Association of VEGF haplotypes with breast cancer risk in North-West Indians

Vasudha Sambyal¹, Kamlesh Guleria¹*, Ruhi Kapahi¹, Mridu Manjari², Meena Sudan³, Manjit Singh Uppal⁴ and Neeti Rajan Singh⁴

Abstract

Background: Angiogenesis is one of the hallmark features of cancer [1]. It is a complex and coordinated process regulated by different growth factors and is one of the hallmark features of cancer. VEGF is one of the most important endothelial cell mitogen and has a critical role in normal physiological and tumor angiogenesis. The objective of this study was to investigate the potential association of haplotypes of six VEGF polymorphisms with breast cancer risk in North-West Indians.

Methods: Samples of 250 breast cancer patients and 250 age and sex matched controls were genotyped for VEGF −2578C/A, −2549I/D, −460T/C, +405C/G, −7C/T and +936C/T polymorphisms. Haplotypes were generated to determine the better contribution of VEGF polymorphisms to breast cancer risk.

Results: Haplotypes CDTCCC (OR = 0.56, 95%CI, 0.38–0.81; p = 0.003) and CDTGCC (OR = 0.63, 95%CI, 0.44–0.92; p = 0.018) of VEGF −2578C/A, −2549I/D, −460T/C, +405C/G, −7C/T and +936C/T polymorphisms were significantly associated with decreased risk of breast cancer. CDTCCC haplotype was also significantly associated with reduced risk of breast cancer in pre and post menopausal as well as both obese and non-obese patients. Haplotype CDTGCC was marginally associated (p = 0.07) with reduced risk of breast cancer in non-obese patients as compared with non-obese controls where as haplotype AICGTC was marginally associated (p = 0.09) with reduced risk of breast cancer in obese patients when compared with non-obese patients. The CDTGCC haplotype was significantly associated with increased risk of breast cancer in premenopausal obese patients (OR = 1.98, 95%CI, 1.10–3.56; p = 0.02).

Conclusions: Our data indicated that CDTCCC and CDTGCC haplotypes of VEGF −2578C/A, −2549I/D, −460T/C, +405C/G, −7C/T and +936C/T polymorphisms were significantly associated with breast cancer risk in North-West Indians. Further studies on multiethnic groups with larger sample size are required to confirm our results.

Keywords: VEGF, Polymorphism, Haplotype, Breast cancer

Background

Angiogenesis is one of the hallmark features of cancer [1]. It is a complex and coordinated process regulated by different growth factors like platelet derived growth factor, transforming growth factor and angiopoietins among which vascular endothelial growth factors (VEGF) play a crucial role [2–4]. VEGF is one of the most powerful endothelial cell mitogen and has a very critical role in normal physiological and tumor angiogenesis [5–7]. It enhances tumor vessel permeability and endothelial cell proliferation, migration, differentiation, capillary formation and also has proinflammatory actions [8–12].

The VEGFA also known as VEGF is located at 6p21.3 and it comprises eight exons and seven introns (Fig. 1) [13]. It is highly polymorphic with several polymorphisms in the promoter, 5′-untranslated region (5′-UTR) and 3′-UTR [14, 15]. Polymorphisms in the promoter and UTRs have been reported to regulate
VEGF expression via alternative initiation of transcription and internal initiation of translation [16, 17]. Functional genetic polymorphisms which alter the regulation of gene expression are predicted to have a significant impact on disease pathogenesis [18]. VEGF −2578C/A, −2549I/D, −460T/C, −116G/A, +405C/G and +936C/T polymorphisms have been associated with differential expression of VEGF [14, 15, 19–22]. The importance of VEGFA in breast cancer has been described in several studies [23, 24]. Increased expression of VEGF has been documented in invasive and non-invasive breast cancer tissue [25, 26]. Polymorphisms in promoter, 5′-UTR and 3′-UTR of VEGF have been reported to affect translation efficiency, circulating plasma concentrations and tumor tissue expression of VEGF [19, 27]. It has been documented that VEGF polymorphisms influencing VEGF expression in normal cells might have an impact on tumorigenesis, tumor progression, and response to anti-VEGF agents [22, 28–30].

Haplotype analysis could be a better predictive approach rather than investigating individual polymorphism. It estimates more specific risk and reduces the dimension of association tests and increase statistical power [31]. Due to the important role of VEGF in carcinogenesis, the present study aimed to investigate the association of haplotypes of VEGF −2578C/A (rs699947), −2549I/D (rs35569394), −460T/C (rs833061), +405C/G (rs2010963) −7C/T (rs25648) and +936C/T (rs3025039) polymorphism with breast cancer risk.

