

polymorphism estrogen receptor gene of epithelial ovarium carcinoma.pdf

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Research Report

Polymorphism Estrogen Receptor α Gene of Epithelial Ovarian Carcinoma*Polimorfisme Gen Reseptor Estrogen α terhadap Karsinoma Ovarium Epitel*

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Abstract

Objective: To know the hypothesis that genetic polymorphisms of the ER- α gene may be associated with epithelial ovarian carcinoma.

Method: This research was population-based case control study which included 40 women who were diagnosed with primary histopathologically-confirmed epithelial ovarian carcinoma and 40 women who did not have any malignancy conducted in Dr. Mohammad Hoesin Hospital Palembang started from January 2010 until December 2011.

Results: In PvuII polymorphisms approximately 62.5% of cases and 32.5% of controls were heterozygous genotype TC, and 25% of cases and 27.5% of controls were homozygous genotype CC. Based on X^2 statistical analysis the obtained ORs = 4.667; 95% CI (1.50-14.45), and p value was 0.005. In XbaI polymorphisms were found 70% of cases and 30% of controls were heterozygous genotype AG, and 20% of cases and 27.5% of controls were homozygous genotype GG. Based on Fisher statistical analysis the obtained p value was 0,027 with ORs = 4.333; CI (1.27-14.77).

Conclusion: Results in this study indicated that genetic polymorphisms intron 1 (rs2234693) PvuII genotype TC - CC and (rs9340799) XbaI genotype AG - GG **estrogen receptor α gene** may play role in the etiology of ovarian carcinoma.

[Indones J Obstet Gynecol 2011; 35-4:218-24]

Keywords: epithelial ovarian cancer, ESR1, single nucleotide polymorphisms

Abstrak

Tujuan: Mengetahui hipotesis adanya pengaruh polimorfisme pada gen reseptor estrogen α terhadap terjadinya karsinoma ovarium jenis epitel.

Metode: Penelitian ini merupakan studi kasus-kontrol, termasuk kelompok kasus 40 perempuan yang didiagnosis karsinoma ovarium epitel yang telah dikonfirmasi secara histopatologi dan 40 kelompok kontrol yang tidak termasuk keganasan, yang dilakukan di Rumah Sakit Dr. Mohammad Hoesin Palembang sejak Januari 2010 sampai Desember 2011.

Hasil: Pada polimorfisme PvuII didapatkan kasus 62,55 dan 32,55 kontrol yang termasuk genotype heterozigot TC, dan sebanyak 25% kelompok kasus dan kelompok kontrol 27,5% yang merupakan genotype homozigot CC. Berdasarkan analisis statistik X^2 didapatkan nilai OR=4,667; 95% CI (1,50-14,45), dan nilai p = 0,005. Pada polimorfisme XbaI didapatkan pada kelompok kasus 70% dan kelompok kontrol sebesar 30% dengan genotype heterozigot AG dan genotype homozigot GG terdapat pada 20% kasus dan 27,5% kelompok kontrol. Berdasarkan uji Fisher didapatkan nilai p=0,027 dengan ORs = 4,333; CI (1,27-14,77).

Kesimpulan: Terdapat pengaruh genotype TC dan CC polimorfisme intron 1 (rs2234693) dengan enzim PvuII dan genotype AG dan GG polimorfisme intron 1 (rs9340799) dengan enzim XbaI gen reseptor estrogen α pada kejadian karsinoma ovarium epitel.

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Kata kunci: karsinoma ovarium epitel, ESR1, single nucleotide polymorphisms

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INTRODUCTION

Polymorphism is one of risk factors of ovarian cancer or ovarian carcinoma. Polymorphism is an extra variation of one phenotype that is caused by allele difference genetically.¹ Every individual in population has different genetic variation. Polymorphism in estrogen receptor gene α (ESR1) can induce ovarian epithelial via proliferation induction and cell apoptosis so this can influence the vulnerability of a person to have ovarian cancer.

