Measurement of Vitamin A Level in Patients with Malignant and Benign Ovarian Tumors

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Pendahuluan: Tumor ovarium ganas adalah salah satu tumor ganas ginekologi yang mempunyai angka kematian tertinggi. Beberapa penelitian telah dilakukan untuk mengetahui etiologi atau faktor risiko tumor ovarium ganas. Beberapa penelitian dilakukan seperti faktor genetik, kontaminasi kimiawi, penggunaan kontrasepsi. Penelitian faktor predisposisi sangat penting dalam upaya untuk mencegah terjadinya tumor ganas ovarium. Vitamin A adalah vitamin yang bekerja mengatur proliferasi sel dan diferensiasi sel. Defisiensi vitamin A diduga menyebabkan gangguan metabolisme p53 sehingga proliferasi tidak dapat dikendalikan atau dikontrol.

Tujuan: Membandingkan kadar vitamin A pada pasien tumor ganas ovarium dengan tumor ovarium jinak.

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Bahan dan cara kerja: Penelitian potong lintang pada kasus tumor ganas ovarium dan tumor ovarium jinak yang memenuhi kriteria penerimaan. Contoh darah diambil dari kedua kelompok dan dilakukan pemeriksaan kadar vitamin A. Kadar vitamin A diperiksa dengan HPLC (*high performanced liquid chromatography*). Dengan proporsi pengaruh tumor ovarium jinak 0,1 dan risiko relatif 3, dibutuhkan sampel 39 kasus setiap grup. Dilakukan analisis statistik secara Anova untuk menilai adakah perbedaan kadar vitamin A pada kedua kelompok.

Hasil: Sejumlah 71 kasus yang masuk dalam penelitian untuk dianalisis. Faktor paritas tampak adanya peningkatan risiko sebesar 2,1 kali pada paritas yang meningkat setelah paritas tiga. Faktor keluarga yang menderita tumor ganas ovarium terdapat hanya pada kelompok tumor ovarium ganas. Kadar vitamin A pada tumor ganas ovarium sebesar 28,2 μg/100 ml dengan standar deviasi 7,3 μg/100 ml, sedangkan kadar vitamin A rata-rata pada kelompok tumor ovarium jinak 33,5 μg dengan standar deviasi 8 μg/100 ml. Perbedaan ini secara statistik bermakna.

Kesimpulan Terdapat perbedaan bermakna, kadar vitamin A rata-rata dari penderita tumor ovarium ganas pada penelitian ini, yaitu 28,3 μg/100 ml dibandingkan dengan 33,5 μg/100 ml kadar rata-rata tumor ovarium jinak.

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Kata kunci: tumor ovarium, vitamin A.

Background: *Ovarian malignant tumor is one of the gynecological malignant tumors with highest rate of mortality. Several predisposition factors studied included genetic factors, chemical contamination factors, and contraception. Study of the predisposition factors is considered to be great importance for the efforts to prevent the incidence of ovarian malignant tumor. Vitamin A is one of the vitamins where function is to regulate cell regulate cell proliferation and cell differentiation. Vitamin A deficiency will interfere with p53 metabolism, and with it cell proliferation cannot be suppressed or controlled.*

Objective: *To compare vitamin A levels in the patients with malignant ovarian tumor and the patients with benign ovarian tumor.*

Setting: *Department of Obstetrics and Gynecology, Faculty of Medicine University of Indonesia/Dr Cipto Mangunkusumo Hospital, Jakarta.*

Material and methods: *Cross-sectional, observational study on the cases of malignant ovarian tumor and benign ovarian tumor meeting the inclusion criteria. Blood samples were taken from both groups for the examination of vitamin A level. The examination of vitamin A level was performed with HPLC (high performance liquid chromatography) method. With the proportion of effect on benign ovarian tumor of 0.1 and the relative risk of 3, as many as 39 cases from each group were needed for the calculation. Based on the examination results, Anova statistical test was performed to observe the difference in vitamin A levels in both groups.*

