Journal of BUON **13:** 61-64, 2008
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ORIGINAL ARTICLE

Factor V 1691 G-A (Leiden) polymorphism and cancer-related venous thromboembolism: a meta-analysis of published studies

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Summary

Purpose: *Although one of the most common genetic polymorphisms that predispose to venous thromboembolism (VTE) is factor V 1691 G-A (Factor V Leiden; FVL), the effect of this polymorphism on the development of VTE in cancer patients is unclear. We have therefore performed a meta-analysis to estimate the risk of VTE associated with FVL among cancer patients.*

Materials and methods: *Relevant studies published before May 2006 were retrieved from Pubmed/Medline. We selected studies comparing the prevalence of FVL in cancer patients with VTE with cancer patients without VTE. Both fixed and random effect models were used. P-values and odds ratios (ORs) with 95% confidence intervals (95% CI) were calculated by Fisher's exact test.*

Results: *Pooled results from 9 studies, comprising 397 cancer patients with VTE and 678 cancer patients without VTE revealed that the prevalence of FVL was higher among cancer patients with VTE (7.3%) than those without VTE (4.6%) ($x^2 = 34.633 > x^2_{18;\,0.05} = 28.869$) ($p=0.013$). It was also found that mean effect size of FVL was 0.22 (95% CI 0.051-0.4892). Using the homogeneity test, there was evidence of statistical heterogeneity ($Q_{hom} = 46.334 > x^2_{8;\,0.05} = 15.507$) ($p=0.0000$).*

Conclusion: *Although the published studies were small and the meta-analysis demonstrated an association of FVL with cancer-related thrombosis, testing for FVL can be routinely used as part of clinical thrombophilia assessment in cancer patients from the regions with high incidence of FVL.*

Key words: cancer, factor V Leiden, meta-analysis, thrombosis

Introduction

Thrombosis results from interaction of multiple causes, both genetic and acquired. Several genetic risk factors for thrombophilia have been described. G-A transition at nucleotide 1691 in exon 10 of the factor V gene (FVL) causing activated protein C resistance (APCR) is the most common inherited risk factor of VTE. The presence of FVL increases the risk of thrombosis approximately 7-fold. Heterozygosity for this mutation confers a 5-to 10-fold increased risk of VTE, whereas the estimated risk for the homozygosity is 80-100-fold higher than the general population [1,2].

Hypercoagulability in cancer is well known since the days of Trousseau, nevertheless the pathogenesis of VTE in cancer patients has not been entirely established. Multiple interactions between malignancy and coagulation have been reported [3,4]. The overall risk of venous thrombosis is increased 7-fold in cancer patients. Although it is well known that FVL is associated with an increased risk of thrombosis, its correlation with the development of VTE in cancer patients remains controversial. Moreover, several studies on the association of FVL with cancer and its treatment-associated thromboembolism have shown conflicting results [5-17]. Herein, we present the results of a meta-analysis we have conducted of previously reported studies to clarify the role of FVL on the development of VTE in cancer patients.

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Received 01-07-2007; Accepted 08-08-2007

Materials and methods

Data collection

Using a search of Medline/Pubmed database from 1970 to May 2006, we identified all studies correlating FVL and VTE in cancer. The key words used for search were "cancer", "thrombosis", "pulmonary embolism", "factor V Leiden", "venous thrombosis", "mutation", "polymorphism" and "genetic". We considered only studies which had a group of cancer patients with thrombosis and a comparable group of control subjects as cancer patients without thrombosis. All patients had to have undergone genetic testing for FVL.

Statistical analysis

In the primary analysis, the rate of presence of FVL mutation was calculated among patients with VTE (i.e. cases) and patients without VTE (i.e. controls) for each study. The prevalence rates of FVL among cases and controls were pooled using the random effects model. An unadjusted OR and its 95% CI were calculated using both the fixed and random effects models.

For each study, p-values were calculated using Fisher's exact test method [18,19]. Pooled p-value was calculated by using Fisher's method according to the formula:

$$-2\sum_{i=1}^{K}\log(p_i)$$

(K: number of studies).

The effect size (d) of FVL for each study and then the mean effect size were assessed using the following formulae, respectively [18,19]:

$$d=\frac{(p_t-p_c)}{\sqrt{p_c(1-p_c)}}$$

(p_t and p_c represent the proportion of subjects with the event in the test and control arm, respectively);

$$\bar{d}=\frac{\sum_{i=1}^{K} n_i d_i}{\sum_{i=1}^{K} n_i}=D$$

(n_i represents the corresponding numbers of subjects and K the number of studies).

Heterogeneity across studies was assessed using the formula:

$$Q_{hom}=K\,var(d)/var(e)$$

(var(d) is the variance of the effect size; var(e) is the sample error variance of the effect size [19]. Q_{hom} is approximately distributed according to a x^2 distribution with K-1 degrees of freedom).