Some studies from different countries suggested that 2 estrogen receptor α polymorphism is in intron 1 (rs2234693) with PvuII enzyme and (rs9340799) with XbaI enzyme. The condition was based on study conducted in some ethnicity and race of Asia, Caucasian, and African-American.²

From medical record in Dr. Mohammad Hoesin hospital (RSMH) Palembang could be seen that number of new ovarian carcinoma case tends to increase. In 2002, it was 27.9%, in 2003 increased to 36.6% and in 2004 increased to 32.9%. Pathology Anatomy department Faculty of Medical Faculty of Sriwijaya University/Dr. Mohammad Hoesin Hospital Palembang, in 2006-2008 suggested that ovarian carcinoma was on the third rank of all carcinoma in women it reached 10%.

Ovarian carcinoma was affected by estrogen either endogenous or exogenous. Estrogen affects various physiological process in human, starting from reproduction process, cardiovascular system, bone, cognitive and behaviour. Estrogen can also initiate some malignancies such as breast cancer, ovarian cancer, colorectal cancer, prostate cancer, endometrial carci-

noma, neurodegenerative, heart, osteoporosis, insulin resistance, SLE, endometriosis and obesity. Effect of this estrogen emerges via estrogen receptor, known that most ovarian epithelial carcinoma developed from ovarian surface epithelial. On ovarian surface epithelial there are estrogen receptors which are responsive to estrogen.^{3,4}

Estrogen has 2 receptors namely α dan β estrogen. Estrogen α receptor is estrogen receptor found on surface of ovarian epithelial cell. Estrogen α receptor is located in 6 q24-q27 chromosome. Mutation in this gene can affect the structure and function estrogen α receptor. Polymorphism in intron or exon can also play in the development of malignancy.⁵

METHODS

It was an analytical observational, case control study conducted in January 2010 - December 2010 in Dr. Mohammad Hoesin Hospital, Palembang.

Subjects of the study

Patients diagnosed with ovarian epithelial carcinoma from histopathological study result were included in case group (n= 40), while patients undiagnosed with malignancy were included in control group. Subjects meeting the criteria were informed about procedure and benefit of the study. Subjects signed the informed consent. In the first phase, blood sample collection was performed. Three cc of blood sample was taken from antecubiti vein puncture or visible vein for, put into the ethylene diamine tetraacetic (EDTA) tube.

DNA extraction

Extraction was performed with DNA Chelex-100 method by using Phosphate Buffer Saline (PBS) pH 7.4; Safonin 0.5% in PBS; dan Chelex 20% in dd H₂O pH 10.5.

PCR-RFLP

In this study, the assessment of estrogen α gene receptor polymorphism presence in 6 q24-q27 chromosomal locus in intron 1 in (rs2234693) and (rs9340799) using a pair of primary oligonucleotide forward 5'-CTGCCACCCTATCTGTATCTTTTCCTATTCTCC-3' and reverse 5'-TCTTTCTCTGCCACCCTGGCGTCCATTATCTGA-3' yielding 1300 bp fragment. PCR amplification was performed in DNA Thermal cycle merk ICycler BIO-RAD Laboratories GB with the following steps: performing denaturation in 95°C for 5 minutes, followed by annealing 30 amplification cycles in 94°C for 1 minute, in 62°C for 1 minute and in 72°C for 1 minute, and final extension 72°C for 6 minutes. (rs2234693) was restricted by PvuII enzyme and (rs9340799) was restricted by XbaI enzyme. Product resulted from PCR-RFLP was visualized after electrophoresis with agarose gel 4% with colouring ethidium bromide.

Electrophoresis and visualization. 2 gram Agarose was put into Erlenmeyer scale glass. Added with 40 μ l TAE buffer. Mixed and heated in microwave till boiled. Added with 4 μ l ethidium bromide, then chi-

lled on mold for 30 minutes. PCR product 5 μ l was mixed with long buffer and inserted into the electrophoresis tool. Then the tool was set at 75 mV voltage, 350 amperes for 30 minutes. The visualization used ultraviolet irradiation equipment using Gel-Doc-made BIO-RAD Laboratories, USA which was connected to a computer, then the visualized results were analyzed by computer using the program Quantity one. Sequencing was performed to confirm the presence of allele polymorphism, sequencing was done in the laboratory of biomolecular Eijkman, Jakarta.

