current issues in molecular biology

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Review

Contribution of Endothelial Dysfunction to Cancer Susceptibility and Progression: A Comprehensive Narrative Review on the Genetic Risk Component

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Abstract: Venous thromboembolism (VTE) is a challenging clinical obstacle in oncological settings, marked by elevated incidence rates and resulting morbidity and mortality. In the context of cancer-associated thrombosis (CAT), endothelial dysfunction (ED) plays a crucial role in promoting a pro-thrombotic environment as endothelial cells lose their ability to regulate blood flow and coagulation. Moreover, emerging research suggests that this disorder may not only contribute to CAT but also impact tumorigenesis itself. Indeed, a dysfunctional endothelium may promote resistance to therapy and favour tumour progression and dissemination. While extensive research has elucidated the multifaceted mechanisms of ED pathogenesis, the genetic component remains a focal point of investigation. This comprehensive narrative review thus delves into the genetic landscape of ED and its potential ramifications on cancer progression. A thorough examination of genetic variants, specifically polymorphisms, within key genes involved in ED pathogenesis, namely *eNOS*, *EDN1*, *ACE*, *AGT*, *F2*, *SELP*, *SELE*, *VWF*, *ICAM1*, and *VCAM1*, was conducted. Overall, these polymorphisms seem to play a context-dependent role, exerting both oncogenic and tumour suppressor effects depending on the tumour and other environmental factors. In-depth studies are needed to uncover the mechanisms connecting these DNA variations to the pathogenesis of malignant diseases.

Keywords: thrombosis; venous thromboembolism; neoplasm; genetic polymorphism; endothelium

Citation: de Melo, I.G.; Tavares, V.; Pereira, D.; Medeiros, R. Contribution of Endothelial Dysfunction to Cancer Susceptibility and Progression: A Comprehensive Narrative Review on the Genetic Risk Component. *Curr. Issues Mol. Biol.* **2024**, *46*, 4845–4873. https://doi.org/10.3390/cimb46050292

Academic Editor: Tomasz Popławski

Received: 14 April 2024
Revised: 9 May 2024
Accepted: 13 May 2024
Published: 16 May 2024

1. Introduction

Venous thromboembolism (VTE), also referred to as venous thrombosis, is a prevalent and intricate cardiovascular condition. The disease has two main manifestations: when the thrombus first forms in a deep vein—deep vein thrombosis (DVT)—followed by its migration into the bloodstream and subsequent lodging in the lungs—pulmonary embolism (PE) [1]. In Europe, VTE affects around one to two individuals per 1000 annually [2]. Although the incidence rate in the United States of America (USA) is greatly similar, it varies significantly from a global perspective, indicating a potential regional influence on the occurrence of thrombotic events. Indeed, VTE has been associated with multiple risk determinants, comprising acute (e.g., surgery) and subacute (e.g., oral contraceptive use) triggers; basal/genetic (e.g., genetic polymorphisms, such as Factor V Leiden (*F5* rs6025) and Prothrombin G20210A (*F2* rs1799963)) and acquired (e.g., autoimmune diseases) risk

factors [2,3]. One acquired risk factor of VTE that warrants prominent consideration is cancer. With an estimated annual incidence of VTE at 0.5% among cancer patients, compared to 0.1% in the general population, these statistics underscore the markedly heightened vulnerability to venous thrombogenesis among individuals with malignant diseases [4]. In recent years, the link between cancer physiopathology and VTE has attained increasing attention, leading to the emergence of the concept of cancer-associated thrombosis (CAT). This constitutes a bidirectional relationship, wherein both cancer and VTE serve as mutual risk factors for each other, as well as exert a significant impact on each other's mortality rates [5]. Compared to VTE in the general population, CAT seems to be a distinct and more complex disorder. Mechanistically, tumour cells produce pro-coagulant, anti-fibrinolytic and pro-inflammatory substances, which trigger pro-thrombotic and pro-inflammatory cascades leading to venous thrombogenesis [4].

