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Original scientific paper

INHERITED THROMBOPHILIC RISK FACTORS IN SERBIAN BREAST CANCER PATIENTS

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Breast cancer is the leading cause of cancer-related death among women. An increased burden of thrombotic events among breast cancer patients, leading to higher mortality and morbidity rates, is well established. There are a number of genetic risk factors associated with thrombosis, but their contribution to thrombotic tendencies in patients with cancer is not completely elucidated. We aimed to investigate possible role of FV Leiden, FII G20210A, MTHFR C677T and PAI-1 4G/5G gene variants in etiopathology of breast cancer and accompanying thrombosis in cohort of Serbian patients. Our study included 316 subject divided in three groups: breast cancer patients with (97) or without (99) accompanying thrombosis and healthy control group (120). According to our results, the prevalence for all four prothrombotic gene variants were similar in cancer patients with and without thrombosis and no statistically significant difference was observed between these groups. We detected lower frequency of MTHFR 677TT genotype in breast cancer patients when compared to control group (P=0.014; OR=0.145 (95%CI 0.031-0.679)),

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indicated that MTHFR C677T homozygosity could play a protective role in breast cancer susceptibility. Our study noted the lack of association between common prothrombotic gene variants and increased prothrombotic risk in Serbian breast cancer patients. Also, our results point out possible role of MTHFR 677TT genotype in etiology of breast cancer, but further studies on larger cohort of patients are needed.

Keywords: breast cancer, venous thromboembolism, genetic risk factors, common prothrombotic mutations

INTRODUCTION

Breast cancer is the most common cancer diagnosed among women and the second leading cause of cancer death after lung cancer (DESANTIS *et al*., 2014). The most common breast cancer risk factors include age, personal and family history, lifestyle, use of oral contraceptives and hormone replacement therapy (MCPHERSON *et al*., 2000; SAUTER, 2018) Cancer is a recognized risk factor of venous thromboembolism (VTE) as it induces a prothrombotic state through various mechanisms due to present malignancy, administrated therapy and other disease-related complications (KHORANA *et al.*, 2007; EROĞLU and AKAR, 2011; SPEED *et al*., 2018) . Increased incidence of venous and arterial thromboembolism remains a major complication in patients with breast cancer and it contributes significantly to higher mortality and morbidity rates. The risk is even higher in metastatic disease and after first three months following cancer diagnosis (DENTALI *et al*., 2008; KYRIAZI, 2012; TINHOLT *et al*., 2016). Pathophysiology behind thromboembolism development in breast cancer is complex and not completely elucidated.

It is well known that certain genetic abnormalities of coagulation are associated with higher risk of thrombosis occurrence. FV Leiden and FII G20210A mutations are the most common inherited thrombophilic genetic risk factors. Overall, the risk of developing thrombotic episodes for a heterozygous carrier of FV Leiden mutation is five to ten-fold increased, while the estimated risk for the homozygous carrier is eighty to one hundred-fold higher than in the general population. The FII G20210A mutation increases the risk of VTE by 3- to 5-fold (SELIGSOHN and LUBETSKY, 2001; PRESTON *et al*., 2019).

Other genetic factors such as allelic variants in methylene tetrahydrofolate reductase (MTHFR C677T) and plasminogen activator inhibitor type 1 (PAI-1 5G/4G) have been studied for their potential role in pathogenesis of thrombosis, but the significance of this genetic variants as risk factors for the development of thromboembolic events is still unclear (FROSST *et al*., 1995; SEGUÍ *et al*., 2000; LIU *et al*., 2017; VUCKOVIC *et al*., 2018).

Our preliminary results indicate possible association between prothrombotic gene variants and thrombosis development in breast cancer patients in Serbian population (KOVAC *et al*., 2012). The aim of this study was to further explore the role of FV Leiden, FII G20210A, MTHFR C677T and PAI-1 4G/5G variants in etiopathology of breast cancer and prothrombotic states which occur in breast cancer patients.

