Factor 5 Leiden Gene Mutation in Endometrium Cancer

Rengin KARATAYLI[1], Suna ÖZDEMİR[1], Çetin ÇELİK[1], Osman BALCI[1], Süleyman NERGİS[2], Hasan ACAR[2]

Konya, Turkey

OBJECTIVE: In this study, our aim was to investigate the frequency of mutations on factor 5 Leiden gene (G1691A, A4070G, A5279G loci) in endometrial cancer patients.

STUDY DESING: 216 patients who admitted to Selcuk University Meram Faculty of Medicine Obstetrics and Gynecology Department with similar complaints (such as postmenopausal bleeding and dysfunctional uterine bleeding) were included in the study. Patients were divided into 2 groups. In the 1st group, there were 105 endometrioid type endometrial adenocarcinoma patients and in the second group, there were 111 patients whose endometrial pathology reported as benign. Two groups are compared according to frequency of mutations on factor 5 Leiden gene (especially G1691A, A4070G, A5279G loci).

RESULTS: There were not any statistically significant differences between groups according to frequency of mutations on factor 5 Leiden gene (p=0.743).

CONCLUSION: There is no correlation between mutations of factor 5 Leiden gene with endometrial cancer

Key Words: Endometrial cancer, Thrombophilia, Factor 5 leiden

Gynecol Obstet Reprod Med;2010;16:173-7

Introduction

Currently, researches are focused on the way that thrombosis itself is a primary pathological mechanism that promotes cancer development and progression, rather than being a complication of cancer. Especially, estimating thrombophilia itself as a risk factor for cancer development, genes related with thrombophilia and mutations on these genes are carefully investigated in many cancer types.

Nowadays, there are several proven important genetic mutations related with thrombosis and thrombophilia. The most important and mostly investigated ones among all are, mutations on factor 5 Leiden gene (especially G1691A, A4070G, A5279G loci), prothrombin gene (G20210A locus), and MTHFR gene (C677T locus). In many studies, these mutations were investigated in several cancer types, several results were reported.

Selcuk University Meram Medicine Faculty, [1]Departments of Obstetrics & Gynecology and [2]Genetics, Konya

Address of Correspondence: *Rengin Karataylı*
Selcuk University Meram Medical School Department of Obstetrics and Gynecology Akyokuş, Konya
renginkarataylı@hotmail.com

Submitted for Publication: *24. 05. 2010*
Accepted for Publication: *23. 06. 2010*

In this study, our aim was to investigate the frequency of mutations on factor 5 Leiden gene (especially G1691A, A4070G, A5279G loci) in endometrial cancer patients.

Material and Method

216 patients who admitted to Selcuk University Meram Faculty of Medicine Obstetrics and Gynecology Department between August 2006 and August 2008 with similar complaints (such as postmenopausal bleeding and dysfunctional uterine bleeding) and those with the histopathological result of endometrial adenocancer and benign endometrial pathologies such as proliferative endometrial tissue, secretuary endometrial tissue, endometritis etc were included into the study. Patients were divided into 2 groups. In the 1st group, there were 105 endometrioid type endometrial adenocarcinoma patients and in the second group, there were 111 patients whose endometrial pathology reported as benign. Detailed history, including age, obstetrical history, menopausal status, duration of menopause, and any risk factors for endometrial cancer was taken from each patient included into the study. Patients were all examined for previous estrogen or hormone replacement therapy, oral contraceptive usage, familial cancer history, obesity, any systemic disease such as diabetes and hypertension, and smoking. Body mass indices [BMI: kilogram (kg)/ (Height) 2 (m)] were calculated for each patient to evaluate obesity. In both patient groups, pelvic examination results and

endometrial thicknesses measured by transvaginal ultrasonography prior to endometrial sampling were all recorded. According to the complaints of patients at admission, indications for endometrial sampling were categorised. Besides, patients with endometrium cancer were evaluated for surgical stage and prognostic factors (grade, nuclear grade, tumor size, lymphovascular space invasion). In the first group, patients with coexisting secondary cancer, previous history of thrombosis, presence of thrombotic complications in perioperative period and patients involuntary were excluded from study, on the other hand in the second control group, patients those have endometrial hyperplasia in endometrial sampling, and those with coexisting secondary cancers and history of thrombosis previously were excluded from the study.