The pathogenesis of VTE, both in the general population and among cancer subjects, can be explained by the Virchow Triad, which integrates three promoting factors: stasis of blood flow, blood hypercoagulability, and endothelial dysfunction (ED) (Figure 1) [4,6]. ED refers to an alteration in the normal function of the endothelial cells (ECs) lining the interior of blood vessels. The first step of this disorder is endothelial stimulation (type I activation) followed by delayed endothelial activation (type II activation), both reversible upon cessation of the stimulus. In advanced stages, ED also encompasses EC apoptosis and necrosis, which leads to endothelial detachment, giving rise to circulating endothelial cells (CECs) [7]. Apart from contributing to VTE, ED is a critical factor in the pathogenesis of other cardiovascular and metabolic diseases, including atherosclerosis, hypertension, coronary artery disease, chronic heart failure, peripheral artery disease, diabetes, and chronic renal failure [8–10]. Importantly, a relevant bridge to cancer is also formed as the pro-inflammatory state of ED promotes tumour growth and progression. Additionally, the inhibition of vasodilation (characteristic of ED) supports cell proliferation and anti-apoptotic responses, reinforcing its association with cancer [11,12].

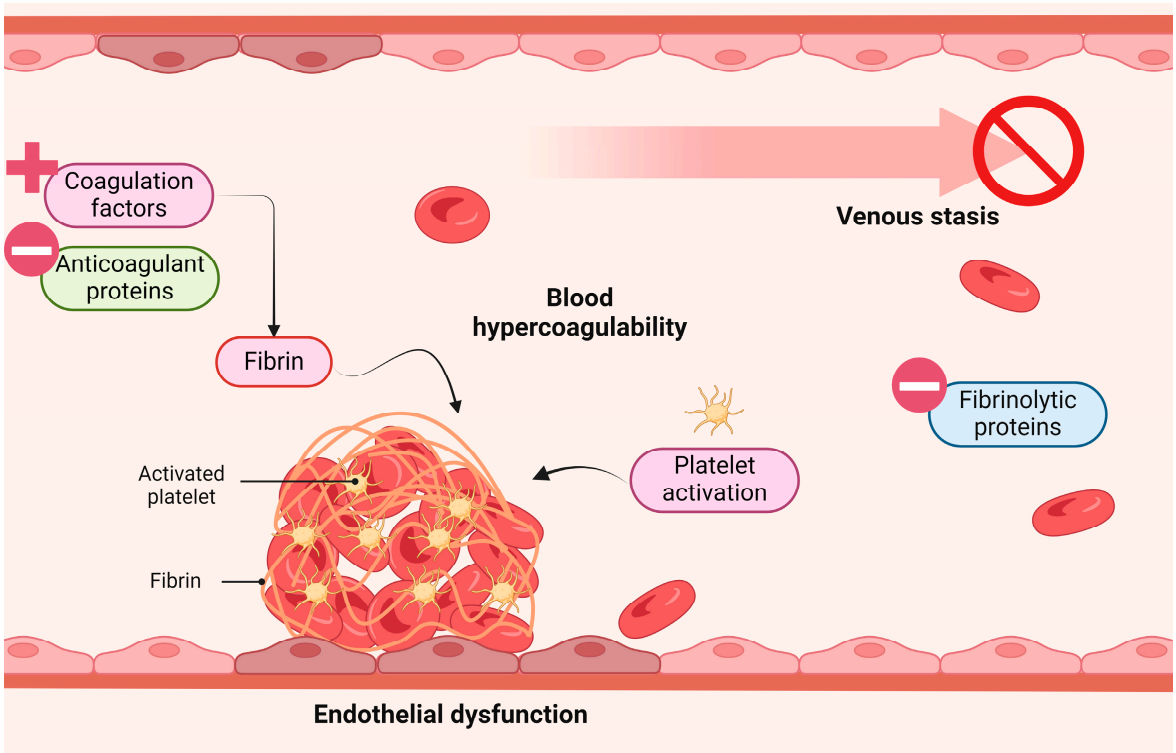

Figure 1. Virchow triad. Venous thrombosis is suggested to be promoted by three important factors: blood hypercoagulability, venous stasis and endothelial dysfunction. Figure created with Biorender.com (accessed on 13 April 2024).