MATERIALS AND METHODS

Subject population

This study comprised 316 subjects divided into 3 groups. Participants were recruited from single-center cohort study, conducted between June 2010 and December 2015. During this period, 97 women (median 61 years; interquartile range (IQR 10) with breast cancer who developed thrombosis (BCVTE group) and 99 women (median 58 years; IQR 11) with breast

cancer who did not develop thrombosis (BC group) were included in the study. The inclusion criterion for BCVTE group was at least one episode of an objectively documented thrombotic event, confirmed by findings at a compression ultrasound examination; lung perfusion-ventilation scan or/and multi-slice computer tomography. Excluding criteria for all patients was advanced cancer disease. Also, family members of the participants were excluded from the study.

Additionally, 120 healthy women (median 33.5 years; IQR 15), from same geographic area, with no history of thrombosis and breast cancer were involved in this study (CN group). An approval from local ethics committee was obtained, as well as written consent from subjects included in this study.

Laboratory methods

Peripheral blood was taken on 3.8% sodium citrate as anticoagulant (BD Vacutainer® 9NC 0,105M Buff. Na-Citrate, 4.5mL). Genomic DNA was purified from 200µLof whole blood using QIAamp DNA blood mini kit (QIAGEN, Germany) according to manufacturer's protocol.

All samples were tested for FV Leiden, FII G20210A, MTHFR C677T and PAI-1 4G/5G variants using previous described PCR-RFLP analysis (BERTINA *et al*. 1994; FROSST *et al*. 1995; POORT *et al.* 1996; BROWN *et al*. 2001). Normal and mutated alleles were distinguished by the size of the restriction fragments, which were separated using electrophoresis on 10% polyacrylamide gels and visualized by silver staining.

Statistical analysis

Analysis was performed by using Statistical Package for Social Sciences 20.0 for Windows (SPSS Inc., Chicago, Illinois, USA). Comparison of frequencies of FV Leiden, FII G20210A, MTHFR C677T and PAI-1 4G/5G gene variants between studied groups were performed by Pearson Chi-Square test and risk assessment was presented by the odds ratio (OR) and 95% confidence interval (95%CI). P value less than 0.05 was considered as statistically significant. In assessment of prognostic marker for thrombotic event or cancer diagnosis, binary logistic regression was used with risk assessment for all examined mutations.

RESULTS

The overall frequencies of genotypes for analyzed variants are given in Table 1. We detected 6 (6.1%) FV Leiden carriers in heterozygous state and 1 (1.0%) carrier in homozygous state in the BC group. In the group of BCVTE cancer patients, we detected 12 (12.4%) heterozygous carriers and 2 (2.1%) homozygous carriers of FV Leiden (Table 1). Comparison of the FV Leiden prevalence between BCVTE and BC groups did not show statistically significant increase (p=0.126) (Table 1).

As for the FII G20210A variant, we detected 3 heterozygous carriers (3.1%) in the BCVTE group, the same number detected in the BC group (3.0%). No homozygous carriers were detected in these two groups.

Regarding the MTHFR C677T and PAI-1 4G/5G variants, the distribution of genotypes was similar in all tested groups and no statistically significant difference was observed between these groups (Table 1).

In order to assess the significance of these four prothrombotic variants as prognostic markers for breast cancer development or thrombosis occurrence in cancer patients, we

performed comparison between patient's groups and healthy control group by binary logistic regression analysis with adjustment to the age (Table 2).

Table 1. Genotype distributions of tested variants and comparison of variant frequencies

Variants genotype	Study groups			P
	BCVTE N=97 (%)	BC N=99 (%)	CN N=120 (%)	BCVTE vs. BC
FV Leiden heterozygous	12 (12.4)	6 (6.1)	4 (3.3)	0.126
FV Leiden homozygous	2 (2.1)	1(1.0)	0	0.549
FII G20210A heterozygous	3 (3.1)	3 (3.0)	5 (4.2)	0.980
FII G20210A homozygous	0	0	0	0
MTHFR C677T heterozygous	43 (44.3)	50 (50.5)	56 (46.7)	0.387
MTHFR C677T homozygous	13 (13.4)	6 (6.1)	20 (16.7)	0.082
PAI1 4G/5G heterozygous	48 (49.5)	55 (55.6)	57 (47.5)	0.395
PAI1 4G/5G homozygous	34 (35.1)	27 (27.3)	43 (35.8)	0.240