Results

The studies in which FVL mutation was assessed both among cancer patients with and without VTE were included in the meta-analysis. A total of 9 studies [5-13] and 1075 cases served as the basis of our final analysis. The pooled analysis of studies investigating

Table 1. Characteristics of study participants and the number and rate (in parentheses) of FVL mutation in cases and controls from 9 studies

Study	*Ref*	*Year*	*Source and definition*	*Patients with VTE FVL mutation*			*Patients without VTE FVL mutation*		
				Positive n (%)	*Negative n (%)*	*Total n*	*Positive n (%)*	*Negative n (%)*	*Total n*
Sifontes et al.	5	1997	US pediatric cancers with VTE	1 (3.1)	31 (96.9)	32	0	35 (100)	35
Haim et al.	6	2001	Israeli patients with VTE	1 (2)	54 (98)	55	4 (7)	54 (93)	58
Ravin et al.	7	2002	US gynecological cancers with VTE	2 (5)	38 (95)	40	5 (15)	29 (85)	34
Pihusch et al.	8	2003	German gastrointestinal system cancers with VTE	5 (17.9)	23 (82.1)	28	7 (4.8)	140 (95.2)	147
Mitchell et al.	9	2003	US pediatric cancers with TE	0	22	22	2 (5.3)	36 (94.7)	38
Ramacciotti et al.	10	2003	Brazilian cancer patients with VTE	1 (1.5)	63 (98.5)	64	4 (2.7)	143 (97.3)	147
Mandala et al.	11	2003	Italian women with breast cancer with catheter related DVT	5 (20)	20 (80)	25	2 (4)	48 (96)	50
Eroglu et al.	12	2004	Turkish cancer patients with VTE	9 (30)	21 (70)	30	4 (5.8)	64 (94.2)	68
Kennedy et al.	13	2005	US cancer patients with VTE	5 (5)	96 (95)	101	3 (3)	98 (97)	101
Total number of patients				29 (7.3%)	368 (92.7%)	397	31 (4.6%)	647 (95.6%)	678

FVL: factor V Leiden, VTE: venous thromboembolism, TE: thromboembolism, DVT: deep venous thrombosis

the prevalence of FVL in cases and controls is summarized in Table 1. The pooled prevalence of FVL was higher among 397 cancer patients with VTE (7.3%) than 678 cancer patients without VTE (4.6%).

The estimated p-values and ORs with 95% CI of the studies are listed in Table 2. Among them only 3 studies showed a statistically significant relationship between the presence of FVL and the development of VTE in cancer patients. When pooled p-values were calculated by the Fisher's method, a significant difference was seen between cases and controls ($x^2 = 34.633 > x^2_{18;\,0.05} = 28.869$; p=0.013). The overall relationship on the basis of the 9 studies was modest with OR of 2.07 (95% CI 1.17-3.67) and 1.63 (95% CI 0.66-3.99) according to the fixed and random effect models, respectively.

The mean of the effect size was 0.22 with 95% CI 0.051-0.4892. In addition, there was a statistical heterogeneity according to the homogeneity test ($Q_{hom} = 46.334 > x^2_{8;\,0.05} = 15.507$; p=0.0000).

Discussion

Cancer patients bear a high risk of VTE, however the studies over the association of FVL with cancer-related thrombosis present conflicting results. Some studies have reported a statistically significant association between the FVL and VTE [8,11,12], while others have shown that FVL does not play a significant role in the development of VTE and that high risk of VTE comes from the cancer itself and its treatment, not from an underlying inherited tendency to thrombophilia [5-7,9,10,13-15]. However, some authors have reported a high prevalence of FVL in cancer patients [17].

It is unclear why the association of FVL with cancer-related thrombosis would differ. The different findings can be explained by the fact that the relevant studies include different tumor types. Recently, a large population-based, case-control study by Bloom and co-workers has revealed that patients with hematological malignancies have the highest risk of VTE, followed by lung cancer and gastrointestinal cancers [17]. In their study, cancer patients with FVL had a 2-fold increased risk of venous thrombosis compared with cancer patients without FVL. Nevertheless, Haim et al. suggested that cancer patients have APCR unrelated to FVL and increased risk of thrombosis [6]. Besides, cancer patients with FVL may have a greater chance of manifesting thrombosis following chemotherapy or hormonal therapy.

Our meta-analysis finding that FVL mutation is associated with an increased risk of VTE in cancer patients is surprising, although 6 of 9 evaluated studies indicated no association between the presence of FVL and the development of thrombosis. This inconsistency could be explained by some potential limitations of the present study. First, a major weakness of the present study was the small number of pooled studies.

Second, it is important to acknowledge the heterogeneity within patient demographics. It is well known that genetic polymorphisms usually vary among different ethnic populations. The prevalence of FVL mutation also shows a geographic distribution [20]. Its frequency is approximately 5% in the general Caucasian populations. The most high prevalence of FVL mutation is observed in Southern Europe, Middle East, and Eastern Mediterranean region [21-24] but the mutated allele is not seen in certain populations, such as Japanese and Chinese [25,26]. According to the geographic distribution it might be said that high frequency of FVL mutation in cancer patients with VTE is found in the regions showing high prevalence. The presence of statistical heterogeneity detected in this meta-analysis might be explained by the variety of the countries included herein.

In conclusion, this meta-analysis demonstrated an association of FVL with thrombosis in cancer patients; however, routine screening for FVL in all cancer patients with VTE is probably not warranted because of ethno-geographic differences of FVL. When performed, it should be restricted to patients who live in the regions with high incidence of this mutation.

Table 2. Odds ratio (OR) with 95% confidence interval (CI) and p-values of the pooled studies

Study	*Ref*	*OR*	*95% CI*	*p-value*
Sifontes et al.	5	3.38	0.13-86.12	0.478
Haim et al.	6	0.25	0.03-2.31	0.365
Ravin et al.	7	0.31	0.06-1.69	0.236
Pihusch et al.	8	4.35	1.27-14.87	0.026
Mitchell et al.	9	0.32	0.02-7.07	0.528
Ramacciotti et al.	10	0.57	0.06-5.18	1.00
Mandala et al.	11	6.00	1.07-33.53	0.037
Eroglu et al.	12	6.86	1.91-24.58	0.002
Kennedy et al.	13	1.70	0.40-7.32	0.721

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