Results: *Seventy-one cases were analyzed in this study. Parity factor showed an increased risk of 2.1 times in the parity increase after parity three. No significant difference was found in age, use of oral contraceptives and use of talc. Factor of family who suffered malignant tumor was noted only in the group of malignant ovarian tumor. Mean vitamin A level in the group of malignant ovarian tumor was 28.2 μg/100 ml with deviation standard of 7.3 μg/100 ml, while mean vitamin A level in the group of benign ovarian tumor was 33.5 μg/100 ml with standard deviation of 8 μg/100 ml. The difference was not statistically significant.*

Conclusion: *A significant difference was found in the mean of serum vitamin A level of malignant ovarian tumor in this study, i.e. 28.3 μg/100 ml in comparison with 33.5 μg/100 ml in the mean of vitamin A level of benign ovarian tumor.*

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Keywords: *ovarian tumor, vitamin A.*

INTRODUCTION

Ovarian malignant tumor is one of the gynecological malignant tumors with highest rate of mortality. This condition is associated with either the advanced stage of disease or the limitations in its management. At Dr Cipto Mangunkusumo Hospital, 40% of mortalities due to gynecological cancers are associated with ovarian malignant tumor. A number studies were performed to identify the etiological factors or risk factors responsible for the incidence of this ovarian malignant tumor. Several predispo-

sition factors studied included genetic factors, chemical contamination factors, and contraception. Study of the predisposition factors is considered to be of great importance for the efforts to prevent the incidence of ovarian malignant tumor.

In the genetic studies, it was demonstrated that there is a relationship between breast malignant tumor and ovarian malignant tumor; in the family group with genealogical line of both types of tumor, it proves that the risk of ovarian malignant tumor is high. BRCA 1 and BRCA 2 are the two genes that have been studied and displayed a close correlation with ovarian malignant tumor. BRCA is a tumor-suppressor gene, and the mutation occurring in the both genes results in uncontrollable growth. The study on BRCA 1 demonstrates that BRC 1 mutation presents the risks for ovarian malignant tumor of 23 % in the women aged 30 years, this risk increases to 63% in women aged 70 years.

In view of the data studied, it is certain that there are other factors responsible for the occurrence of ovarian malignant tumor. Vitamin A is one of the vitamins whose function is to regulate cell proliferation and cell differentiation. This vitamin works at p 53 metabolism which is a tumor-suppressor gene. Vitamin A deficiency will interfere with p 53 metabolism, and with it cell proliferation cannot be suppressed or controlled.

The study on vitamin A level in hydatidose mole, which is a pregnancy anomaly with proliferation of trophoblastic cells, finds that vitamin A level is lower in pregnant women than in normal women. In the light of these findings, it is of interest to study the role of vitamin in ovarian malignant tumor. At the preliminary stage, the status of vitamin A was studied in the patients with ovarian malignant tumor. The results of this current study are expected to prove whether vitamin A is one of the risk factors for the occurrence of ovarian malignant tumor. This finding is expected to give valuable contribution to the efforts for preventing the incidence of ovarian malignant tumor.

MATERIALS AND METHODS

This study was a cross-sectional study in which the case group was the patients with ovarian malignant tumor and the control group was ovarian benign tumor. This study was conducted at Dr Cipto Mangunkusumo Hospital, Jakarta. Blood samples were taken from both groups for the examination of vitamin A level.

The number of required samples was based on the calculation of the number of samples, and as many as 39 cases were required for each of the groups. Inclusion criteria of the studied cases included: ovarian tumor patient with the normal liver function tests, did not receive vitamin A therapy.

Vitamin A level was examined using HPLC (*high performance liquid chromatography*) at the laboratory of Nutrition Research and Development Center, Bogor Department of Health. The blood samples were stored in the glass tubes covered with aluminum foil, kept at -4 to -15° C.