BCVTE: Breast cancer patients with accompanying thrombosis
BC: Breast cancer patients without accompanying thrombosis
CN: Control group of healthy volunteers
P- P value Pearson Chi-Square

Table 2. Binary regression model of risk assessment for tested variants

Gene variant	CN vs BC				BC vs BCVTE				CN vs BCVTE			
	p	OR	95% CI for OR		p	OR	95% CI for OR		p	OR	95% CI for OR	
FV Leiden	0.286	2.603	0.449	15.101	0.102	2.303	0.847	6.265	0.091	5.302	0.766	36.704
FII G20210A	0.562	0.535	0.065	4.436	0.875	1.143	0.217	6.011	0.870	0.816	0.072	9.205
MTHFR C677T*	0.117	0.507	0.217	1.185	0.796	1.086	0.580	2.033	0.534	0.723	0.260	2.010
PAI1 4G/5G*	0.773	1.165	0.412	3.292	0.965	0.982	0.426	2.262	0.505	1.575	0.414	5.996
age	**0.000**	**1.196**	**1.144**	**1.251**	0.054	1.035	0.999	1.071	**0.000**	**1.235**	**1.163**	**1.311**
FV Leiden	0.324	2.538	0.399	16.149	0.091	2.366	0.871	6.426	0.088	5.956	0.764	46.408
FII G20210A	0.501	0.511	0.072	3.604	0.915	1097	0.201	5.985	0.817	0.758	0.073	7.885
MTHFR C677T**	**0.014**	**0.145**	**0.031**	**0.679**	0.501	1.489	0.466	4.758	0.062	0.249	0.058	1.070
PAI1 4G/5G**	0.164	0.531	0.217	1.296	0.359	1.366	0.701	2.660	0.821	1.122	0.414	3.043
age	**0.000**	**1.201**	**1.147**	**1.258**	0.064	1.033	0.998	1.070	**0.000**	**1.246**	**1.168**	**1.328**

BCVTE: breast cancer patients with accompanying thrombosis
BC: Breast cancer patients without accompanying thrombosis
CN: Control group of healthy volunteers
Risk factors: *heterozygous and homozygous carriers; ** homozygous carriers, OR: Odds ratio; CI- Confidence interval

Risk assessment for tested variant showed that MTHFR C677T homozygous carriers have lower risk for breast cancer development (p=0.014; OR=0.145 (95%CI 0.031-0.679)) in ratio to healthy control group. Other tested variants did not show statistical differences between groups in any case (Table 2).

DISCUSSION

The clinical impact of hereditary thrombophilia in cancer patients is not yet well defined, due to multifactorial nature of this disease and abundance of other contributing factors, like chemotherapy (KENNEDY *et al*., 2005; KHORANA *et al*., 2007). VTE is the most common complication in cancer patients and second leading cause of mortality, besides cancer (DENTALI *et al*., 2008). The evidences from various studies regarding the role of genetic risk factors in the etiology of thrombosis in cancer patients are very conflicting. There are significant geographic differences in mutations distribution, as well as differences in cancer type, administrated therapy and selection criteria for participation in the studies (FALVELLA *et al.*, 2016).

In order to clarify the significance of thrombophilia genetic markers in Serbian breast cancer patients, we investigated the prevalence of four most common prothrombotic genetic variants (FV Leiden, FII G20210A, MTHFR C677T and PAI-1 4G/5G) in breast cancer patients with or without accompanying thrombosis, as well as in healthy control group.

