Original Article
Thrombophilic polymorphisms are not associated with disease-free survival in breast cancer patients

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Abstract: Background: Thrombosis is one of the most common complications in cancer patients, however the effect of thrombophilic polymorphisms on cancer specific survival is still unclear. Objectives: The aims of the study were to analyze the effect of factor V Leiden (FVL), prothrombin (PT) G20210A, and methylenetetrahydrofolate reductase (MTHFR) C677T polymorphisms on disease-free survival (DFS) in breast cancer and to evaluate the proportional odds model. Methods: Relationship between thrombophilic polymorphisms and DFS was evaluated in 197 breast cancer patients. Data regarding patient's age, menopausal status, tumor size (T), lymph node status (N), cancer stage, tumor grade (G), estrogen and progesterone receptors, c-erbB2 expression, MTHFRC677T, FVL, and PTG20210A polymorphisms in DFS were examined by log-rank test and multivariate analyses. The proportional odds model was tested as an alternative to Cox model because of its insufficient proportional hazards assumption. Results: According to log-rank test, T, N, G, tumor stage, and c-erbB2 were associated with DFS. T, N, G, and c-erbB2 were significantly related to DFS by log-normal regression model. PTG20210A, MTHFRC677T and FVL polymorphisms were not related to DFS in breast cancer (P>0.05). Conclusion: Our study suggests that thrombophilic polymorphisms are not associated with DFS when the proportional odds model is applied.

Keywords: Breast cancer, factor V Leiden, prothrombin G20210A, MTHFR, polymorphism, survival, proportional odds model

Introduction

Cancer and its treatment can induce hypercoagulability due to many factors including activation of clotting system, expression of haemostatic proteins on tumor cells, alteration of endothelial surface, and impaired fibrin polymerization. The genetic polymorphisms of thrombophilic factors in cancer patients have been investigated during the last few years. Several genetic risk factors related to the haemostatic system are known to influence the thrombosis risk. Inherited resistance to activated protein C is a prothrombotic condition resulting from a gain-of-function mutation of coagulation factor V, commonly referred to as FV Leiden (FVL) [1]. This mutation is the most common inherited risk factor for venous thromboembolism (VTE), with a prevalence of 5% in Caucasian population and 20-50% among patients with VTE.

Another prothrombotic gain-of-function mutation has been identified in the 3' untranslated region of the prothrombin (PT) gene (the substitution of A for G at position 20 210). The mutant allele is present in 2% of the general population and increases the risk of VTE by three- to five-fold [2]. The methylenetetrahydrofolate reductase (MTHFR) enzyme, which is encoded by the MTHFR gene, is one of the factors of the coagulation system. A C-T polymorphism at nucleotide 677 in the MTHFR gene leads to increased levels of homocysteine, which is a risk factor for thrombosis [3]. A few previous reports investigated the relationship between the cancer development and thrombophilic polymorphisms were found no association between the polymorphisms and the various types of cancer [4-8]. Contrary to this perception, some previous reports addressed increased the relationship between thrombophilic polymorphisms and cancer [9].

In medical science, in investigating the survival data of epidemic diseases or chronic diseases and determining the factors which affects these diseases, proportional hazards (Cox regression) model which is proposed by D.R. Cox (1972) is the most commonly used regression model. The simple interpretation of the regression parameter of the model in terms of the relative risks makes the model more useful. The aim of this model is exploring the relationship between the survival time and the subject specific characteristics. For instance, in cancer research, the researchers might wish to investigate the relationship between the survival time and various variables, such as age, tumor size, stage, treatment's type [10, 11].

Let T be a random variable representing failure time and S (t) be the survivor function,

$$S(t) = P(T \geq t) \quad (1)$$

the model can be written as,

$$\lambda(t/z) = \lambda_0(t)e^{z_1\beta_1 + z_2\beta_2 + \cdots + z_p\beta_p} = \lambda_0(t)e^{z^T\beta} \quad (2)$$

Where z is px1 vector of covariates and β is px1 vector of regression coefficients. The baseline hazard function, $\lambda_0(t)$ in the model can take any shape as a function of t [12].

The main assumption of the Cox regression model is proportional hazards. That means that the hazard ratio is constant over time or that the hazard for an individual is proportional to the hazard for any other individual [11]. However, this assumption is inappropriate in some situations, in particular when the hazard rates of different individuals converge to the population mortality rate [10]. In that case, different models should be used to deal with non-proportionality of hazards.