Statistical analysis

X² and Fisher test was used to determine the relationship between ESR1 gene polymorphisms and the incidence of epithelial ovarian carcinoma, with 95% confidence, and $\alpha = 0.005$. All data were analyzed using SPSS 12.0 for Windows program to assess the distribution, allele frequency of rs2234693 in intron 1 and rs9340799 in patient groups and its comparison.

Parity	Case		Control	
	N	%	N	%
Nullipara	15	37.5	3	7.5
Primipara	7	17.5	12	30.0
Multipara	6	15.0	10	25.0
Grandemultipara	12	30.0	15	37.5
Total	40	100.0	40	100.0

RESULT

The following are the characteristics of data subjects.

General characteristics of subjects

Age

The mean age of subjects was 43.13 \pm 10.74, then the subjects of study were divided into 2 groups based on the mean of age. Age \geq 43 was classified to be the case group, which consisted of 27 subjects (67.5%), while age < 43 was classified to be the control group, which consisted 21 subjects (52.5%). However, the statistical test Chi Square, found no significant difference ($p = 0.070$). Distribution of age of the subject in detail can be seen in Table 1.

Table 1. Distribution of age.

Age (years)	Case		Control	
	N	%	N	%
< 43	13	32.5	21	52.5
\geq 43	27	67.5	19	47.5
Total	40	100.0	40	100.0

Chi Square test; $p = 0.070$

Parity

Largest proportion of parity in the case group was nullipara, 15 subjects (37.5%) and in the control group was at grandemultipara as many as 15 subjects (37.5%). Based on Chi Square test, there was no significant difference in parity between the study groups ($p = 0.140$). Parity distribution of the subject are completely shown in Table 2.

Table 2. Distribution of parity.

Parity	Case		Control	
	N	%	N	%
Nullipara	15	37.5	3	7.5
Primipara	7	17.5	12	30.0
Multipara	6	15.0	10	25.0
Grande multipara	12	30.0	15	37.5
Total	40	100.0	40	100.0

Clinical Characteristic of Two Study Groups

History of Hormonal Contraception Use

History of hormonal contraceptive use on 16 subjects (40%) in the case group consisted of 7 subjects (17.5%) with a pill, 7 subjects (17.5%) with a syringe and 2 subjects (5.0%) with a pill and syringes. Meanwhile, 21 subjects (52.5%) in the control group consisted of 4 subjects (10.0%) with the pill, 15 subjects (37.5%) with a syringe and 2 subjects (5.0%) with pills and injections. Based on Chi Square test, there are no significant differences in history of hormonal contraceptive use on research subjects ($p=0.230$). Distribution history of the use of hormonal contraceptives on subject in detail can be seen in Table 3.

Table 3. Distribution history of the use of hormonal contraceptives.

Hormonal Contraception	Case		Control	
	N	%	N	%
Pill	7	17.5	4	10.0
Syringe	7	17.5	15	37.5
Pill + Syringe	2	5.0	2	5.0
No	24	60.0	19	47.5
Total	40	100.0	40	100.0

Chi Square test; $p=0.230$

Duration of Hormonal Contraceptive Use

The largest distribution of subjects based on duration of hormonal contraceptives use in the case group is in the range of <3 years of the 6 subjects (15.0%) whereas in the control group is in the range of 1-3 years of the 12 subjects (30.0%). Based on Chi Square

test, there was no significant difference in duration of hormonal contraceptive use on research subjects ($p = 0.277$). Distribution of duration of hormonal contraceptive use can be seen completely in Table 4.

Table 4. Distribution of duration of hormonal contraceptive use.