Two groups are compared according to frequencies of mutations on factor 5 Leiden gene (especially G1691A, A4070G, A5279G loci). NLM (Italian) stripe kits were used in order to detect mutations in three different loci (Faktör-V R506Q, Faktör-V H1299R, Faktör-V Y1702C), and NLM kit protocol was carried out. In our study, in statistical analysis, chi-square test was performed for categoric variable. When necessary, student t-test was used for numerical variables with normal distribution, and Mann-Whitney U test was used for numerical variables with abnormal distribution.

Differences between groups with p values of <0.05 were accepted as significant.

Results

The mean age of endometrium cancer patients in the first group was 59.65±9.2 (33-82) and mean age in the second group was 58.84±9.1 (41-83). There was no any statistically significant difference between two groups regarding age (p=0.270). In the first group and second group respectively, mean gravidity was 4.2±2.5 (0-14) ve 4.7±2.4 (0-15), mean parity was 3.3±2.0 (0-11) ve 3.8±2.0 (0-13), mean alive children number was 2.9±1.7 (0-8) ve 3.3±1.5 (0-8), mean abort rate was 0.83±0.9 (0-4) ve 0.76±0.9 (0-5), according to these all parameters, there were no any statistically significant difference between two groups (p=0.202, p=0.141, p=0.132, p=0.812).

In the first group 81 patients (77.1%) were at postmenopausal status, while 24 patients (22.9%) were in premenopausal period. In the second group, 60 patients (54.0%) were in postmenopausal period, while 51 patients (46.0%) were in premenopausal period. The mean duration of menopause in endometrium cancer patients were 9.78±9.2 (0-38) years. In the second group mean duration of menopause was 7.23±9.3 (0-36) years. There were statistically significant differences between two groups regarding menopausal status and mean duration of menopause (p=0.001, p=0.004).

In the first endometrium cancer patient group, 37 patient (35.2%) had diabetes, 65 patients (61.9%) had hypertension, 31 patients (29.5%) had hypercholesterolemia, on the other hand, in the second group, 41 patients (36.9%) had diabetes, 64 patients (57.6%) had hypertension, 29 patients (26.1%) had hypercholesterolemia. When patient groups were compared according to coexisting systemic diseases, there were not any statistically significant differences between groups for diabetes, hypertension, hypercholesterolemia (p=0.887, p=0.580, p=0.649).

When cancer history in the family was considered, in the first group, 9 patients (8.5%) had a history of breast cancer, 3 patients (2.8%) had history of endometrium cancer, 2 patients (1.9%) had breast and endometrium cancer coexistence, 3 patients (2.8%) had cancer of gastrointestinal tract, on the other hand in the second group 13 patients (11.7%) had history of breast cancer in the family, 4 patients (3.6%) had history of endometrium cancer, 1 patient (0.9%) had history of ovarian cancer, 1 patient (0.9%) had coexisting breast and endometrium cancer, 2 patients (1.8%) had family history of cancer of gastrointestinal tractus. There was no any statistically significant difference between two groups regarding family history of cancer (p=0.812).

In endometrium cancer patient group, 15 patients (14.2%) had smoking history, 7 patients (6.6%) had history of hormon replacement theraphy, 8 patients (7.6%) had history of oral contraceptive usage, in control group, 22 patients (19.8%) had smoking history, 7 patients (6.3%) had history of hormon replacement therapy, 11 patients (9.9%) had history of oral contraceptive usage. There were not any statistically significant differences between groups regarding these variables consecutively (0.789, p=0.619, p=0.635).

When patients were evaluated according to body mass indices, in the first group BMI score was <25 in 3 patients (2.8%), 25-30 in 20 patients (19.0%), 31-35 in 60 patients (57.1%), 36-40 in 21 patients (20%) and >40 in only one patient (0.9%), in the second group BMI score was <25 in 3 patients (2.7%), 25-30 in 33 patients (29.7%), 31-35 in 62 patients (55.8%), 36-40 in 13 patients (11.7%). According to body mass indices, there was no any statistically significant difference between patients (p=1.000).