When the proportional hazards assumption is not satisfied, the proportional odds model might be a useful alternative to the proportional hazards model. The proportional odds model is suggested in order to modeling of ordinal data. However, Bennett [13] has extended the model to the modeling of continuous survival data. Besides the proportional odds model, the accelerated failure time models (exponential, weibull, log-logistic, log-normal regression models) or extended Cox regression model can be used instead of Cox. When one is willing to assume a parametric form for the distribution of survival time, the survival data can be analyzed with accelerated failure time [14]. In

extended Cox regression model, the Cox regression model is extending to a model which contains time-dependent covariates and the product of these covariates with a function of time [11].

We previously demonstrated that FVL and PT G20210A polymorphisms were not associated with disease-free survival (DFS) in breast cancer when Cox regression model was applied [15]. In the present study we have focused on the effects of FVL, PT G20210A, and MTHFR C677T on the DFS in breast cancer with a greater number of patients according to the proportional odds model.

Materials & methods

A total of 197 women with primary breast cancer who underwent surgical intervention were appropriate for the present study. Ethical committee approval was previously obtained for the molecular researches on thrombosis (FVL, PT G20210A, and MTHFR C677T polymorphisms). Informed consent was taken from all patients for the analysis of molecular correlate. The old extracted genomic DNA from peripheral blood was used for the study. FVL, MTHFR C677T and PT G20210A polymorphisms were determined using commercially available LightCycler kits (Roche Diagnostic, Roche Molecular Biochemicals, Mannheim, Germany) [16].

Data regarding patient's age, menopause status, tumor size, lymph node status, tumor stage, tumor grade, estrogen receptor (ER), progesterone receptor (PR), c-erbB2 expression, FVL, PT G20210A and MTHFR C677T polymorphisms, recurrence ratio were examined by chi-square test, Kaplan-Meier method, log-rank test and multivariate analyses (Cox regression model and the alternative models which are the proportional odds model, the accelerated failure time models and extended Cox regression model). All the variables were listed in **Table 1**.

The chi-square test was applied to examine the association between the defined variables and recurrence of breast cancer. The Kaplan Meier method was applied to examine the influence of individual variables on DFS. The significance of the observed difference between groups was calculated by the log-rank test. The proportional hazards assumption of the Cox regression model violated for some variables. In that case, using Cox regression model for the data

Table 1. Variables and categories in 197 patients with breast cancer

Variable	Categories	Frequencies (%)	Frequency of Recurrence (%)
Age	≤40	43 (21.8)	12 (27.9)
	>40	154 (78.2)	29 (18.8)
Menopause	Pre	101 (51.3)	19 (18.8)
	Post	96 (48.7)	22 (22.9)
Tumor Size (T)	T1	60 (30.5)	1 (1.7)
	T2	113 (57.4)	26 (23.0)
	T3	24 (12.1)	12 (58.3)
Lymph Node Metastasis	Absent	92 (46.7)	8 (8.7)
	Present	105 (53.3)	33 (31.4)
Tumor stage	Stage 1	46 (23.4)	1 (2.2)
	Stage 2a	59 (29.9)	8 (13.6)
	Stage 2b	41 (20.8)	8 (19.5)
	Stage 3	51 (25.9)	24 (47.1)
Tumor grade	Grade x	40 (20.3)	13 (32.5)
	Grade1	48 (24.4)	2 (4.2)
	Grade2	54 (27.4)	10 (18.5)
	Grade3	55 (27.9)	16 (29.1)
ER	Negative	54 (27.7)	17 (31.5)
	Positive	141 (72.3)	24 (17.0)
PR	Negative	78 (40.8)	21 (26.9)
	Positive	113 (59.2)	18 (15.9)
C-erbB2	Negative	148 (79.1)	18 (12.2)
	Positive	39 (20.9)	18 (46.2)
FVL mutation	no	179 (90.9)	38 (21.2)
	yes	18 (9.1)	3 (16.7)
PT G201210A	no	186 (94.4)	40 (21.5)
	yes	11 (5.6)	1 (9.1)
MTHFR	CC	94 (47.7)	23 (24.5)
	CT	86 (43.7)	15 (17.4)
	TT	17 (8.6)	3 (17.6)

square test results, there was no statistically significant difference between the categories of age, menopausal status, PR expression, FVL, PT G20210A and MTHFR C677T polymorphisms in terms of recurrence (P>0.05). However, there was a statistically significant difference between the categories of tumor size, lymph node metastasis, ER expression, c-erbB2 expression, tumor stage and tumor grade in terms of recurrence (P<0.05). **Table 2** showed the results of Kaplan-Meier method. Analysis revealed that tumor size, lymph node status, tumor stage, tumor grade, c-erbB2 expression were prognostic indicators for DFS (P<0.05). There was no statistically significant difference with regard to age, menopausal status, ER and PR expression, FVL, PT G20210A, and MTHFR C677T polymorphisms (P>0.05).