Methods

Subjects
The study was performed according to Declaration of Helsinki and was approved by the Ethics Committee of Guru Nanak Dev University, Amritsar, Punjab, India. All the subjects gave a written informed consent with a signature or thumb impression. A total of 500 subjects (250 breast cancer patients and 250 healthy controls) were analyzed in this study. The patients were investigated at Sri Guru Ram Das Institute of Medical Sciences and Research, Vallah, Amritsar, Punjab (India). The selection criteria of patients and controls have been described in our previous study [32]. All the subjects gave 5 ml blood samples for genetic analyses.

Genotyping of VEGF polymorphisms and analyses of data
The DNA was extracted from EDTA-anti-coagulated blood samples using organic method [33] with few modifications. Three promotor (VEGF −2578C/A, −2549I/D, −460T/C), two 5′-UTR (+405C/G, −7C/T), and one 3′-UTR (+936C/T) polymorphisms were analyzed in this study (Fig. 1). The VEGF −2549I/D polymorphism was analyzed by direct PCR. VEGF −460T/C, −2578C/A +405C/G and VEGF +936C/T polymorphisms of VEGF were analyzed using PCR–RFLP method. VEGF −7C/T polymorphism was analyzed by ARMS-PCR. Ten percent of randomly selected samples were sequenced to validate the PCR based assay genotyping and results of both sets of analyses were 100% concordant. The detail of reaction conditions and analysis of genotype data have been described in our published studies [34, 35]. To determine...
the better contribution of VEGF polymorphisms to breast cancer risk, haplotypes of six VEGF polymorphisms were generated using the online SNPStats software [36]. Further we predicted the possible influence of studied VEGF polymorphisms on the transcription factor binding sites using online software TFSEARCH (http://www.cbrc.jp/research/db/TFSEARCH.html).

Results

Characteristics of study participants

The demographic characteristics of study participants were presented in Table 1. The mean age of patients was 49.38 ± 11.87 years and of controls was 49.34 ± 11.85 years. Of the 250 breast cancer patients, 234 (93%) had infiltrating ductal carcinoma, 4 (2%) had infiltrating lobular carcinoma and 12 (5%) had other types of cancer like medullary carcinoma, mucinous carcinoma, Paget’s disease and phyllodes tumor. In the present study, 127 (51%) cases had tumor in left breast, 112 (45%) in right breast and 11 (4%) cases had tumor in both breasts. Of the 250 breast cancer patients, 65 (26%) had stage I, 119 (48%) had stage II, 48 (19%) had stage III, and 18 (7%) had stage IV tumor.

Table 1 Characteristics of Breast cancer patients and healthy controls

| Variable                        | Patients | %   | Controls | %   |
|---------------------------------|----------|-----|----------|-----|
| Total No. of subjects           | 250      |     | 250      |     |
| Sex                             |          |     |          |     |
| Males                           | 7        | 2.8 | 7        | 2.8 |
| Females                         | 243      | 97.2| 243      | 97.2|
| Age at diagnosis (years)        |          |     |          |     |
| ≤40                             | 66       | 26.4| 66       | 26.4|
| >40                             | 184      | 73.6| 184      | 73.6|
| Mean age                        | 49.38 ± 11.87 | 49.34 ± 11.85 |
| Range                           | 25–85    | 25–85|          |     |
| Habitat                         |          |     |          |     |
| Rural                           | 186      | 74.4| 186      | 74.4|
| Urban                           | 64       | 25.6| 64       | 25.6|
| Diet                            |          |     |          |     |
| Vegetarian                      | 147      | 58.8| 154      | 61.6|
| Non vegetarian                  | 103      | 41.2| 96       | 38.4|
| Obesity                         |          |     |          |     |
| Non obese                       | 62       | 24.8| 70       | 28.0|
| Obese                           | 188      | 75.2| 180      | 72.0|
| Menstrual status                |          |     |          |     |
| Premenopausal                   | 114      | 46.9| 150      | 61.73|
| Postmenopausal                  | 129      | 53.0| 93       | 38.27|
| Mean age at menarche            | 14.74 ± 1.78 | 14.75 ± 1.47 |
| Mean age at first child birth   | 22.70 ± 4.08 | 22.45 ± 3.43 |
| Breastfeeding                   |          |     |          |     |
| Yes                             | 215      | 88.48| 224 | 92.18|
| No                              | 28       | 11.52| 19  | 7.82|
| Oral Contraceptives             |          |     |          |     |
| Yes                             | 21       | 8.64| 16       | 6.58|
| No                              | 222      | 91.36| 227 | 93.42|