RESULTS

Of the 78 samples found only 71 samples that could be processed in this study, 36 samples from ovarian malignant tumors and 35 samples from ovarian benign tumors. To achieve equivalency between both groups, analysis on several confounding factors was performed.

Characteristics of samples

Table 1. Distribution of characteristics in the case and control groups

Characteristics	Group		P value
	Case (n=36)	Control (n=35)	
Age (mean year)	36.7	3.6	0.5080
Parity (mean)	2.4	1.8	0.0295

The age that was calculated statistically against mean values of both groups did not show different distribution values. The characteristic of age in the group of ovarian malignant tumor demonstrated the highest incidence rate in the group age between 31 and 40 years, i.e. 42 %, while in the age group > 50 years, the incidence rate was only 17%, in the age group < 20 years 17 %, while in the age group between 41 and 50 years the incidence rate was only 10%. The distribution in the cases studied did not fully correlate with epidemiological data on the risk factors since the epidemiological data found that the incidence of ovarian malignant tumor was higher in the age group > 50 years.

The distribution of parity is of some interest since the incidence of ovarian malignant tumor in this study was found to be highest in the nullipara group, i.e. 22%, which decreased in the case group with parity one and two, i.e. 14% respectively, and increased in the parity three and four, i.e. 25% respectively.

Risk factors

Table 2. Factors of oral contraception, use of talc

	Group		P value
	Case (n=36)	Control (n=35)	
Contraception *Oral contraception*	2 (5.5)	2 (5.7)	0.94
Use of talc *Talc user*	5 (13.8%)	11 (31.4%)	0.079

In this study, the factor of oral contraception in both groups distributes evenly. The factor of contraceptive use was important in the sense that the use of oral contraception constituted one of the factors for preventing the occurrence of malignant ovarian tumor malignant tumor group had a close family history of malignant breast. The use of talc was suspected to be one of the risk factors for the incidence of ovarian malignant tumor; however, the data of the study did not show the presence of such risks. The risk factor that was also noted in this study was the history of malignant breast cancer in the family. Our data of the study showed four cases of the ovarian cancers. However, no history was found in the group of ovarian benign tumor.

Multivariant analysis

Table 3. Significance and beta exponential values in several variables

Variable	Significance	Beta exponential
Age	0.9729	1.0013
Parity	0.0501	2.1057
Oral contraception	0.7377	0.7735
Use of talc	0.3070	0.5350
History of breast malignant cancer	0.8787	69.528

The most important factor in the multivariant analysis is family history of breast malignant cancer. This finding is consistent with several studies associated with genetic factors.

Vitamin A level in serum

Table 4. Vitamin A level

	Group	
	Case	Control
Mean values	28.3	33.5
DS	7.3	6.8
P values		0.00027

Table 4 shows that vitamin A level in the group of ovarian malignant tumor is higher than that in the group of ovarian benign tumor.

DISCUSSION

In the epidemiological study, the incidence of ovarian malignant tumor was found to be highest in the age group of > 50 years. This high incidence of ovarian malignant was associated with degenerative factors such that mutations frequently occurred in the degenerative age. In our study, the samples collected were mostly the cases or 42% of the cases were distributed in the sample group of 31 to 40 years of age. These samples certainly do not represent the epidemiological distribution. The distribution of cases aged above 50 years was only 17%. Similarly, the distribution of cases aged less than 20 years was only 17%. In the epidemiological study conducted at Dr Cipto Mangunkusumo Hospital from 1989 to 1995, it was found that the incidence of ovarian malignant tumor increased in the age group of 20 years all the way to the age group of 40 - 49 years, which again decreased in the age group above 50 years. Since the cases are not confined to the histopathological types, the distribution showed that of 36 cases of ovarian malignant tumor, 14 cases were of germinal malignant tumor types. However, of the overall germinal malignant ovarian tumors, there were only 2 cases aged less than 20 years. This finding is different from the most epidemiological studies reported since malignant tumors of germinal type were generally developed by young patients. One of the malignant tumors of germinal type is chemosensitive such that the administration of conservative cytostatic adjuvant therapy postoperatively provides favorable response of treatment with high survival rate of 5 years.

