ORIGINAL ARTICLE

Association of age at menarche, parity, and hormonal contraceptive use with the histologic type of ovarian cancer

Firda Azizah[1] , **Pungky Mulawardhana[2]** , **Willy Sandhika[3]**
[1]Midwifery Program, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia, [2]Department of Obstetrics and Gynecology, Faculty of Medicine, Universitas Airlangga, Dr. Soetomo General Academic Hospital, Surabaya, Indonesia, [3]Department of Pathology, Faculty of Medicine, Universitas Airlangga, Dr. Soetomo General Academic Hospital, Surabaya, Indonesia.

ABSTRACT

Objectives: This study analyzed the relationship between age at menarche, parity, and contraceptive use with histologic type of ovarian cancer.

Materials and Methods: This study used an observational analytic with a retrospective cross-sectional approach. The research samples were 128 patients with ovarian cancer at Dr. Saiful Anwar Hospital, Malang, Indonesia, in 2017-2019. All patients underwent primary staging laparotomy. The histologic types of the ovarian cancer consisted of serous type as many as 45, mucinous 45, endometrioid 10, clear cell 20, and others 4. Data analysis used chi-square test.

Results: The p value for the relationship between age of menarche and histologic type of ovarian cancer was p=0.500 (p> 0.05), parity p=0.313, and contraceptive use p=0.824. The distribution of clear cell was more common in multiparous, 40% of endometrioid found in nulliparous, while serous were more common in women with hormonal contraceptive use ≥5 years, whereas mucinous were more common in those with history of use of <5 years.

Conclusion: There was no significant relationship between age of menarche, parity, and hormonal contraceptive use on histologic type of ovarian cancer.

Keywords: Ovarian cancer; histologic type; menarche age; parity; hormonal contraceptive

ABSTRAK

Tujuan: Penelitian ini bertujuan untuk menganalisis hubungan riwayat usia menarche, paritas, dan penggunaan KB hormonal terhadap jenis histopatologi kanker ovarium.

Bahan dan Metode: Penelitian ini menggunakan metode analitik observasional dengan pendekatan cross sectional bersifat retrospektif. Sampel penelitian adalah 128 penderita kanker ovarium di RSUD Dr. Saiful Anwar, Malang, Indonesia, pada tahun 2017-2019 semua pasien dilakukan tindakan surgical staging. Didapatkan jenis serous sebanyak 49; mucinous 45; endometrioid 10, clear cell 20, dan others 4. Uji analisis data menggunakan chi square.

Hasil: Nilai p untuk hubungan usia menarche dengan jenis histopatologi adalah p=0,500 (p>0,05), paritas p=0,313, penggunaan KB hormonal p=0,824. Sebaran jenis clear cell lebih banyak ditemukan pada multipara, jenis endometrioid 40% pada nullipara, serous lebih banyak ditemukan pada wanita dengan riwayat penggunaan KB hormonal ≥5 tahun, sedangkan jenis mucinous lebih banyak ditemukan pada riwayat penggunaan < 5 tahun.

Simpulan: Tidak ada hubungan yang signifikan antara usia menarche, paritas, dan penggunaan KB hormonal terhadap jenis histopatologi kanker ovarium.

Kata kunci: Kanker ovarium; tipe histologi; usia menarche; paritas; kontrasepsi hormonal

*Correspondence: Willy Sandhika, Departemen Patologi Fakultas Kedokteran Universitas Airlangga Jl. Prof.Dr. Moestopo 47 Surabaya, Jawa Timur, Indonesia. E-mail: willysand@fk.unair.ac.id

INTRODUCTION

Ovarian cancer is a gynecological malignant tumor that is difficult to find its clinical symptoms at an early stage. This type of cancer is often diagnosed at an advanced stage, with poor prognosis. This causes ovarian cancer to be the most lethal gynecological cancer.[1] According to the Centers for Disease Control and Prevention (CDC) in 2019, ovarian cancer is the fifth leading cause of death in women from cancer in the United States. Based on GLOBOCAN data in 2018, new cases of ovarian cancer were identified as many as 295,414 or 3.4% of all cancer cases suffered by women worldwide, while the death rate from ovarian cancer were 4.4% of all deaths caused by cancer worldwide. In Indonesia, ovarian cancer accounts for 7.1% of all new case findings, or around 13,310 women were diagnosed with ovarian cancer in 2018.[2] At Dr. Saiful Anwar Hospital, Malang, Indonesia, ovarian cancer cases were recorded as much as 37.8% of all gynecological cancer cases that had been treated in the 2017-2019 period, while the most cases were cervical cancer.