Like VTE, ED presentation can also be influenced by genetic polymorphisms, which are DNA variations present in greater than 1% of a given population. These variations include single-nucleotide polymorphisms (SNPs), copy number variations (CNVs), insertions and deletions (Indels), and tandem repeats [13,14]. Starting with SNPs, they represent genetic alterations characterised by single nucleotide substitutions [15]. CNVs arise from the deletion or duplication of DNA segments, ranging from kilobases to megabases, leading to a varied number of copies of a specific DNA sequence on homologous chromosomes [16]. In contrast, indels are small insertions or deletions of nucleotides in the DNA sequence [17]. Regarding tandem repeats, these genetic variations comprise repetitive DNA sequences spanning one or more nucleotides within both coding and non-coding regions. Their classification depends on the length of the repeated sequence. Namely, simple sequence repeats (SSRs), also known as short tandem repeats (STRs), consist of short repeating units (two to six nucleotides). SSRs represent a subset of a variable number of tandem repeats (VNTRs), characterised by their varying lengths [18]. Overall, genetic polymorphisms have the potential to modulate gene expression, disrupt gene function and alter protein-coding sequences, thereby affecting protein levels and/or activity. Consequently, these DNA variations can modulate the susceptibility to several disorders, including ED and its manifestations (e.g., VTE) [14].

Considering the roles of ED in cancer-related thrombogenesis and tumorigenesis, it is important to explore how genetic determinants implicated in this disorder could aid in the identification of at-risk populations and pinpoint potential therapeutic targets for a more personalised treatment in Oncology [14]. Given the implications for clinical application, this thorough narrative review seeks to delve into the influence of genetic variations linked to ED on tumorigenesis and cancer patient's prognosis. The review concentrates on examining polymorphisms in pivotal ED-related genes such as *endothelial nitric oxide synthase* (*eNOS*), *endothelin 1* (*EDN1*), *angiotensin I converting enzyme* (*ACE*), *angiotensinogen* (*AGT*), *coagulation factor 2* (*F2*), *selectin P* (*SELP*), *selectin E* (*SELE*), *von Willebrand factor* (*VWF*), *intercellular adhesion molecule 1* (*ICAM1*), and *vascular cell adhesion molecule 1* (*VCAM1*). A thoughtful research was conducted by reviewing the PubMed database's occurrences until 6th March 2024 using different combinations of keywords: "SNP", "SNPs", "polymorphism", "polymorphisms", "cancer", "*eNOS*", Endothelin-1", "ET-1", "Angiotensin II", "AGT", "ACE" and "Angiotensin Converting Enzyme", "F2", "Prothrombin", "SELP", "P-selectin", "SELE", "E-selectin", "E-selectin", "Von Willebrand factor", "VWF", "CD54", "ICAM1", "ICAM-1", "VCAM1", "VCAM-1" and "CD106". Only studies with significant associations were selected. Additionally, matching publications were cross-referenced and screened for pertinent bibliographic references. Studies were excluded if the polymorphisms lacked functional relevance and/or the associations were observed solely considering specific therapeutic interventions. A total of 826 articles underwent review, resulting in the selection of 149 papers that met the inclusion and exclusion criteria.

2. Vascular Homeostasis

Gatekeeping the integrity of ECs is crucial for human well-being and illness management as these cells are responsible for vascular tone regulation, haemostasis and thrombosis control, cellular adhesion, smooth muscle cell proliferation, and vascular inflammation [6,19]. Under physiological conditions, ECs mediate multiple anti-coagulant and anti-platelet aggregation processes, restricting coagulation to only vascular sites where needed, thus preventing disseminated thrombotic complications (Figure 2) [20]. They do so by continuously expressing and/or releasing components that block platelet activity (prostacyclin (prostaglandin I2 (PGI2), nitric oxide (NO) and ectonucleoside triphosphate diphosphohydrolase-1 (E-NTPDase1)), inhibit coagulation progression (antithrombin III (ATIII)), thrombomodulin (TM) and tissue factor pathway inhibitor 1 (TFPI1)) and promote fibrinolysis (urokinase-type plasminogen activator (u-PA) and tissue-type plasminogen activator (tPA)) [21–24]. In opposition, when the vascular endothelium is disrupted, ECs

shift to an adhesive, pro-inflammatory and pro-clotting phenotype [21]. The initial response to vascular damage is vasoconstriction, which slows the blood flow to prevent excessive blood loss. This mechanism is the basis for blood coagulation [25]. Parallelly, induced by pro-inflammatory cytokines, ECs express cell-surface adhesion molecules essential for the recruitment and attachment of immune cells against possible pathogens [26]. Once an immune barrier is established and haemostasis is restored, a process of vascular repair is initiated [27]. However, under pathological conditions (such as hyperhomocysteinaemia, hyperglycaemia, hypercholesterolaemia and accumulation of NO inhibitors), the endothelium loses its natural properties, shifting towards reduced vasodilation, inflammation and thrombosis, which overall defines ED [28]. Essentially, a dysfunctional endothelium arises when there is an imbalance between endothelium-derived relaxation (EDRFs) and constriction (EDCFs) factors. The former includes NO, prostacyclin and endothelium-derived hyperpolarizing factor (EDHF), while endothelin (ET-1), angiotensin II (Ang II), thrombin and thromboxane A2 (TXA2) represent EDCFs [6]. It is worth noting that prostacyclin, EDHF and TXA2 fall outside the scope of this review.