Duration of hormonal contraceptive use	Case		Control	
	N	%	N	%
< 1 y	6	15.0	4	10.0
1 - 3 y	5	12.5	12	30.0
> 3 y	5	12.5	5	12.5
None	24	60.0	19	47.5
Total	40	100.0	40	100.0

Chi Square test; $p=0.277$

Menopause status

Largest proportion of menopausal status was found in the case group, about 25 subjects (62.5%) in menopause and in the control group about which in the menopause has not been as many as 24 subjects (60.0%) in not menopause. Based on Chi Square test, there were significant differences in menopausal status between the study groups ($p = 0.044$). Distribution of subjects in full menopause status is displayed in Table 5.

Table 5. Distribution of menopausal status of subjects.

Menopausal status	Case		Control	
	N	%	N	%
Not yet menopause	15	37.5	24	60.0
Menopause	25	62.5	16	40.0
Total	40	100.0	40	100.0

Chi Square test; $p=0.044$

Family History of Ovarian Carcinoma

Distribution of family history of ovarian cancer can be seen in Table 6. Most subjects in both case and control group had no family history of ovarian cancer on which in case group was 39 subjects (97.5%) and control group was 36 subjects (90.0%). Based on Fishers test, there were no significant differences intergroup in family history of ovarian cancer ($p=0.359$).

Table 6. Distribution of subjects' family history of ovarian cancer.

Family history of ovarian cancer	Case		Control	
	N	%	N	%
Yes	1	2.5	4	10.0
None	39	97.5	36	90.0
Amount	40	100.0	40	100.0

Chi Square test; $p=0.359$

Genotype INTRON 1 (rs2234693) PvuII and (rs9340799) XbaI estrogen α receptor genes in ovarian epithelial carcinoma group and control group

Polymorphism has variation more than one phenotype that is genetically caused by allele difference. Polymorphism in estrogen α receptor gene if there is any mutation in intron 1 (rs2234693) can be identified using PvuII restriction enzyme and (rs9340799) with XbaI enzyme. ER α gene is a gene located in locus 6 chromosome q24-q27 identified via DNA extraction process and genotype analysis with PCR-RFLP method from blood sample.

Intron 1 (rs2234693) with PvuII enzyme Estrogen α receptor gene in epithelial ovarian carcinoma group (case) and control group

Result of PCR amplification will yield 1300bp fragment length. Individual without polymorphism in estrogen α receptor gene in intron 1 is suggested in wild type allele with TT genotype, found no restriction in other site. Polymorphism in estrogen α receptor gene will initiate substitution T base into C in nucleotide 905. Individual with homozygous mutant allele with CC genotype site PvuII restriction enzyme yielded PCR products to be sliced into 2 bands, 850 bp and 450 bp. Meanwhile individual with wild type allele and mutant (heterozygous) with TC genotype will obtain PCR result RFLP 3 bands, 1300bp, 850bp and 450 bp.

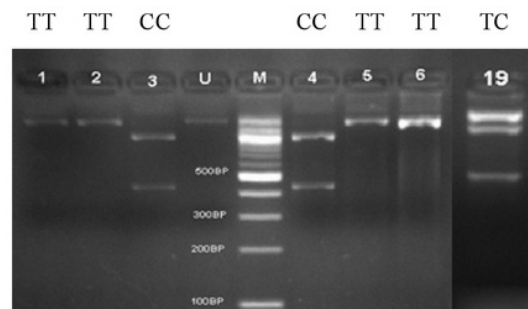


Figure 1. Result of RFLP with PvuII enzyme in case group.
note: Genotype TT located in lane 1,2,5,6, Genotype CC located in lane 3,4, Genotype TC located in lane 19

In Figure 1, seen in case 1,2,5 is wild type (AA) individual. In case 3 and 4, it is a homozygous (GG) mutant individual on which enzymes was sliced into 2 bands with fragment length 450 bp and 850 bp, respectively. While in case 19 is homozygous mutant individual (TC) on which enzymes was sliced into 3 bands with fragment length 400 bp, 900 bp and 1300 bp.