In our study, we detected increased frequency of FV Leiden variant in breast cancer patients with thrombosis (12.4%), but there was no statistically significant difference in comparison to FV Leiden frequency in breast cancer patients without thrombosis (6.1%). Additionally, the data regarding the importance of FV Leiden in the etiology of cancer-related thrombosis is contradictory. BLOM *et al*. (2005) found that cancer patients who were carriers of FV Leiden had 2.4-fold increased risk for VTE compared to patients with cancer and without mutation, while that risk increase 12-fold when compared to subjects without cancer or mutation. The similar results were obtained in the Tromso Study, where GRAN *et al*. (2016) found that active cancer is associated with nearly 9-fold increased risk for thrombosis, suggesting a synergistic effect of FV Leiden and cancer. FALVELLA *et al*. (2016) also reported increased frequency of FV Leiden in patients with metastatic colorectal cancer. On the other hand, MANDALA *et al*. (2010) found no association of FV Leiden and cancer-related thrombosis in prospective study which included patients with breast and gastrointestinal cancers (p=0.976). RAMACCIOTTI *et al*. (2003) also did not confirm association of FV Leiden and VTE in cancer patients, with only 1.5% of FV Leiden carriers in cancer patients with VTE and 2.7% of FV Leiden carriers in cancer patients without VTE. GARBER *et al.* (2010) showed that FV Leiden frequency is increased in breast cancer patients receiving tamoxifen (18.5%) compared to healthy control subjects (4.8%) (P<0.001). This study suggests that women with breast cancer should be tested for FV Leiden mutation before prescription of adjuvant tamoxifen. Our previous research also associated FV Leiden mutation with an increased risk of VTE in women with breast cancer during adjuvant tamoxifen in Serbian population (KOVAC *et al*., 2015).

In our study, frequency of heterozygous FII G20210A variant carriers was similar in breast cancer patients with or without thrombosis (3.1% and 3.0%, respectively). Our results suggest that FII G20210A mutation is not associated with thrombosis in Serbian breast cancer patients. This result is consistent with the study of Eroglu et al. who reported that no significant difference was seen in distribution of FII G20210A genotype frequency between two groups of breast cancer patients who have or have not history of thrombotic events (EROĞLU and AKAR,

2011). FALVELLA *et al*. (2016) reported that VTE was significantly more frequent among carriers of the FII G20210A heterozygous genotype (71.4%) than in those without it (27.3%; P=0.012), but they stated that the data regarding both FV Leiden and FII G20210A variants remains inconclusive regarding their role in the cancer-related VTE. However, results of the Multiple Environmental and Genetic Assessment study, a large population-based case–control study, indicated that cancer patients, carriers of FII G20210A, had a 2.5-fold increased risk for cancer-related thrombosis (BLOM *et al*., 2005).

Various epidemiologic studies have shown that folate deficiency may be connected to several types of cancers, including breast cancer (KIM, 1999). MTHFR C677T variant is associated with decreased MTHFR activity, leading to altered distribution of folate (FROSST *et al*., 1995). In addition, MTHFR C677T mutation was associated with increased genomic DNA methylation when folate supply was adequate, though, in the setting of folate inadequacy, this mutation was associated with decreased methylation. According to results of Sohn and coworkers MTHFR C677T mutation induces cell-specific changes in genomic DNA methylation: which can be a possible molecular basis for the site-specific cancer risk modification (SOHN *et al*., 2009). The number of studies implicated the potential role of this variant in the pathogenesis of cancer. In performed meta-analysis, which included 50 studies and over 45000 subjects, demonstrated that MTHFR C677T variant may be a risk factor for breast and ovarian cancer, especially in Asians (HE and SHEN, 2017). In other hand, Kotsopoulos and coworkers reported the lack of association between variants in six folate-related genes (including MTHFR C677T) and breast cancer risk in approximately 2000 Caucasian patients and controls (KOTSOPOULOS *et al.*, 2008). According to our results, in Serbian population, the MTHFR C677T variant presents protective factor for developing breast cancer (for TT genotype: P=0.014; OR =0.145 (95%CI 0.031-0.679)) (Table 2).