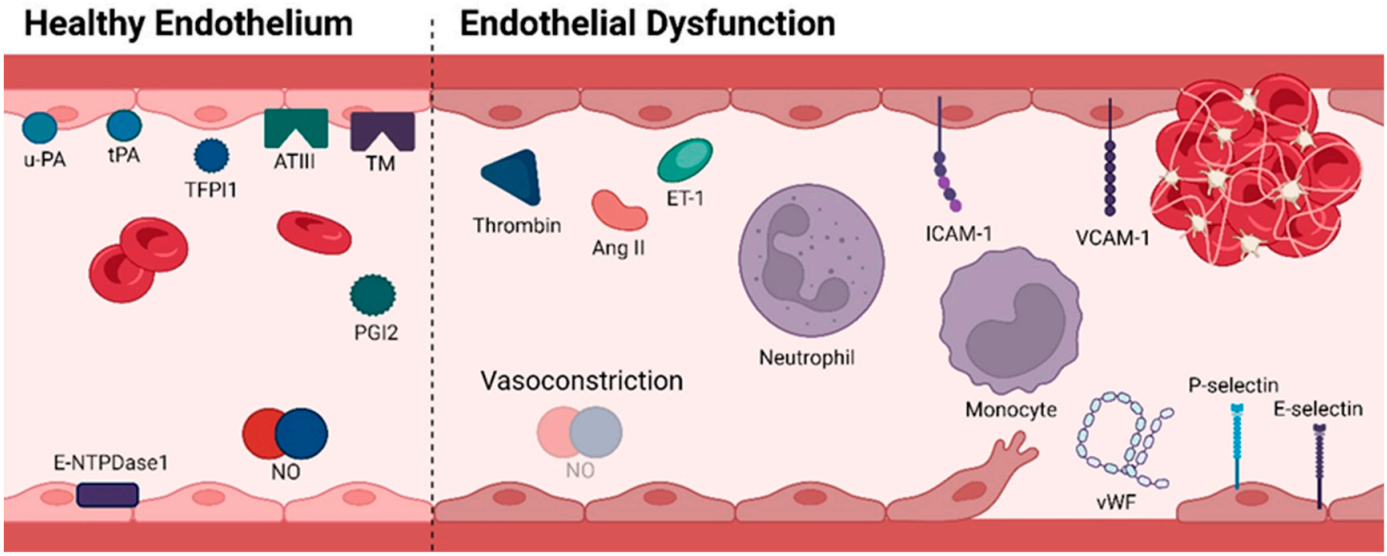

Figure 2. Molecular profile of a healthy endothelium characterized by anti-thrombotic mechanisms (**left**); Molecular profile of endothelial dysfunction with the display of adhesive, pro-inflammatory, and pro-clotting properties (**right**). Abbreviations: ATIII, antithrombin III; ET-1, Endothelin-1; E-NTPDase1, ectonucleoside triphosphate diphosphohydrolase-1; ICAM-1, intercellular adhesion molecule-1; NO, nitric oxide; PGI2, prostaglandin I2; TFPI1, tissue factor pathway inhibitor 1; TM, thrombomodulin; tPA, tissue-type plasminogen activator; u-PA, urokinase-type plasminogen activator; VCAM-1, vascular cell adhesion molecule-1; vWF, von Willebrand factor. Figure created with Biorender.com (accessed on 13 April 2024).

Nitric Oxide (NO)

The most well-defined EDRF is NO, which is the protector of the vascular wall, with anti-inflammatory and antioxidant properties [6,10,29,30]. In addition to being a potent vasodilator gatekeeping endothelial health, NO is also a concentration-dependent cell proliferation and apoptosis modulator, as low relative concentrations appear to promote cell proliferation and anti-apoptotic responses and vice-versa [12,31,32]. Furthermore, as previously mentioned, it possesses platelet inhibitor properties [21]. Consequently, a decrease in NO bioavailability usually occurs in tandem with a pro-thrombotic and pro-inflammatory cascade and a less flexible endothelial state [6,28,30].