In both groups, mutations related to factor 5 Leiden gene were evaluated in 3 different regions (G1691A, A4070G, A5279G). There was not any mutations related to factor 5 Leiden A5279G region among 216 patients included into the study.

There was heterozygous form of mutation in factor 5 Leiden (G1691A) region in 12 patients (11.4%) in first group, there was not any homozygous form of mutation in any patients, in other 93 patients (88.6%) there was not any muta-

tions related to this region. In the second group, there was heterozygous form of mutation in factor 5 Leiden (G1691A) region in 9 patients (8.2%), there was not any homozygous form of mutation in any patients, in other 102 patients (91.8%) there was not any mutations related to this region (Table 1). When both groups are compared according to mutations of factor 5 Leiden (G1691A) region, there was not any statistically significant difference (p=0.493).

There was heterozygous form of mutation in factor 5 Leiden (A4070G) region in 6 patients (5.7%) in first group, there was not any homozygous form of mutation in any patients, in other 99 patients (94.3%) there was not any mutations related to this region. In the second group, there was heterozygous form of mutation in factor 5 Leiden (A4070G) region in 11 patients (9.9%), there was not any homozygous form of mutation in any patients, in other 100 patients (90.1%) there was not any mutations related to this region (Tablo 2). When both groups are compared according to mutations of factor 5 Leiden (A4070G) region, there was not any statistically significant difference (p=0.493).

When all three mutations at different loci of Factor 5 Leiden gene are considered together as a single mutation, in 18 patients (17.1%) there was heterozygous form of mutation in factor 5 Leiden gene, in other 87 patients (82.9%) there were not any mutations. In the second group, there were mutations in 19 patients (17.1%) and there were not any in other 92 patients (82.9%) (Table 3). There was not any statistically significant difference between groups regarding factor 5 Leiden mutations (p=1.000).

Discussion

Current studies are focused on thrombosis as a primary pathogenetic mechanism that promotes cancer development and progression rather than being a cancer complication. Especially, thrombophilia is hypothesized as a risk factor for cancer development and thrombophilia related genes and associated mutations of these genes are investigated in several cancer types.[1,2-12, 13,14]

When literature is checked, it is obvious that studies about genetic mutations related with thrombophilia in gynecologic cancers are not enough, and there are limited studies about MTHFR gene mutation in endometrium cancer.[2,3,5]

Recently, a number of genetic mutations related with hereditary thrombophilia have been investigated. The most common and popular genes of these mutations are MTHFR (C677T), prothrombin gene, and factor V Leiden mutations [15,16,17]

Table 1: The distribution of mutations at Factor 5 Leiden (G1691A) region

Patient Groups	**Factor 5 Leiden (G1691A) mutations**						
	normal	**%**	**heterozygous**	**%**	**homozygous**	**%**	**Total**
1st.group (n:105)	93	88.6	12	11.4	0	0	105 (%100)
2nd.group (n:111)	102	91.8	9	8.2	0	0	111 (%100)
Total (n:216)	195	90.3	21	9.7	0	0	216 (%100)

Tablo 2: The distribution of mutations at Factor 5 Leiden (A4070G) region

Patient Groups	**Factor 5 Leiden (A4070G) mutations**						
	normal	**%**	**heterozygous**	**%**	**homozygous**	**%**	**Total**
1st group (n:105)	99	94.3	6	5.7	0	0	105 (%100)
2nd group (n:111)	100	90.1	11	9.9	0	0	111 (%100)
Total (n:216)	199	92.1	17	7.9	0	0	216 (%100)

Table 3: The distribution of total mutations at 3 regions in Factor 5 Leiden gene