Table 2 Association between VEGF haplotypes and breast cancer risk

| Haplotypea | Cases (%) | Controls (%) | OR (95%CI) | p value |
|------------|-----------|--------------|------------|---------|
| AICGCC     | 31.3      | 23.8         | 1 (Reference) |         |
| CDTGCC     | 23.7      | 28.9         | 0.56 (0.38–0.81) | 0.003   |
| AICGCT     | 19.6      | 25.6         | 0.63 (0.44–0.92) | 0.018   |
| AICGCT      | 9.0      | 9.3           | 0.75 (0.43–1.30) | 0.31    |
| AICGCTT     | 3.1      | 1.8           | 1.22 (0.40–3.74) | 0.73    |
| AICGTTT     | 1.7      | 2.0           | 0.76 (0.25–2.33) | 0.64    |
| CDTCTCT     | 1.4      | 1.5           | 0.65 (0.13–3.35) | 0.61    |

Significant p values are shown in bold
OR odds ratio, CI confidence interval

a In order of −2578C/A, −2549I/D, −460T/C, +405C/G, −7C/T and +936C/T
non obese patients (Tables 6 and 7). Haplotype CDTGCC was marginally associated ($p = 0.07$) with reduced risk of breast cancer in non-obese patients as compared with non-obese controls (Table 7) where as haplotype AICGTC was marginally associated ($p = 0.09$) with reduced risk of breast cancer in obese patients when compared with non-obese patients (Table 8). Further we compared pre menopausal obese patients with post menopausal obese patients and observed that CDTGCC

### Table 3 VEGF haplotypes and breast cancer risk in premenopausal subjects

| Haplotype | Pre menopausal cases (%) | Pre menopausal controls (%) | OR (95%CI) | p value |
|-----------|--------------------------|-----------------------------|------------|---------|
| AICGCC    | 29.0                     | 24.5                        | 1 (Reference) |          |
| CDTCCC    | 20.6                     | 28.5                        | 0.65 (0.43–0.99) | 0.04    |
| CDTGCC    | 25.0                     | 26.3                        | 0.95 (0.64–1.42) | 0.81    |
| AICGTC    | 9.0                      | 9.9                         | 0.90 (0.50–1.64) | 0.73    |
| AICGTT    | 3.1                      | 1.4                         | 2.23 (0.67–7.43) | 0.18    |
| CDTGCT    | 3.2                      | 1.5                         | 2.27 (0.69–7.51) | 0.16    |
| CDTGCC    | 3.3                      | 2.1                         | 1.87 (0.46–7.56) | 0.38    |

Significant $p$ values are shown in bold
OR odds ratio, CI confidence interval

* In order of $−2578C/A, −2549I/D, −460T/C, +405C/G, −7C/T and +936C/T

### Table 4 VEGF haplotype and breast cancer risk in post menopausal subjects

| Haplotype | Post menopausal cases (%) | Post menopausal controls (%) | OR (95%CI) | p value |
|-----------|---------------------------|-----------------------------|------------|---------|
| AICGCC    | 31.9                      | 23.4                        | 1 (Reference) |          |
| CDTCCC    | 24.8                      | 33.3                        | 0.52 (0.30–0.92) | 0.02    |
| CDTGCC    | 17.6                      | 22.4                        | 0.59 (0.31–1.12) | 0.11    |
| AICGTC    | 9.2                       | 7.9                         | 0.82 (0.34–1.99) | 0.66    |
| AICGCT    | 3.3                       | 2.4                         | 1.05 (0.16–6.83) | 0.96    |
| AICGTT    | 0.7                       | 3.3                         | 0.27 (0.04–1.94) | 0.19    |