FVL polymorphism was detected in 18 breast cancer patients and the recurrent disease was developed in 3 of them. FVL polymorphism was not related to DFS in breast cancer (P=0.560). PT G20210A polymorphism was detected in 11 patients and the recurrent disease was developed only in one patient. PT G20210A polymorphism was not related to DFS in breast cancer (P=0.444). It was also found that MTHFR C677T polymorphism was not related to DFS in breast cancer (P=0.670).

In addition to the Cox regression model, we applied the alternative models and the results of the models were given in **Table 3**. The results of AIC in our study demonstrated that the log-normal regression model was found as the best model. The results of the log-normal regression model were listed in **Table 4**. In order to find the fittest model that contains the factors which influence the time of recurrence, the log-normal

set was not proper. Thus, besides Cox regression model, the alternative models were also applied to the data. In order to determine the most proper model, Akaike Information Criteria (AIC) was used. The smallest AIC gave the fittest model for the data set. The combined and independent effects of the factors on DFS were examined using the AIC long-normal regression model. The statistical analyses were performed using IBM SPSS Statistics V21.0 and R for Windows 2.15.0. For all test, a *p* value of less than 0.05 was considered to be significant.

Results

Recurrent disease occurred in 41 patients (21.0%) among 197 patients. From the chi-

Table 2. Kaplan-Meier survival probability estimates and log-rank test results

Variable	Categories	Year (%)			p-value
		3	5		
Age	≤40	73.0	73.0		0.129
	>40	87.7	80.8		
Menopause	Pre	84.0	82.3		0.601
	Post	85.0	76.0		
					0.000*
Tumor Size (T)	T1	100	97.6	1-2	0.000*
	T2	86.1	77.8	1-3	0.000*
	T3	66.7	66.7	2-3	0.000*
Lymph Node Metastasis	Absent	97.6	96.0		0.000*
	Present	72.9	63.0		
					0.000*
Tumor Stage	Stage 1	100	97.1	1-2a	0.056
	Stage 2a	94.0	94.0	1-2b	0.005*
	Stage 2b	95.0	77.2	1-3	0.000*
	Stage 3	48.1	42.8	2a-2b	0.225*
				2a-3	0.000*
				2b-3	0.000*
					0.001*
Tumor grade	Grade x	67.2	67.2	x-1	0.000*
	Grade1	100	97.3	x-2	0.174
	Grade2	85.6	81.5	x-3	0.989
	Grade 3	82.2	66.0	1-2	0.005*
				1-3	0.000*
				2-3	0.108
ER	Negative	80.7	71.2		0.078
	Positive	86.1	82.3		
PR	Negative	84.0	77.2		0.119
	Positive	86.2	81.2		
C-erbB2	Negative	92.9	89.0		0.000*
	Positive	56.6	37.7		
FVL mutation	no	84.4	78.8		0.560
	yes	87.7	87.7		
PT G201210A	No	84.6	78.8		0.444
	yes	85.7	85.7		
MTHFR	CC	84.0	76.4		0.670
	CT	84.8	81.0		
	TT	88.2	88.2		

*P<α=0.05.

regression model was applied to the data set using forward and stepwise selection methods. These results were given in **Tables 5** and **6**, respectively.

According to the forward selection model (**Table 5**), the average survival time of the patients with T3 tumor had 2.5 times shorter faced by patients with T1 tumor. The average survival time of the patients with stage 2b had 2.6 times shorter and patients with stage 3 had 3.4 times shorter compared with stage 1 patients. The average survival time of the patients with c-erbB2 expression had 2.9 times shorter compared with the patients without this expression.

As seen in **Table 6**, tumor size, tumor grade, lymph node metastasis and c-erbB2 expression were found to be significant prognostic factor for DFS when log-normal regression model, stepwise selection method was applied.