Deficiencies of NO can be caused by alterations in nitric oxide synthase 3 (NOS3), also known as eNOS [33]. The linkage between NO, ED and cancer is reinforced by the cell proliferation and anti-apoptotic pathways activated when this vasodilator is reduced,

which enables tumour spread, angiogenesis and metastasis [34]. According to the literature, there is a total of 168 genetic polymorphisms located within or close to *NOS3*, of which three have emerged as particularly noteworthy due to their shared impact on reducing NO levels and their established associations with cancer: rs2070744, rs1799983, and rs869109213 (Table 1) [33].

Regarding rs2070744 (T>C), this intronic variant consists of the substitution of thymine (T) to cytosine (C) at codon -786 in the 5′-flanking region of *NOS3*. This alternation leads to diminishing gene promoter activity, with consequent serum NO reduction, enabling proliferation pathways and inhibiting tumour cell apoptosis [12,35,36]. To date, many meta-analyses associated rs2070744 with the risk of overall cancer, particularly among individuals of Caucasian descent. Further clustering by cancer type links the C allele (the minor and also ancestral allele) to a higher risk of breast (BC), prostate (PCa), and bladder (BLCA) cancers [33,36–41]. In a study regarding oral squamous cell carcinoma (OSCC), individuals with the TC genotype faced an increased likelihood of progressing to an advanced clinical stage (III/IV) compared to those with the TT genotype [42]. Similarly, BC patients carrying the C allele exhibited a significantly higher risk of disease recurrence or mortality compared to those with the TT genotype [12]. Carriers of the C allele are also more prone to colorectal cancer (CRC) [43]. Likewise, the CC genotype was associated with a five-fold increased risk for gastric cancer (GC) development [34]. On the other hand, regarding PCa in the Turkish population, the C allele was found to be less prevalent among patients compared to healthy controls, suggesting a protective effect of this allele [44,45]. Moreover, the C allele among uterine cervical cancer (UCC) patients was associated with a reduced risk of advancing to later disease stages, invasion of the parametrium, and metastasis to pelvic lymph nodes [46].

Another important polymorphism of *NOS3* is rs1799983 (G>T). This missense SNP leads to a glutamate-to-aspartate (Glu-to-Asp) substitution at position 298 in exon 7 [36,47]. This variant is linked to a substantial reduction in eNOS enzyme activity. Notably, this SNP exhibited associations with PCa, BLCA, and BC [33,36,38–40,45]. Concerning BC development, the effect of the T allele (minor allele) depends on the menopause status, exerting a protective effect on postmenopausal women [48]. Contrariwise, the presence of this allele was associated with an increased susceptibility to CRC [43]. Different populational studies have suggested a negative effect of the T allele concerning CRC, BLCA and endometrial carcinoma (EMCA) [47,49,50]. Furthermore, two investigations have identified noteworthy associations between this SNP and lung cancer (LC) and urothelial cell carcinoma (UC), respectively. The first one demonstrated a link to EGFR-mutated lung adenocarcinomas, particularly with exon 19 in-frame deletions, suggesting this SNP as a potential predictor of tumour invasiveness and responsiveness to therapy [51]. The second study denoted a propensity for increased tumour size development among UC patients carrying the rs1799983 T allele [52].

The variant rs869109213 (4a/b) is a VNTR polymorphism (27 bp) in the intron 4 of *NOS3* consisting of two alleles: 4a (with four repeats) and 4b (with five repeats). This DNA variation is linked to modified eNOS activity, affecting the baseline production of plasma NO. Specifically, the 4a allele carries present lower NO levels compared to those with the 4b/4b genotype [53]. Similarly to rs2070744, rs869109213 is associated with overall cancer risk in Caucasians, particularly PCa [33,37,38,40]. The 4a allele is linked to a higher risk of CRC in an early-onset (under 60 years old) [54]. Moreover, the heterozygous genotype (4a/4b) was found to be more common in BC patients when compared with a control group [55]. In the context of LC, a noteworthy association was also identified, however, linking the 4b allele to a higher risk for disease development [56]. In another study, the rs869109213 4a/4b genotype in combination with the rs2070744 CC genotype, as well as the C/G/4b haplotype for rs2070744/rs1799983/rs869109213 exhibited a 21-fold and 11-fold escalation in the risk of developing OSCC, respectively [57].

Table 1. Epidemiological studies on the role of *NOS3* polymorphisms on cancer susceptibility and progression.