RAMACCIOTTI *et al*. (2003) showed no association of MTHFR C677T variant and VTE development in cancer patients, but FALVELLA *et al*. (2016) observed an increased risk of thrombosis in colorectal cancer patients bearing the homozygous MTHFR 677TT genotype. In our study, detected frequencies of MTHFR C677T were similar between cancer patients groups, suggesting no significant role of this variant in thrombosis development among women with breast cancer.

Regarding the PAI-1 gene and cancer patients, the literature is very scarce. PAI-1, the primary inhibitor of the plasminogen activation system, has an important role in signal transduction, cell adherence and migration. Studies of several types of cancers, including breast cancer, have shown that increased PAI-1 levels are associated with aggressive tumor behavior and poor prognosis (HARBECK *et al*., 2004). Possible mechanisms by which PAI-1 contributes to cancer dissemination include prevention of excessive degradation of the extracellular matrix, modulation of cell adhesion, and stimulation of angiogenesis and cell proliferation (HARBECK *et al*., 2004). A common variant in the PAI-1 gene promotor, 4G/5G insertion/deletion leads to increased PAI-1 expression (LOSKUTOFF *et al*., 1993), thus contributing to cancer dissemination. A meta-analysis by WANG *et al*. (2014) established PAI-1 4G allele as a thrombotic risk factor, especially when additional risk factors are present. However, the exact role of PAI-1 4G/5G polymorphism in etiology of cancer-related thrombosis remains unknown. In our study, the prevalence of PAI-1 4G/5G polymorphism was similar in all tested groups, suggesting that this polymorphism does not represent significant risk factor for thrombosis occurrence in Serbian breast cancer patients. On the other hand, FALVELLA *et al*. (2016) found that carriers of PAI-1 4G

allele have 3.5-fold increased risk for cancer-related VTE compared to PAI-1 4G allele non-carriers (p=0.033) in colorectal cancer patients. Additional research is required to further explore the role of PAI-1 in the pathogenesis of cancer-associated thrombosis.

In conclusion, our study reviled no association of common prothrombotic gene variants and cancer-related thrombosis in Serbian breast cancer patients. Also, obtained results suggest that MTHFR 677TT genotype reduce breast cancer risk, but further validation studies are required.

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NASLEDNI TROMBOFILNI FAKTORI RIZIKA KOD BOLESNIKA SA TUMOROM DOJKE IZ SRBIJE

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Izvod

Tumor dojke je vodeći uzrok smrtnosti žena obolelih od tumora. Razvoj trombotičkih događaja često komplikuje klinički tok bolesti i predstavlja jedan od vodećih uzroka morbiditeta i mortaliteta kod obolelih. Postoji veliki broj genetičkih faktora rizika povezanih sa trombozom, ali njihov doprinos trombotičkim događajima kod bolesnika sa tumorom nije potpuno razjašnjen. Cilj ove studije je ispitivanje moguće uloge FV Leiden, FII G20210A, MTHFR C677T i PAI-1 4G/5G genskih varijanti u etiopatologiji tumora dojke i pratećih tromboze u grupi ispitanika iz Srbije.

Studija je obuhvatila 316 ispitanika, koji su podeljeni u tri grupe: bolesnice sa tumorom dojke sa (97) ili bez (99) tromboza i kontrolna grupa koju su činile zdrave ispitanice (120). Prema našim rezultatima učestalost sve četiri protrombotičke varijante je slična kod obolelih sa ili bez tromboze. U poređenju sa kontrolnom grupom (P = 0,014; OR = 0,145 (95% CI 0,031-0,679)) utvrđena je manja učestalost MTHFR 677TT genotipa kod obolelih sa tumorom dojke, što ukazuje da MTHFR C677T može potencijalno imati zaštitnu ulogu u razvoju tumora dojke.

Naša studija je nije utvrdila povezanost između protrombotičnih genskih varijanti i povećanog trombotičkog rizika kod obelelih od tumora dojke u srpskoj populaciji. Takođe, naši rezultati ukazuju na moguću ulogu genotipa MTHFR 677TT u etiologiji tumora dojke, ali su potrebna dalja istraživanja kod većih grupa ispitanika.

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