cancer. The results of this study were in line with the research conducted by Natphopsuk et al. (2012) which showed that the distance between age and age of first sexual activity of <6 years had a significantly increased risk of cervical squamous cell carcinoma. During puberty, immaturity of cervical cells undergone many changes that might be more susceptible to damage and HPV infection

and/or other sexually transmitted diseases. This study showed that delaying for 6 or more years after menarche before intercourse would be safer and as a protective factor for sexually transmitted diseases (including HPV infection) and susceptibility to cervical cancer.

5. The relationship between parity and the incidence of cervical cancer

The analysis showed that there was a positive relationship between parity and cervical cancer incidence and it was statistically significant. Women who have 3 or more pregnancies were 3.94 times more likely to have cervical cancer. This research was relevant to the research conducted by Stewart et al. (2018) which showed the significant results with p= 0.008. Irimie et al. (2011) showed number of child ≥3 in cervical cancer patients reached 37.5%. The large number of children lead to high parity which increased the risk factors for cervical cancer. Trauma related to labor can increase the likelihood of HPV infection (Raychaudhuri and Mandal, 2012).

6. The relationship between age at first sexual activity and the incidence of cervical cancer

The results of the analysis showed that there was a negative relationship between the age of the first sexual activity and the incidence of cervical cancer. This study was in line with Sharma and Pattanshetty, 2018) which showed that women who had sexual activity <18 years were 5.44 times more likely to have cervical cancer (OR= 5.44; CI 95%= 2.73 to 6.38; p<0.001).

Baussano et al. (2017) stated that the first HPV infection occurred at an early age at first sexual activity, this was shown in women who showed a very sharp increase in HPV sensitivity in the year after the beginning of sexual activity. Early age in the first HPV infection was associated with a longer duration of infection and a higher risk of cervical cancer, because the probability of the cancer increased as the time exposures to the relevant carcinogens.

7. The relationship between family history and the incidence of cervical cancer

The result of analysis showed that there was a positive relationship between family history and the incidence of cervical cancer. This study showed that women who have a family history of cervical cancer were 5.63 times more likely to have cervical cancer. The results of this study were in line with Seng et al. (2018) which showed significant results with p value <0.001. Women with a family history of cervical cancer, especially in first-degree relatives, have the risk of cervical cancer by 2 times (El-Moselhy et al., 2016).

A positive family history of cervical cancer was found among 13.3% of cervical cancer patients, the youngest patient has a history of positive cervical cancer in first-degree relatives (mother) (Irimie *et al.*, 2011).

Natural and human-made chemicals can contribute to DNA damage that made the cells become cancerous. Carcinogen-induced mutations can also cause chromosome rearrangements including aneuploidy, a condition that occurred during cell division when the chromosome did not separate well between two child's cells. Extra or missing chromosomes were often seen in cervical cancer (Haverkos *et al.*, 2017).

Based on the result of the study, it can be concluded that the increased incidence of cervical cancer was affected by obesity, oral contraceptive use for ≥5 years, exposure to cigarette smoke, parity ≥3 children, and family history. The risk of cervical cancer decreased followed by the distance between age of menarche and age at first

sexual activity ≥6 years and age of first sexual activity of ≥18 years.

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