Patient Groups	**Factor 5 Leiden mutation**						
	normal	**%**	**heterozygous**	**%**	**homozygous**	**%**	**Total**
1st group (n:105)	87	82.9	18	17.1	0	0	105 (%100)
2nd group (n:111)	92	82.9	19	17.1	0	0	111 (%100)
Total (n:216)	179	82.9	37	17.1	0	0	216 (%100)

Mozsik et al. researched the frequency of factor V Leiden mutation in patients with esophageal, gastric, liver, pancreatic and colorectal cancers. They found that the prevalence of factor V Leiden mutation was significantly higher in patients with gastrointestinal cancers.[8]

Miller et al in their study reported that there is increased incidence of neoplasias of gastrointestinal tract in patients with persistant activation of coagulation cascade.[1]

In order to support this study, in other two studies it is reported that tumor development depends on angiogenesis and is promoted by thrombin as shown in several experimental studies.[19,20]

In literature, there are no studies investigating the incidence of factor 5 Leiden gene mutation in gynecological cancers. In this study, in both groups factor 5 Leiden gene mutations are investigated in 3 different regions (G1691A, A4070G, A5279G). There were no mutations related to factor 5 Leiden A5279G among 216 patients included into the study.

When mutations at three different regions of factor 5 Leiden gene are evaluated as a single mutation heading, in the first group heterozygous form of mutation was detected by %17.1, in the second group same mutation was observed by %17.1. There was not any statistically significant difference between groups regarding incidences of factor 5 Leiden mutations (p=1.000). In this study, it is detected that FVL mutation is not increased in endometrium cancer. Since there is no similar study in literature, results could not be compared.

Conclusion

As a result we concluded that there is no increase in frequencies of these three genetic mutations of factor 5 Leiden gene in endometrial cancer cases.

Endometriyum Kanserinde Faktör 5 Leiden Gen Mutasyonu

AMAÇ: Endometriyum kanserli hastalarda faktör 5 Leiden gen (G1691A, A4070G, A5279G bölgeleri) mutasyon sıklığını araştırmak.

GEREÇ VE YÖNTEM: Selçuk Üniversitesi Meram Tıp Fakültesine benzer şikayetlerle (postmenopozal kanama ve disfonksiyonel uterin kanama) başvuran toplam 216 hasta çalışmaya dahil edildi. Hastalar iki gruba ayrıldı. Ilk grupta, endometrioid tipte adenokarsinomu olan 105 hasta, ikinci grupta endometriyal patoloji sonucu benign olan 111 kontrol hastası yer aldı. Her iki grup, factor 5 Ledien genine ait mutasyon sıklıkları (G1691A, A4070G, A5279G bölgeleri) açısından kıyaslandı.

BULGULAR: Her iki grup arasında factor 5 Leiden mutasyon sıklığı açısından istatistiki olarak anlamlı fark bulunmadı (p=0.743).

SONUÇ: Faktör 5 Leiden mutasyonu ile endometriyum kanseri arasında ilişki bulunamamıştır.