Intron 1 (rs9340799) with XbaI enzyme Estrogen α receptor gene in epithelial ovarian carcinoma group (case) and control group

Intron 1 of amplification result will yield 1300 bp fragment. Non-polymorphism in estrogen α receptor

gene in intron 1 suggested that wild type with AA genotype, XbaI restriction enzyme was not slicing other site. Polymorphism in estrogen α receptor gene in intron 1 caused base A substitution into G in nucleotide 951. Individual having homozygous mutant allele with GG genotype site XbaI restriction enzyme caused its PCR product to be sliced into 2 bands, 900 bp and 400 bp. Meanwhile individual with wild type allele and mutant (heterozygous) with AG genotype will obtain PCR result RFLP 3 bands 1300 bp, 900 bp and 400 bp.

GG AA AG AG AG AG AG AG AG AG

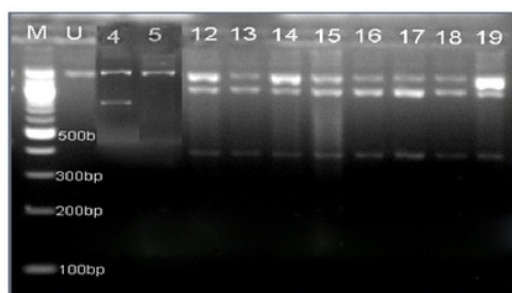


Figure 2. Result of RFLP with XbaI enzyme in case group.
note: Genotype AA located in lane 5, Genotype GG located in lane 4, Genotype AG located in lane 12-19

In Figure 2, seen in case 5 is wild type (AA) individual with fragment length 1300 bp. In case 4, it is a homozygous (GG) mutant individual on which enzymes was sliced into 2 bands with fragment length 400 bp and 900 bp, respectively. While in case 12 to 18 is heterozygous mutant individual (AG) on which enzymes was sliced into 3 bands with fragment length 400 bp, 900 bp and 1300 bp. In case 19, it was performed sequencing due to unclear fragment length 1300, after being sequenced, the result is AG.

Effects of Polymorphism of Intron 1 (Rs2234693) With PvuII Enzyme And (Rs9340799) With XbaI Enzyme Estrogen α Receptor Gene on the Incidence of Epithelial Ovarian Carcinoma

Effects of polymorphism Intron 1 (rs2234693) with PvuII enzyme Estrogen α receptor gene on the incidence of epithelial ovarian carcinoma.

It was found that 25 subjects (62.5%) in case group had TC genotype, while in control group was least, 13 subjects (32.5%). For CC genotype, there were 10 subjects (25.0%) in case group 11 subjects (27.5%) in control group. Meanwhile, TT genotype mostly belong to control group, 16 subjects (40%), while case group had only 5 subjects (12.5%). Distribution of polymorphism genotype Intron 1 (rs2234693) with PvuII enzyme estrogen α receptor gene can be completely seen on Table 7.

Table 7. Distribution of polymorphism genotype Intron 1 (rs2234693) with PvuII enzyme estrogen α receptor gene

Polymorphism genotype intron 1 (rs2234693) with PvuII enzyme	Group			
	N	%	N	%
TT (Wild type)	5	12.5	16	40.0
TC (Wild type/ mutant)	25	62.5	13	32.5
CC (Mutant)	10	25.0	11	27.5
Total	40	100.0	40	100.0

Based on statistical analysis test of Chi Square there was the significant effect of polymorphism genotype intron 1 (rs2234693) with PvuII enzyme estrogen α receptor gene on the incidence of epithelial ovarian carcinoma ($p=0.005$) with Odd Ratio 4.667. Effects of polymorphism genotype Intron 1 (rs2234693) with PvuII enzyme estrogen α receptor gene on epithelial ovarian carcinoma completely seen in Table 8.