Due to the complexity of the ovarian organ, the anatomical structure of the tissue, endocrine function, and the lack of early symptoms, it becomes a challenge in determining the degree of malignancy and histo-logical classification of ovarian cancer.[3] Ovarian cancer has a more diverse histological classification compared to other gynecological cancers, so that the interpretation of histological examination results in patients must be carefully considered in accordance with internationally accepted guidelines. Each type of histology has different molecular properties that affect the level of sensitivity to chemotherapy drugs, metastatic patterns, and patient survival.[4]

In the last twenty years, there has been a major evolution in the classification of epithelial ovarian cancer. In the past, ovarian cancer was thought to originate from the epithelial tissue of the ovaries alone. However, studies on morphology, immunohistology, and molecular genetics have categorized epithelial ovarian cancer based on its pathogenesis and organ origin. Epithelial ovarian cancer is divided into two types, namely: type 1 and type 2.[5] Type 1 includes low grade serous carcinoma, endometrioid, clear cell, and serous. This type develops locally, with slow growth and metatasis. Type 2 includes high grade serous carcinoma, carcinosarcoma, and undifferentiated carcinoma. This type grows aggressively and is malignant, mostly found at an advanced stage. Type 1 epithelial ovarian cancer is associated with mutations in the KRAS, ARID1A, PIK3CA, PTEN, and BRAF genes. Meanwhile, type 2 is associated with mutations in the TP53 gene.[6]

The study of Reid[7] states that there is a relationship between age at menarche and the risk of ovarian cancer. This is related to the incessant ovulation hypothesis where a large frequency of ovulation will increase the risk of ovarian cancer. In addition, according to Yang[1] the relationship for the effect per year of age at menarche on the incidence of ovarian cancer has not been studied. The protective effect provided by a history of parity also influences the histologic type of ovarian cancer. Women with a history of aterm pregnancy have a 20% lower risk of suffering from serous carcinoma, while for clear cell and endometrioid types the risk is reduced by 50-70%.[7] According to Cook,[8] hormonal contraceptive use, especially those containing estrogen and progesterone, such as combination oral contraception taken before the first term of pregnancy, can give protective effect against high grade serous types.

Research results of Wentzensenv[9] concluded that etiological studies regarding the subtypes of ovarian cancer are important considering the heterogeneous relationship between the risk factors and the types of ovarian cancer histopathology. This is necessary to develop new strategies in the prevention of ovarian cancer.

MATERIALS AND METHODS

This reasearch was an observational analytic study using secondary data with a retrospective cross-sectional approach. The study population was 261 new ovarian cancer patients who were diagnosed for the first time in 2017-2019 period. Sampling was based on inclusion and exclusion criteria with a total sampling technique. The research sample obtained as many as 128 medical records that met the research requirement. The inclusion criteria were women with ovarian cancer who under-went primary surgical staging at Dr. Saiful Anwar Hospital, Malang, Indonesia, and had complete medical records covering age at menarche, parity, history of contraceptive use, and histologic type examination result. The exclusion criteria were incomplete medical records and patients who did not perform any primary surgical staging.

Data collection was carried out in August-October 2020 starting with the determination of the research sample. Data collection from patient medical records then processed and analyzed using chi-square test and alternative fisher exact test using SPSS application.

RESULTS AND DISCUSSION

Most of the respondents were at menopause stage (29.7%), but the proportions were not much different from the adult and perimenopause (25% and 24%), a small proportion (0.8%) found in child stage and were not found in adolescent. Most of the patients (95.3%) were married, and the rest were unmarried.