Significant $p$ values are shown in bold
OR odds ratio, CI confidence interval

* In order of $−2578C/A, −2549I/D, −460T/C, +405C/G, −7C/T and +936C/T

### Table 5 Association of VEGF haplotypes with breast cancer risk in pre menopausal and post menopausal patients

| Haplotype | Pre menopausal (%) | Post menopausal (%) | OR (95%CI) | p value |
|-----------|-------------------|---------------------|------------|---------|
| AICGCC    | 29.0              | 31.9                | 1 (Reference) |          |
| CDTCCC    | 20.6              | 24.8                | 0.95 (0.54–1.67) | 0.86    |
| CDTGCC    | 25.0              | 17.6                | 1.42 (0.82–2.47) | 0.22    |
| AICGTC    | 9.0               | 9.2                 | 1.05 (0.48–2.33) | 0.90    |
| AICGCT    | 9.0               | 9.2                 | 0.70 (0.32–1.59) | 0.68    |
| CDTGCT    | 3.1               | 1.1                 | 3.01 (0.55–16.65) | 0.21    |

OR odds ratio, CI confidence interval

* In order of $−2578C/A, −2549I/D, −460T/C, +405C/G, −7C/T and +936C/T

### Table 6 Association of VEGF haplotypes with breast cancer risk in obese subjects

| Haplotype | Obese patients (%) | Obese controls (%) | OR (95%CI) | p value |
|-----------|--------------------|--------------------|------------|---------|
| AICGCC    | 31.2               | 24.6               | 1 (Reference) |          |
| CDTCCC    | 25.2               | 28.9               | 0.63 (0.41–0.99) | 0.04    |
| CDTGCC    | 19.3               | 25.0               | 0.76 (0.49–1.19) | 0.23    |
| AICGTC    | 7.0                | 9.3                | 0.70 (0.35–1.95) | 0.31    |
| AICGTT    | 3.0                | 1.9                | 1.27 (0.39–4.12) | 0.69    |
| CDTGCT    | 2.4                | 1.7                | 1.23 (0.29–5.22) | 0.78    |
| AICGCT    | 1.8                | 1.7                | 0.77 (0.14–4.26) | 0.76    |
| CDTGCT    | 1.8                | 1.5                | 1.17 (0.26–5.18) | 0.84    |

Significant $p$ values are shown in bold
OR odds ratio, CI confidence interval

* In order of $−2578C/A, −2549I/D, −460T/C, +405C/G, −7C/T and +936C/T

### Table 7 Association of VEGF haplotypes with breast cancer risk in non obese subjects

| Haplotype | Non-obese patients (%) | Non-obese controls (%) | OR(95%CI) | p value |
|-----------|------------------------|------------------------|-----------|---------|
| AICGCC    | 34.1                   | 23.7                   | 1 (Reference) |          |
| CDTCCC    | 20.9                   | 31.2                   | 0.44 (0.21–0.93) | 0.03    |
| CDTGCC    | 18.2                   | 22.7                   | 0.47 (0.21–1.05) | 0.07    |
| AICGTC    | 13.5                   | 9.5                    | 1.11 (0.38–3.21) | 0.85    |
| CDTGTC    | 1.2                    | 1.4                    | 0.46 (0.02–12.99) | 0.65    |

Significant $p$ values are shown in bold
OR odds ratio, CI confidence interval

* In order of $−2578C/A, −2549I/D, −460T/C, +405C/G, −7C/T and +936C/T
Table 8 Association of VEGF haplotypes with breast cancer risk in obese and non-obese patients

| Haplotype | Obese (%) | Non-obese (%) | OR (95%CI) | p value |
|-----------|-----------|---------------|------------|---------|
| AICGCC    | 31.2      | 34.1          | 1 (Reference) |         |
| CDTCCC    | 25.1      | 20.9          | 1.28 (0.70–2.34) | 0.42    |
| CDTGCC    | 19.3      | 18.2          | 1.11 (0.61–2.03) | 0.73    |
| AICGTC    | 7.0       | 13.5          | 0.48 (0.21–1.12) | 0.09    |
| CDTGCT    | 3.1       | 1.2           | 2.74 (0.33–22.40) | 0.35    |
| AICGCT    | 1.8       | 4.8           | 0.27 (0.04–1.91) | 0.19    |

Significant p values are shown in bold

Table 9 Association of VEGF haplotypes with breast cancer risk in premenopausal obese and postmenopausal obese patients

| Haplotype | Premenopausal obese (%) | Postmenopausal obese (%) | OR (95%CI) | p value |
|-----------|-------------------------|--------------------------|------------|---------|
| AICGCC    | 25.0                    | 35.1                     | 1 (Reference) |         |
| CDTCCC    | 21.8                    | 25.5                     | 1.13 (0.60–2.13) | 0.7     |
| CDTGCC    | 27.6                    | 15.0                     | 1.98 (1.10–3.56) | 0.02    |
| CDTGCT    | 1.8                     | 2.7                      | 1.45 (0.27–7.71) | 0.66    |
| AICGCT    | 8.6                     | 7.9                      | 1.27 (0.50–3.24) | 0.62    |

Significant p values are shown in bold

haplotype was significantly associated (p = 0.02) with increased risk of breast cancer in premenopausal obese patients (Table 9).