Anahtar Kelimeler: Endometriyum kanseri, Trombofili, Factor 5 leiden

References

1. Miller GJ, Bauer KA, Howarth DJ, Cooper JA, Humphries Se, Rosenberg RD. Increased incidence of neoplasia of the digestive tract in men with persistant activation of the coagulant pathway. J Thromb Haemost, 2004;2:210714.
2. Esteller M, Garcia A, Martinez-Palones JM, Xercavins J, Reventos J. Germ line polymorphisms in cytochrome-P450 1A1 (C4887 CYP1A1) and methylenetetrahidrofolate reductase (MTHFR) genes and endometrial cancer susceptibility. Carcinogenesis,1997;18:2307-11.
3. Paynter RA, Hankinson SE, Hunter DJ, De Vivo I. No association between MTHFR C->T or 1298 A->C polymorphisms and endometrial cancer risk. Cancer Epidemiol Biomarkers Prev,2004;13:1088-9.
4. Ma J, Stampfer MJ, Giovannucci E, Artigas C, Hunter DJ, Fuchs C, Willett WC, Selhub J, Hennekens CH, Rozen R. Methylenetetrahidrofolate reductase polymorphism, dietary interactions, and risk of colorectal cancer. Cancer Res,1997;57:1098-102.
5) Kim YI.Methylenetetrahidrofolate reductase polymorphisms, folate and cancer risk: a paradigm of gene-nutrient interactions in carcinogenesis. Nutr Rev, 2000;8:205-9.
6. Hekim N, Ergen A, Yaylım İ, Yılmaz H, Zeybek Ü, Öztürk O, İsbir T. No association between methylenetetrahidrofolate reductase C677T polymorphism and breast cancer. Cell Biochem Funct,2007;25:115-7.
7. Gershoni- Baruch R, Dagan E, İsraeli D, Kasinetz L, Kadouri E, Friedman E. Association of the C677T polymorphism in the MTHFR gene with breast and /or ovarian cancer risk in Jewish women. Eur Cancer,2000;36:2313-6.
8. Reljic A, Simundic A, Topic E, Nikolac N, Justinic D, Stefanovic M. The methylenetetrahidrofolate reductase (MTHFR) C677T polymorphism and cancer rısk: The Croatian case-control study. Clinical Biochemistry, 2007; 40:981-5.
9. Singal R, Ferdinand L, Das PM, Reis IM, Schlesselman JJ. Polymorphisms in the methylenetetrahidrofolate reductase gene and prostate cancer risk. Int J Oncol, 2004; 25:1465-71.
10. Zeybek U, Yaylım I, Yılmaz H, Agachan B, Ergen A, Arikan S, Bayrak S, Isbir T. The methylenetetrahidrofolate reductase (MTHFR) C677T polymorphism in patıents with gastric and colorectal cancer. Cell Biochem Funct, 2007;25:419-22.

11. Miao X, Xing D, Tan W, Qi j, Lu W, Lin D. Susceptibilility to gastric cardia adenocarcinoma and genetic polymorphisms in methylenetetrahidrofolate reductase in an at risk Chinese population. Cancer Epidemiol Biomark prev, 2002; 11:1454-8.

12. Shen H, Xu Y, Zheng Y, Qian Y, Yu R, Qin Y, Wang X, Spitz MR, Wei Q. Polymorphisms of 5,10 methylenetetrahidrofolate reductase and risk of gastric cancer in a Chinese population: a case control study. Int J Cancer, 2001;95:332-6.

13. Pihusch R, Danzl G, Scholz M, Harich D, Pihusch M, Lohse P, Hiller E. Impact of thrombophilic gene mutations on thrombosis risk in patients with gastrointestinal carcinoma. Cancer, 2002;94:3120-6.

14. Paspatis GA, Sfyridaki A, Papanikolaou N, Trian tafyllou K, Livadiotaki A, Kapsoritakis A, Lydataki N. Resistance to activated protein C, factor V Leiden and the prothrombin G20210 A variant in patients with colorectal cancer. Pathophysiol Haemost Thromb, 2002;32:2-7.

15. Mutter GL: Endometrial intraepitelial neoplasia: will it bring order to chaos? The Endometrial Colloborative Group. Gynecol Oncol,2000; 76:278-90.

16. Sosolw RA, Pirog E, Isacson C. Endometrial intraepitelial carcinoma with associated peritoneal carcinomatosis. Am J Sur Pathol,2000; 24 (5):726-32.

17. Amant F, Moerman P, Neven P, Timmerman D, Van Limbergen E, Vergote I. Endometrial cancer. Lancet, 2005; 366:491-505.

18. Berek JS, Adashi EY, Hillard PA. Novak Jinekoloji. Çeviri Editörü: Erk Ahmet, Nobel Tıp Kit Ltd Sti,1996;1058-9.

19. Tsopanoglou NE, Pipili-syenetos E, Maragoudakis ME, Thrombin promotes angiogenesis by a pathway independent of fibrin formation. J Appl Physiol, 1993;264:C1302-7.

20. Caunt M, Huang Y-Q, Brooks PC, karpatkin S. Thrombin induces neoangiogeneisi in the chick chorioallantoic membrane. J Thromb Haemost, 2003;1:2097-102.