Table 8. Effects of polymorphism genotype Intron 1 (rs2234693) with PvuII enzyme estrogen α receptor gene on the incidence epithelial ovarian carcinoma

Polymorphism genotype intron 1 (rs2234693) with PvuII enzyme	Group			
	Case	%	Control	%
TT	5	12.5	16	40.0
TC + CC	35	87.5	24	60.0
Total	40	100.0	40	100.0

OR = 4.667; 95% CI (1.50-14.45), $p = 0.005$.

Effects of polymorphism Intron 1 (rs2234693) with XbaI enzyme Estrogen α receptor gene on the incidence epithelial ovarian carcinoma

It was found that 28 subjects (70.0%) in case group had AG genotype, while in control group was least, 12 subjects (30.0%). For GG genotype, there were 8 subjects (20.0%) in case group and 15 subjects (37.5%) in control group. Meanwhile AA genotype mostly belong to control group, 13 subjects (32.5%) while case group was only 4 subjects (10.0%). Distribution of polymorphism genotype Intron 1 (rs2234693) with XbaI enzyme estrogen α receptor gene can be completely seen on Table 9.

Table 9. Distribution of polymorphism genotype Intron 1 (rs2234693) with XbaI enzyme estrogen α receptor gene

Polymorphism Genotype intron 1 (rs9340799) with XbaI enzyme	Group			
	Case	%	Control	%
AA (Wild type)	4	10.0	13	32.5
AG (Wild type/ mutant)	28	70.0	12	30.0
GG (Mutant)	8	20.0	15	37.5
Total	40	100.0	40	100.0

Based on statistical analysis of Fishers test it was Found the significant effect of polymorphism genotype intron 1 (rs9340799) with XbaI enzyme estrogen α receptor gene on the incidence of epithelial ovarian carcinoma ($p=0.027$) with Odd Ratio 4.333. Effects of polymorphism genotype Intron 1 (rs9340799) with XbaI enzyme estrogen α receptor gene on the incidence of epithelial ovarian carcinoma completely seen in Table 10.

Table 10. Effects of polymorphism genotype Intron 1 (rs9340799) with XbaI enzyme estrogen α receptor gene on the incidence of epithelial ovarian carcinoma

Polymorphism genotype intron 1 (rs9340799) with XbaI enzyme	Group			
	Case	%	Control	%
AA	4	10.0	13	32.5
AG + GG	36	90.0	27	67.5
Total	40	100.0	40	100.0

OR = 4.333; 95% CI (1.27-14.77), $p = 0.027$

Polymorphism allotype Intron 1 (rs2234693) with PvuII enzyme Estrogen α receptor gene on the incidence of epithelial ovarian cancer carcinoma Allotype C (mutant) were mostly found in case group, 45 subjects (56.3%) while in control group was 35 subjects (43.7%). Allotype T was, mostly found in control group which was 45 subjects (56.3%) while in case group was 35 subjects (43.7%). Statistical analysis of Chi-Square test suggested that there was no significant polymorphism intron 1 (rs2234693) with PvuII enzyme estrogen α receptor gene on the incidence of epithelial ovarian carcinoma ($p=0.114$). Distribution of polymorphism intron 1 (rs2234693) with PvuII enzyme estrogen α receptor gene on the incidence of epithelial ovarian carcinoma can be completely seen in Table 11.

Table 11. Distribution of polymorphism intron 1 (rs2234693) with PvuII enzyme estrogen α receptor gene on the incidence of epithelial ovarian carcinoma.

Polymorphism Allotype intron 1 (rs2234693) PvuII	Group			
	Case	%	Control	%
C (Mutan)	45	56.3	35	43.7
T (Wild type)	35	43.7	45	56.3
Total	80	100.0	80	100.0

OR = 1.653; 95% CI (0.88-3.08), $p = 0.114$

Polymorphism allotype Intron 1 (rs9340799) with XbaI enzyme Estrogen α receptor gene on the incidence of epithelial ovarian cancer carcinoma. Distribution of polymorphism intron 1 (rs9340799) with XbaI enzyme was not far different from intron 1 (rs2234693) with PvuII enzyme. Allotype G (mutant) was mostly found in case group, 44 subjects (55.0%) while in control group was 42 subjects (52.5%). Allotype A was, mostly found in control group which was 38 subjects (47.5%) while in case group was 36 subjects (45.0%). Statistical analysis of Chi-Square

test suggested that no significant polymorphism intron 1 (rs9340799) with XbaI enzyme estrogen α receptor gene on the incidence of epithelial ovarian carcinoma (p=0.751). Distribution of polymorphism intron 1 (rs2234693) with XbaI enzyme estrogen α receptor gene on the incidence of epithelial ovarian carcinoma can be completely seen in Table 12.