Age at menarche was divided into three categories ≤ 11 years, 12-13 years, and ≥ 14 years (according to the Medical Research Council National Survey of Health and Development, UK). Most of the respondents experienced menarche at ≥ 14 y.o, followed by the age range of 12-13 y.o of 34.4%, and age ≤ 11 years of 29.7% (Table 1).

Table 1. Characteristic of women with ovarian cancer at Dr. Saiful Anwar Hospital, Malang, Indonesia in 2017-2019

Characteristic	Number of patients (n=128)	.
Age (y.o)		
Child (0-9)	1	0.8
Adolescent (10-19)	0	0
Reproductive age (20-35)	5	3.9
Adult (36-44)	32	25
Perimenopause (45-50)	32	24
Menopause (51-59)	38	29.7
Elderly (≥ 60)	20	15.6
Marital status		
Married	122	95.3
Not Married	6	4.7
Age at menarche (y.o)		
≤ 11	38	29.7
12 - 13	44	34.4
≥ 14	46	35.9
Parity		
Nullipara	36	28.1
Primipara	32	25
Multipara	60	46.9
Hormonal contraceptive use		
Never or using non hormonal contraceptive	97	75.8
Less than 5 years	24	24
≥ 5 years	7	7
Histologic type		
Serous carcinoma	49	38.3
Mucinous carcinoma	45	35.2
Endometrioid carcinoma	10	7.8
Cler cell carcinoma	20	15.6
Others (Transitional, mixed epithelial tumor. undifferentiated and unclassified tumor)	4	3.1

Table 2. The relationship between age at menarche with histologic type of ovarian cancer

	Histologic type of ovarian cancer (expectation frequency)				Total (n=128)	p	
	Serous	Mucinous	Endometrioid	Clear cell & others			
Age at menarche (y.o)						0.500	Confidence Interval (CI) 95%
≤ 11	17 (14.5)	9 (13.4)	2 (3)	10 (7.1)	38		
12 – 13	17 (16.8)	17 (15.5)	3 (3.4)	7 (8.3)	44		
≥ 14	15 (17.6)	19 (16.2)	5 (3.6)	7 (24)	46		
Parity						0.313	
Nullipara	17 (13.8)	9 (12.7)	4 (2.8)	6 (6.8)	36		
Primipara	12 (12.3)	14 (11.3)	3 (2.5)	3 (6)	32		
Multipara	20 (23)	22 (21.1)	3 (4.7)	15 (11.3)	60		
Hormonal contraceptive use						0.824	
Never or using non hormonal contraceptive	39 (37.1)	32 (34.1)	8 (7.6)	18 (18.2)	97		
Less than 5 years	7 (9.2)	11 (8.4)	1 (1.9)	5 (4.5)	24		
≥ 5 years	3 (2.7)	2 (2.5)	1 (0.5)	1 (1.3)	7		

There was no significant difference regarding the age at menarche in each age range. Most of the respondents had parity ≥ 2 (46.9%), while the remaining were nulliparous and primiparous (28.1% and 25%). Most of the respondents (75.8%) had never used family planning or had ever used non-hormonal methods, 19.5% had a history of using hormonal contraceptive for ≥ 5 years, and 4.7% had a history of using hormonal contraceptive <5 years, such as: injections, pills, or implants.

The most common type was serous carcinoma (38.3%) followed by mucinous carcinoma (35.2%), the third was clear cell carcinoma (15.6%), endometrioid (7.8%), and the least was transitional types, mixed epithelial tumors, undifferentiated and unclassified tumors (3.1%).

Table 2 shows the statistical test result of the relationship between age at menarche, parity, and hormonal contraceptive use with the histologic type of ovarian cancer. Statistical data processing used Fisher's exact test. The p value for age at menarche obtained p=0.500, parity p=0.313, and hormonal contraceptive use (p=0.824); indicating that there was no significant association of age at menarche, parity, and hormonal contraceptive use with the histologic type of ovarian cancer.