The TFSEARCH software was used to predict the functional significance of VEGF polymorphisms. Based on the difference in TFSEARCH TFBS scores, VEGF −2578C/A and +405C/G polymorphisms were predicted to alter a transcription factor binding site. VEGF −2578A allele abolishes the binding site of GATA-2 transcription factor where as VEGF +405G allele created the binding site of MZF1 (Myeloid zinc finger 1) transcription factor.

Discussion

In the present study we investigated the potential association of VEGF haplotypes based on six polymorphisms with breast cancer risk. In previous reported studies, by using the single/double or triple polymorphism approach, VEGF −2578C/A, −2549I/D, −460T/C, +405C/G, −7C/T and +936C/T polymorphisms have been analyzed to evaluate their potential association with breast cancer risk in different ethnic groups and results are conflicting (Additional file 1: Table S2).

The ethnicity difference and inadequate sample size could be the potential cause of inconsistent results.

In the present study, we observed that CDTGCC (OR = 0.56, 95% CI, 0.38–0.81; p = 0.003) and CDTGCC (OR = 0.63, 95% CI, 0.44–0.92; p = 0.018) haplotypes of VEGF −2578C/A, −2549I/D, −460T/C, +405C/G, −7C/T and +936C/T polymorphisms were significantly associated with reduced risk of breast cancer. In none of the previous studies, these six polymorphisms have been reported together. In Caucasian subjects, −460T/+405C/−7C/, +936C haplotype was associated with reduced risk of breast cancer [46]. Significant association of VEGF −2578A/−1154A/+405G haplotype with decreased risk of invasive breast cancer has been reported in American population [44]. Haplotype VEGF −1154A/−2578A/−634G/−460C was associated with decreased risk of breast cancer in Moroccan population [39]. The −2578A/−1154G/+405G haplotype was associated with decreased risk whereas haplotype −2578C/−1154G/+405G was associated with increased risk of breast cancer recurrence in Caucasian women [58]. Association of −2578C/+405C haplotype with tumor size and higher histological grade has been documented in breast cancer patients [45]. None of the haplotype of VEGF −2578C/A, −2549I/D, −460T/C, +405C/G, and +936C/T polymorphisms was associated with breast cancer risk in Iranian population [38].

VEGF −460C/+405G/+936T haplotype was associated with increased risk of lung cancer in Koreans [59] and increased risk of esophageal adenocarcinoma in Caucasian [60]. The TGC haplotype of VEGF −460C/T, +405C/G and +936C/T polymorphism was significantly associated with decreased risk of adenocarcinoma among male non-small cell lung cancer patients [61]. In Turkish population, VEGF −2578A/+936T/−460T haplotype has been reported to be associated with increased risk of colorectal cancer [62]. In Tunisians, CIC haplotype of VEGF −2578C/A, −2549I/D and +936C/T polymorphisms was associated with increased risk of urothelial bladder cancer [63].

There are some studies from India on different diseases showing association of VEGF haplotypes with disease risk. The CTIG haplotype of VEGF −2578C/A, −7C/T, −2549I/D, and −1001G/C polymorphisms was associated with increased risk of bladder cancer [64] whereas TACI haplotype of VEGF +936C/T, −1154G/A, −2578C/A and −2549I/D polymorphisms was associated with increased risk of end stage renal disease [65]. Haplotypes CGCC and CGGC of VEGF −460T/C, −1154G/A, +405C/G, and +936C/T polymorphism were associated with aggressiveness of disease in epithelial ovarian cancer patients [66]. No association of VEGF +405C/G
and +936C/T haplotypes with lung cancer risk has been reported in Kashmiri patients [67].