Table 12. Distribution of polymorphism allotype intron 1 (rs2234693) with XbaI enzyme estrogen α receptor gene on the incidence of epithelial ovarian carcinoma

Polymorphism allotype intron 1 (rs9340799) with XbaI enzyme	group			
	Case	%	Control	%
G (Mutant)	44	55.0	42	52.5
A (Wild Type)	36	45.0	38	47.5
Total	80	100.0	80	100.0

OR = 0.904; 95% CI (0.48-1.68); p = 0.751.

DISCUSSION

This research included 80 subjects consisting of 40 subjects diagnosed with epithelial ovarian carcinoma (case) and 40 subjects of normal women (control). The case group was, mostly in the age group ≥ 43 years having percentage of 67.5% whereas the control group on a range of ages < 43 years, having percentage of (52.5%). The incidence of ovarian carcinoma increases with the increasing age, the type of epithelial ovarian carcinomas are rarely acquired at a young age. Incidence of carcinoma of the ovary is 15 to 16 per 100,000 at age 40-44 years, and has the highest 57 per 100,000 at age 70-74 years. Age range of respondents of this study is not so different from the results of research conducted Lurie G et al⁶, which reported that 53% of the subjects obtained with ovarian carcinoma following the 45-64 age range of polymorphism genotype examination in ESR2 and the risk of ovarium carcinoma.⁷ While the research Bardin A et al⁷, reported 63.8% of ovarian cancer patients with age over 50 years.⁶

Largest proportion of parity on the case group was at nullipara (37.5%) and in the control group was at parity grandemultipara (37.5%). History of hormonal contraceptive use in the case group had the percentage of 40.0% with duration of use mostly in the range of < 1 year with percentage of 15.0%. The case group who had experienced menopause there was 62.5%, and the control group not yet menopausal there was 60.0%. The majority of subjects from both case and control group did not have family history of ovarian carcinoma (97.5 to 90.0%).

Jordan et al⁸ reported that women with high parity has the risk of ovarian cancer lower than the nulliparous, ie the relative risk of 0.7. in women who experienced four or more pregnancies at term, the risk of ovarian cancer reduced by 40% when compared with nulliparous women. Similarly, the study by Colombo N, suggested that low parity is a risk factor for ovarian cancer.¹⁸ This is consistent with our results, where the parity nullipara was more common in the case.⁹

Polymorphism in intron or exon may also play a role in the development of malignant disease. The loss of accuracy in the encoding/coding, splicing process variation (splicing), and even control of the replacement of specific alternative cuts can occur during tumor progression. Physiology of the variant products can cut entirely different when compared with wild-type partner. Functional domains can be added or removed from the sequence encoding the protein, based on positive or negative phenotype is more prevalent. SNPs may also affect mRNA folds (folding of mRNA), which will affect the splicing of mRNA, translational regulation and procession.¹⁰

Based on examination of Intron 1 genotype polymorphism (rs2234693) with the enzyme PvuII Estrogen Receptor α Gene, genotype TC had many groups of cases: 62.5% compared to the control group (32.5%). For genotype CC, 25.0% of the cases and 27.5% on the control group. Similarly, the distribution of allotype C (mutant) there are more in case group (56.3%) than the control group (43.7%). For allotype T, the largest was found in the control group 56.3% while in the case group 43.7%. Based on statistical analysis Chi Square test it was found a significant effect of genotype polymorphism Intron 1 (rs2234693) with the enzyme PvuII estrogen receptor α gene on the incidence of epithelial ovarian carcinomas (p = 0.005) with the odds ratio (OR) of 4.667, 95% CI (1.50 to 14.45). OR value of 4.667 indicated that the TC and CC genotypes (mutant) is a risk factor for epithelial ovarian carcinoma. Women who have mutations in the genotype will have 4.6 times greater risk for epithelial ovarian carcinoma to occur than women without the mutation.