The proportion of ovarian cancer histologic type in Dr. Saiful Anwar Hospital, Malang, Indonesia, was slightly different from the proportion based on epidemiological studies in scientific articles published in the period 1925-2018 by Momenimovahed.[11] Based on the epidemiological study, it was found that the proportion of histologic type of ovarian cancer was serous type 70%, mucinous 5%, endometrioid 10%, clear cell carcinoma 10%, and others 5%. Whereas in this study, it was found that the most common histologic type was serous carcinoma (38.3%) followed by mucinous carcinoma (35.2%), clear cell carcinoma (15.6%), endometrioid (7.8%), transitional types, mixed epithelial tumors, undifferentiated and unclassified tumors (3.1%).

This difference may occur due to differences in the number and characteristics of the study sample. The research conducted by Momenimovahed had a very large sample size with diverse characteristics of women from all continents, namely Asia, America, Europe, Africa and Australia. The highest prevalence of ovarian cancer cases was in non-Hispanic white women, followed by Hispanics, black women, followed by Asian and Pacific women. Two-thirds of ovarian cancer deaths were found in high-grade serous cases, with the highest mortality rate in African women, which was associated with poor access to adequate health facilities.

Relationship between age at menarche and the histologic type of ovarian cancer

The results of this study were in line with the opinion of Momenimovahed.[10] that age at menarche does not have an effect on the risk of ovarian cancer or the type of histopathology in patients with ovarian cancer. In addition, according to Yang[1] the association for the effect per year of age at menarche on ovarian cancer incidence had not been studied, and traditional observational studies had scientific methodological flaws and could lead to bias. A literature study conducted by Reid[7] states that the relationship between the age at menarche shows mixed results. These inconsistent findings may be related to differences in definition, memory and bias towards the experiences of respondents with menarche and menopause.

Although many studies suggest that the age at menarche-menopause is closely related to the theory of incessant ovulation and lifetime ovulation cycle (LOC) in women, there are no research results that can explain the carcinogenesis pathway which is influenced by the age at menarche. Likewise, regarding the relationship between age at menarche and histologic type of ovarian cancer, there is no literature that can clearly describe the closeness of the relationship.

Relationship between parity and the histologic type of ovarian cancer

Many epidemiological studies have been conducted and agree that the amount of parity is a protective factor for ovarian cancer. The increase in the amount of parity is inversely related to the risk of ovarian cancer in women. Specifically, research conducted by Siegel[11] found that every aterm pregnancy can reduce the risk of ovarian cancer by up to 19% and each birth experienced by women on average can reduce the risk of ovarian cancer by 6%.[12]

The protective effect obtained due to pregnancy is related to the anovulation process which can reduce the possibility of mutation of epithelial cells into neoplasm cells. Cell mutation may occur as a consequence of ovulation that occurs in a woman's life cycle. When a woman ovulates, several processes occur: ovarian epithelial cells burst, cells are exposed to follicular fluid, and hormonal fluctuations.. Meanwhile, term pregnancy provides a protective effect against ovarian cancer, because it can prevent the growth of precursor lesions that can grow into neoplasm cells.

The popular hypothesis used to underlie the malignant process of ovarian cancer in women is incessant ovulation. This hypothesis was proposed by Casa-grande,[13] in which pregnancy causes cessation on pro-inflammatory process in incessant ovulation (ovulation that occurs continuously in women) through hormonal modification or changes and the process of destroying pre-malignancy cells in the ovaries. during the period of pregnancy or breastfeeding.

The protective effect provided by a history of parity also influences the histologic type of ovarian cancer. Women with a history of aterm pregnancy have a 20% lower risk of suffering from serous carcinoma, whereas for clear cell and endometrioid the risk is reduced by 50-70%.[7] The results of this study are in line with a prospective study conducted by Gaitskell[12] on 1.3 million women in the UK. Gaitskell found nulliparous women were 50% more at risk for endometrioid and almost 70% more at risk for clear cell, whereas for mucinous the risk was lower, and there was no significant risk for the serous, which is the most common type of histopathology.