Discussion

Cancer and its treatment can induce a hypercoagulable state. On the other hand, coagulation and fibrinolysis can play a significant role in tumor growth, invasion, dissemination and metastasis [4-9, 15]. Recently, little conclusive information is available and controversy maintains in literature about the association of cancer hypercoagulability and inherited thrombophilia. In this context, the relation of the MTHFR C677T polymorphism with some types of cancer including thyroid carcinoma [17], bladder cancer [18] and colorectal cancer [19] has been investigated and MTHFR 677TT genotype has been found to be associated with tumor development. However, Kang et al [20] observed no significant difference in the distribution of this polymorphism between colorectal cancer patients and healthy individuals. Jakubowska and coworkers [21] have also reported that there was no relationship between MTHFR

Table 3. The comparison of the alternative models in addition to the cox regression model

Model	Log (L)	Number of parameter	AIC
Cox	-126.99	19	310.98
Proportional odds	-124.387	19	305.77
Extended Cox (t)	-116.75	38	347.50
Extended Cox (Int)	-118.01	38	350.02
AFT Models			
Exponential	-81.22	19	202.44
Weibull	-74.29	19	190.58
Log-normal	-73.26	19	188.52
Log-logistic	-73.84	19	189.68

Table 4. The results of log-normal regression model

Variables	$\hat{\beta}$	Standard Error-($\hat{\beta}$)	p-value
Age >40	0.673	0.351	0.055
Menopause_Post	-0.465	0.299	0.121
Tumor Size_T2	-5.736	268.294	0.983
Tumor Size_T3	-6.682	268.294	0.980
Lymph Node_Present	-1.742	1.029	0.073
Stage2a	4.846	162.738	0.986
Stage2b	6.181	162.746	0.982
Stage3	5.593	162.746	0.983
Grade 1	0.488	0.514	0.310
Grade 2	-0.246	0.372	0.480
Grade 3	-0.424	0.342	0.186
ER_Positive	0.441	0.373	0.204
PR_Positive	0.712	0.361	0.832
C-erbB2_Positive	-0.724	0.261	0.003*
FVL_yes	0.665	0.471	0.138
PT G201210A_yes	-0.198	0.617	0.739
MTHFR_CT	0.403	0.247	0.081
MTHFR_TT	-0.055	0.520	0.912

*P<α=0.05.

C677T polymorphism and breast cancer development.

FVL and/or PTG20210A polymorphisms are also responsible for hypercoagulation. Paspatis et al addressed that the prevalence of both FVL and PT G20210A in patients with colorectal cancer was found to be similar to that of 192 colonoscopically selected control subjects [4]. On the contrary, Pihusch et al reported that the prevalence of PT G20210A polymorphism was significantly increased in patients with gastro-

Table 5. The results of log-normal regression model using forward selection method

Variable	$\hat{\beta}$	Standard Error ($\hat{\beta}$)	p-value
Tumor Size_T3	-0.938	0.345	0.0076*
Stage_2b	-0.708	0.303	0.02*
Stage_3	-1.214	0.311	0.00*
Grade 1	1.048	0.406	0.01*
C-erbB2_Positive	-0.822	0.255	0.001*
Constant	5.685	0.279	0.000*

*P<α=0.05.

Table 6. The results of log-normal regression model using stepwise selection method

Variable	$\hat{\beta}$	Standard Error ($\hat{\beta}$)	P
Tumor Size_T2	-1.025	0.499	0.04*
Tumor Size_T3	-2.266	0.578	0.000*
Grade 1	0.959	0.424	0.022*
Lymph Node_Present	-0.725	0.278	0.009*
C-erbB2_Positive	-0.882	0.248	0.000*
Constant	6.545	0.550	0.000*

*P<α=0.05.

intestinal carcinoma as compared to normal subjects [9]. Miller et al demonstrated an increased incidence of neoplasia of the digestive tract in men with persistent activation of the coagulation pathway [22]. Some studies also evaluated the role of FVL and PT G20210A polymorphisms on tumor development in some types of malignant tumors including oral, gastric, and gynecological cancers [6-8].

There is no sufficient conclusive information about the cause of breast cancer, although different genetic and environmental factors play role in its development. Moreover, the role of thrombophilia polymorphisms on the risk of breast cancer has not been deeply investigated yet. We have previously reported that there was no significant relationship between FVL and PT G20210A polymorphisms and the recurrence-free survival in breast cancer patients [15] by using Cox regression model. In the present study we have showed that the thrombophilic polymorphisms are not associated with DFS when alternative models are applied in addition to Cox regression model.

In summary, alternative models in survival analysis should be applied in addition to Cox

regression model. Our recent data have suggested that the prevalence of FVL, MTHFR or PT G20210A polymorphisms are not significantly correlated with DFS in breast cancer patients based on log-normal regression model.

Disclosure of conflict of interest

None.

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