In the present study, CDTCCC haplotype was significantly associated with reduced risk of breast cancer in pre menopausal as well as in post menopausal patients when compared with pre and post menopausal controls. The breast cancer risk has also been reported to be modulated by menopause [68]. Estrogen exposure has been described as an important risk factor for breast cancer development and progression [69]. It has been documented that estrogen modulates angiogenesis via effects on endothelial cells under both physiologic and pathologic conditions [70]. Association of VEGF −460T/+405G/+936T haplotype with reduced risk of breast cancer has been reported in Chinese premenopausal women [47]. Among post-menopausal breast cancer patients, CCCCC haplotype of VEGF −2578C/A, −2489C/T, −460T/C, +405C/G and −7C/T polymorphisms was associated with reduced risk of distant metastases [71].

The CDTCCC haplotype was significantly associated with decrease risk of breast cancer in obese as well as in non obese patients compared to obese and non obese controls where as CDTGCC haplotype was significantly associated with increased risk of breast cancer in premenopausal obese patients. About 75.2% of patients and 72% of controls were obese in the present study. It has been hypothesized that hormonal mechanisms and metabolic factors are involved in the link between obesity and breast cancer. Insulin resistance and hyperinsulinemia have been reported to be associated with increased breast cancer risk and with worst prognosis in both pre and post menopausal women [72–74]. In mouse model, it has been demonstrated that over expression of VEGFA in adipose tissue provide protection against high fat diet induced obesity and insulin sensitivity [75, 76]. It has been documented that angiogenesis plays an important role in the regulation of adipogenesis [77]. VEGF has been described as an important angiogenic factor in adipose tissue and it regulates the development of new vessels required for the expansion of adipose tissue [76, 78]. It has been reported that adiponectin, a regulator of insulin resistance block angiogenesis by increasing the expression of TP53 and decreasing the expression of VEGF [79].

In the present study we predicted that VEGF −2578A allele of VEGF −2578C/A polymorphism abolished the binding site of GATA-2 transcription factor. The GATA family of transcription factors is regulator of gene expression in hematopoietic cells [80, 81]. Correlation of reduced GATA binding promoter activity has been documented with attenuation of VEGF mediated signaling [82]. G allele of VEGF +405C/G polymorphism created the binding site of MZF1 transcription factor. MZF1 transcription factor has been reported to be involved in transcriptional regulation during myelopoiesis [83]. Disruption of MZF1 transcription factor binding site by VEGF-634C (+405C) allele has also been reported in peripheral blood mononuclear cells [15]. It has been reported that substitution of C by G at +405 position in 5′-UTR may affect internal ribosome entry site (IRES) and increases the transcription of large isoform of VEGFA [84].

Polymorphisms of VEGFA have been reported to be associated with efficacy and toxicity of anti—VEGF agents [41, 85, 86]. Haplotype −460T/+405C/+936C haplotype was associated with better survival among Chinese breast cancer patients [87]. VEGF −2578A/−1154G/+405G haplotype was associated with marginally improved prognosis whereas haplotype −2578C/−1154G/+405G was significantly associated with adverse prognosis in HER2 positive breast cancer patients [88]. Apart from breast cancer, correlation of VEGF haplotypes with therapy response has also been documented in other cancer types. The CACC haplotype of VEGF −460T/C, −116G/A, +405C/G, and +936C/T polymorphism was significantly associated with worse survival in Korean gastric cancer patients [89]. In esophageal cancer, CGC haplotype of VEGF −460T/C, +405C/G and +936C/T polymorphism was associated with poorer outcome as compared to other haplotypes [90]. The AGCGC haplotype of VEGF −2578 C/A, −1154 G/A, −460T/C, +405 G/C and +936C/T polymorphisms was found to be associated with improved progression-free survival in epithelial ovarian cancer patients [91]. Haplotype −2578C/−460T/+405C/+936C and −2578C/−460T/+405C/+936T was associated with inferior response rate in metastatic colorectal cancer patients to first line XELOX treatment [92]. Thus, assessment of haplotypes of VEGF polymorphisms may have implications for aggressiveness and selection of patients suitable for anti-VEGF therapy in context of previously reported literature. The VEGF haplotypes in independent cohorts are insightful for identification of cancer risk.

Conclusions

We report for the first time that CDTCCC and CDTGCC haplotypes of VEGF −2578C/A, −2549I/D, −460T/C, +405C/G, −7C/T and +936C/T polymorphisms were significantly associated with breast cancer risk in North-West Indians. Further studies on multiethnic groups with larger sample size are required to confirm our results.

Abbreviations

VEGF: Vascular endothelial growth factor; UTR: Untranslated region; OR: Odds ratio.
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