The results of the cross-test conducted in this study found that there was no significant relationship between the amount of parity and the histologic type of ovarian cancer, especially in the clear cell and endometrioid that already had references from previous studies. In this study, there were 20 respondents with clear cell. 60% or 12 respondents were multiparous (≥2 aterm pregnan-cies), 30% were primiparous, and 10% were nulliparous. As for the endometrioid, 40% had a history of nulliparous, 30% were primiparous, and 30% were multiparous.

The results showed that clear cell were more common in women with a history of multiparous, in contrast to previous studies which stated that pregnancy can reduce the risk of clear cell by up to 70%. Meanwhile, 40% of the endometrioid type is experienced by women with a history of nulliparous. This is in line with previous studies which state that nulliparous women are at risk of suffering from endometrioid up to 50%. The discrepancy in the results of research with existing theories or studies may be due to the different number of samples.

Relationship between hormonal contraceptive use and the histologic type of ovarian cancer

Most of the patients with hormonal contraceptive use less than five years had mucinous type. The use of hormonal contraceptives more than five years should be able to provide protection for serous, but in this study serous types were more common. Cell mutation to

serous carcinoma is caused due to dysfunction of the BRCA1/2 gene for high grade serous carcinoma and mutations of the KRAS and BRAF genes for low grade serous carcinoma. However, until now it is not known about the mechanism of the protective role of estrogen and progesterone in influencing the formation of cell mutations into certain types. So far, estrogen and progesterone have been given to regulate the female ovulation cycle so as to suppress the continuous inflammatory process that can trigger the growth of neoplasm cells.

According to Cook[8] the use of hormonal birth control, especially those containing the hormones estrogen and progesterone, such as combine oral contraception taken before the first aterm of pregnancy can have a protective effect against high grade serous. Meanwhile, the use of combine oral contraception one year after delivery provides 50% less protective effect. The protective effect is influenced by the duration of use, use before the first term of pregnancy, and the age of the woman when she first took the pill.

The cohort study conducted by Trabert[14] found that the use of hormonal contraceptive was statistically associated with a reduced risk of high grade serous and clear cell ovarian cancer. Trabert studied the effect of increasing the LOC on increasing the risk of ovarian cancer. The study stated that for every 60 LOC increase or within 5 years, women also had an increased risk of ovarian cancer by 14%. This association also had an effect on histologic type of ovarian cancer. Each five year increase in LOC was associated with clear cell risk, high grade serous, and less endometrioid, but not mucinous.[15]

The limitation of secondary data obtained causes the history of hormonal birth control data to only be categorized based on the duration of use. This study did not specifically categorize the types of hormonal contraceptive used by respondents based on the type of hormonal birth control method, age at first use, and history of parity when using hormonal contraceptive. Besides that, very few patients have a history of using hormonal birth control more than 5 years, that is, only seven patients. The use of hormonal birth control as a choice of long-term family planning methods is less popular in Indonesia.

CONCLUSION

It can be concluded that there is no significant relation-ship between age at menarche, parity, and hormonal contraceptive use on the histologic type of ovarian cancer. Therefore, it is necessary to examine the

histopathology to determine the histologic type in patients with certainty. The histologic type of ovarian cancer affects the sensitivity of chemotherapy drugs, prognosis, and the course of the patient's disease. The introduction of risk factors in women is expected to be able to awaken women's awareness about the reproductive health status especially the ovaries.

ACKNOWLEDGMENT

REFERENCES

1. Yang H, Dai H, Li L, et al. Age at menarche and epithelial ovarian cancer risk: A meta-analysis and Mendelian randomization study. Cancer Med. 2019;8(8):4012-4022. doi: 10.1002/cam4.2315. Epub 2019 May 30. PMID: 31145551; PMCID: PMC6639189.

2. Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018 Nov;68(6):394-424. doi: 10.3322/caac.21492. Epub 2018 Sep 12. Erratum in: CA Cancer J Clin. 2020;70(4):313. PMID: 30207593.