Nott et al reported that estrogen receptor α is an estrogen receptor found on the ovarian surface epithelial cells and is located on chromosome 6q24-Q27. ER α is also found in the endometrium, breast cancer cells, liver, adipose, and skeletal muscle hipotalamus.¹¹

On examination of Intron polymorphism genotype 1 (rs9340799) with Estrogen Receptor Gene XbaI enzyme α , there was 70% in case group and 30% in control group which had genotype AG. For the GG genotype, 20.0% in cases and 37.5% in the control group. Distribution allotype Intron polymorphism 1 (rs9340799) with XbaI enzyme was not much different from Intron 1 (rs2234693) with the enzyme PvuII. Allotype G (mutant) was widely more available in the case group (55.0%) than the control group (52.5%). Allotype A was, mostly contained in the control group 47.5% while 45.0% of the cases. Based on statistical analysis of test Fishers found a significant effect of genotype polymorphism Intron 1 (rs9340799) with the enzyme XbaI estrogen receptor α gene on the incidence of epithelial ovarian carcinomas (p = 0.027) with the odds ratio of 4.333, 95% CI (1.27 to 14.77).

OR value of 4.33 indicates that the AG and GG genotypes (mutant) is a risk factor for epithelial ovarian carcinoma. Women who have mutations in the genotype will have a 4.3 times greater risk for epithelial ovarian carcinoma to occur than women without the mutation.

Changes in many gene mutations that occur in the case is relevant with the results of research conducted by Lurie G et al⁶ which reported that if there are ab-

normalities in one or more mutations of these genes, the protein produced can be increased for example, mutated proto-oncogenes into oncogenes. There are also other genes that play a role in maintaining normal fixed cells if the gene mismatch. These genes function to restore the defective gene so the gene is normalized. If the damaged cells had not undergone a process of apoptosis and escape the control mechanisms within the cell cycle, the cells are produced in accordance with the parent and if there is another process that works over and over again in these cells, the cells will grow uncontrollably and end as a malignant cell.⁷

These results indicated that there is influence of intron 1 polymorphism (rs2234693) with enzymes PvuII and (rs9340799) with the enzyme XbaI estrogen receptor α gene on the incidence of epithelial ovarian carcinoma. This is supported by previous studies. Weiderpass et al reported that the receptor α gene polymorphism in epithelial ovarian can induce through the induction of cell proliferation and antipoptosis so that it can affect a person's susceptibility to the occurrence of carcinoma ovarium.¹² Bardin et al also explained that the increase in the ratio of mRNA ESR1/ESR2 observed in ovarian carcinoma showed a decrease in the selective expression of mRNA levels of ESR1 ESR2 without significant variation. The research also proved that there were no significant differences in ESR1 mRNA levels in normal ovary, benign tumors and carcinomas ovarium.⁷ Study by Doherty reported that the T allele of rs2295190, or another allele in disequilibrium was associated with an increased risk of invasive ovarian cancer.¹³

CONCLUSION

The researcher can conclude that the TC + CC genotype and allele C (mutant) were caner more owned by a group of epithelial ovarian carcinomas than the control group with the enzyme PvuII. AG + GG genotype and G allele (mutant) were more owned by a group of epithelial ovarian carcinomas than the control group with the enzyme XbaI.

There was the influence of TC and CC genotype polymorphism of intron 1 (rs2234693) with enzymes PvuII and there was the influence of genotype AG and GG polymorphism of intron 1 (rs9340799) with the enzyme XbaI estrogen receptor α gene on the incidence of epithelial ovarian carcinoma.

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