The distribution of parity in the cases studied is of particular interest since 22% of the cases were nulliparous women, with the highest distribution of cases in the parity of more than three. High parity is consistent with the age factor in that the higher the parity, the higher the age of the patient. However, from the etiological viewpoint it is evident that the parity factor stands in contrast to the theory of ovulation trauma as the causal factor of ovarian malignant tumor. The more frequent the ovary experiences ovulation, the higher the risk for the occurrence of ovarian malignant tumor. Pregnancy is an event that reduces the trauma of ovulation to the extent that it will lower the risks for the occur-

rence of ovarian malignant tumor. The results of multivariant statistical analysis showed that the risks for developing ovarian malignant tumor and the parity may increase 2.1 times. This theory is consistent with the condition of nullipara in 22% of the cases studied.

There were two risk factors accounting for ovarian malignant tumor that were analyzed in this study, i.e. the factor of contraceptive use, and the factor of talc use and family history of breast malignant tumor. The factor of family who developed malignant tumor, particularly breast malignant tumor or ovarian malignant tumor received much attention from the experts. In the cases we studied, it was found that four cases out of 36 cases of ovarian malignant tumor have a history of family factor. By contrast, in the group of ovarian benign tumor no cases were found with family history. The correlation between the incidence of ovarian malignant tumor and breast malignant tumor has been studied genetically, and BRCA 1 or 2 constituted gene suppressor which were found in the studies to correlate with the incidence of the two malignant tumors. The risk for developing ovarian malignant tumor, when the mutation occurred at the age of 30 years, is 23%. This risk increases to 63% at the age of 70 years. Another mutation studied is the mutation at 11p, the mutation of this gene is found only in ovarian malignant tumor, and not in ovarian benign tumor. When comparing with genetic theories, the hypothesis of family factor constitutes the risk factor of malignant ovarian tumor because of the risk of mutation in 17p, 17q, and 11p.

The other two factors, i.e. the factor of oral contraceptive use and talc use did show any difference. The use of oral contraception was found to reduce the frequency of ovulation, and thus the use of oral contraception reduce the incidence of ovarian malignant tumor. By contrast, the use of talc will increase the risk of ovarian malignant tumor.

Based on the multivariant analysis, only the family factor that represents the solid evidence as the risk factor of ovarian malignant tumor.

The examination of vitamin A level only showed the status of this vitamin in the body circulation. This level has not been specific in indicating the intracellular status of vitamin A; however, vitamin A level in the serum was easier to identify than the intracellular vitamin A level. This is beneficial for facilitating the examination and treatment when necessary. It has been known that the family factor is solid risk factor; however, the occurrence of malignant ovarian tumor has not been fully understood to the extent that the hypothesis of multi-factors responsible for the occurrence of ovarian malignant tumor provides further opportunity for studying other risk factors. Vitamin A is an important nutrient in the human body, and this vitamin plays the role in controlling cell proliferation or cell growth and cell differentiation through p53 which is a tumor suppressor gene.

Epidemiological studies demonstrate a correlation between the low vitamin A level and the incidence of breast malignant tumor, lung and skin malignant tumor. The studies on vitamin A level and the incidence hydatidose mole also reveal a correlation between the two factors. In this study, vitamin A level in the serums of ovarian malignant tumor group was found to significantly lower than that in the group of ovarian benign tumor. The results of this study showed that the low vitamin A level in the serum represents one of risk factors for the occurrence of ovarian malignant tumor.

CONCLUSIONS

1. Mean vitamin A level in the serum of ovarian malignant tumor group (28.3 μg/100 ml) was lower than that in ovarian benign tumor group (33.5 μg/ 100 ml).
2. The family factor constituted a risk factor for the occurrence of ovarian malignant tumor.

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