3. Meinhold-Heerlein I, Hauptmann S. The heterogeneity of ovarian cancer. Arch Gynecol Obstet. 2014;289(2):237-9. doi: 10.1007/s00404-013-3114-3. PMID: 24318356.

4. Matz M, Coleman MP, Sant M, et al. The histology of ovarian cancer: worldwide distribution and implications for international survival comparisons (CONCORD-2). Gynecol Oncol. 2017;144(2):405-413. doi: 10.1016/j.ygyno.2016.10.019. Epub 2016 Dec 6. Erratum in: Gynecol Oncol. 2017 Dec; 147(3):726. PMID: 27931752; PMCID: PMC6195192.

5. Kurman RJ, Shih IeM. Molecular pathogenesis and extraovarian origin of epithelial ovarian cancer--shifting the paradigm. Hum Pathol. 2011;42(7): 918-31. doi: 10.1016/j.humpath.2011.03.003. PMID: 21683865; PMCID: PMC3 148026.

6. Terada KY, Ahn HJ, Kessel B. Differences in risk for type 1 and type 2 ovarian cancer in a large cancer screening trial. J Gynecol Oncol. 2016;27(3) :e25. doi: 10.3802/jgo.2016.27.e25. PMID: 27029746; PMCID: PMC4823356.

7. Reid BM, Permuth JB, Sellers TA. Epidemiology of ovarian cancer: a review. Cancer Biol Med. 2017;14(1):9-32. doi: 10.20892/j.issn.2095-3941.2016.0084. PMID: 28443200; PMCID: PMC5365187.

8. Cook L, Pestak C, Leung A et al. Combined oral contraceptive use before the first birth and epithelial ovarian cancer risk. Br J Cancer 2017;116:265–9. doi: 10.1038/bjc.2016.400.

9. Wentzensen N, Poole EM, Trabert B, et al. Ovarian cancer risk factors by histologic subtype: An analysis from the ovarian cancer cohort consortium. J Clin Oncol. 2016;34(24):2888-98. doi: 10.1200/JCO.2016.66.8178. Epub 2016 Jun 20. PMID: 27325851; PMCID: PMC5012665.

10. Momenimovahed Z, Tiznobaik A, Taheri S, Salehiniya H. Ovarian cancer in the world: epidemiology and risk factors. Int J Womens Health. 2019;11:287-299. doi: 10.2147/IJWH.S197604. PMID: 31118829; PMCID: PMC6500433.

11. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. CA Cancer J Clin. 2015;65(1):5-29. doi: 10.3322/caac.21254. Epub 2015 Jan 5. PMID: 25559415.

12. Gaitskell K, Green J, Pirie K, et al. Million Women Study Collaborators. Histological subtypes of ovarian cancer associated with parity and breastfeeding in the prospective Million Women Study. Int J Cancer. 2018;142(2):281-289. doi: 10.1002/ijc.31063. Epub 2017 Oct 12. PMID: 28929490; PMCID: PMC5725697.

13. Fathalla MF. Incessant ovulation and ovarian cancer - a hypothesis re-visited. Facts Views Vis Obgyn. 2013;5(4):292-7. PMID: 24753957; PMCID: PMC3987381.

14. Trabert B, Tworoger SS, O'Brien KM, et al. The risk of ovarian cancer increases with an increase in the lifetime number of ovulatory cycles: an analysis from the ovarian cancer cohort consortium (OC3). Cancer Res. 2020;80(5):1210-1218. doi: 10.1158/0008-5472.CAN-19-2850. Epub 2020 Jan 13. PMID: 31932455; PMCID: PMC7056529.

15. Yang HP, Murphy KR, Pfeiffer RM, et al. Lifetime number of ovulatory cycles and risks of ovarian and endometrial cancer among postmenopausal women. Am J Epidemiol. 2016;183(9):800-14. doi: 10.1093/aje/kwv308. Epub 2016 Apr 15. PMID: 27190045; PMCID: PMC4851993.