First Author (Year)	Country/Ethnic Background	Population Characteristics	Study Design	Studied Polymorphisms
Choi et al. (2006) [12]	South Korea/Unclear	1039 BC patients 995 non-cancer controls	Cohort study	rs2070744 rs1799983
Lu et al. (2006) [41]	USA/non-Hispanic Caucasian	421 BC patients 423 non-cancer controls	Case–control study	rs2070744 rs1799983 rs869109213
Yeh et al. (2009) [54]	Taiwan/Taiwanese	727 CRC patients 736 healthy controls	Case–control study	rs2070744 rs1799983 rs869109213
Oztürk et al. (2011) [47]	Turkey/Turkish	89 EMCA patients 60 total hysterectomy controls	Case–control study	rs1799983 rs869109213
Arıkan et al. (2012) [49]	Turkey/Turkish	84 CRC patients 99 healthy controls	Case–control study	rs1799983
Jang et al. (2013) [43]	South Korea/Korean	528 CRC patients 509 healthy controls	Case–control study	rs2070744 rs1799983 rs869109213
Ramírez-Patiño et al. (2013) [55]	Mexico/Mexican	429 BC patients 281 healthy women	Case–control study	rs869109213
Wu et al. (2014) [36]	Mixed	4169 cancer cases and 4185 controls (rs2070744) 7775 cancer cases and 7817 controls (rs1799983) 3430 cancer cases and 3842 controls (rs869109213)	Meta-analysis	rs2070744 rs1799983 rs869109213
Zhang et al. (2014) [37]	Mixed	4220 cancer cases and 4016 controls (rs2070744) 8359 cancer cases and 9575 controls (rs1799983) 2873 cancer cases and 3338 controls (rs869109213)	Meta-analysis	rs2070744 rs1799983 rs869109213
Gao et al. (2015) [33]	Mixed (meta-analysis) Han Chinese (case–control)	873 BC patients 1034 healthy women (case–control)	Meta-analysis Case–control study	rs2070744 rs1799983 rs869109213
Krishnaveni et al. (2015) [34]	India/South Indian	150 GC patients 150 healthy controls	Case–control study	rs2070744
Polat et al. (2015) [50]	Turkey/Turkish	75 BLCA patients 143 healthy controls	Case–control study	rs2070744 rs1799983 rs869109213
Diler et al. (2016) [45]	Turkey/Turkish	84 PCa patients 116 healthy controls	Case–control study	rs2070744 rs1799983 rs869109213
Polat et al. (2016) [39]	Turkey/Turkish	50 PCa patients 50 healthy controls	Case–control study	rs2070744 rs1799983 rs869109213
Chen et al. (2018) [48]	Taiwan/Taiwanese	139 premenopausal and 144 postmenopausal BC patients 100 premenopausal and 100 postmenopausal healthy women	Case–control study	rs2070744 rs1799983 rs869109213
Huang et al. (2018) [51]	Taiwan/Taiwanese	277 LC patients	Cohort study	rs2070744 rs1799983
Su et al. (2018) [42]	Taiwan/Taiwanese	1044 OSCC patients 1200 healthy controls	Case–control study	rs2070744 rs1799983
Hung et al. (2019) [46]	Taiwan/Taiwanese	117 UCC patients 95 patients with cervical precancerous lesions 330 healthy controls	Case–control study	rs2070744 rs1799983

Table 1. *Cont.*

First Author (Year)	Country/Ethnic Background	Population Characteristics	Study Design	Studied Polymorphisms
Nan et al. (2019) [38]	Mixed	41 case–control studies	Meta-analysis	rs2070744 rs1799983 rs869109213
Tsay et al. (2019) [52]	Taiwan/Taiwanese	431 UC patients 862 healthy controls	Case–control study	rs2070744 rs1799983
Abedinzadeh et al. (2020) [40]	Mixed	4464 cancer cases and 4347 controls (rs1799983) 589 cancer cases and 789 controls (rs869109213) 588 cancer cases and 692 controls (rs2070744)	Meta-analysis	rs2070744 rs1799983 rs869109213
Carkic et al. (2020) [57]	Serbia/Serbian	50 OSCC patients 110 healthy controls	Case–control study	rs2070744 rs1799983 rs869109213
Koçer et al. (2020) [56]	Turkey/Turkish	107 LC patients 100 healthy controls	Case–control study	rs1799983 rs869109213
Balci et al. (2023) [44]	Turkey/Unclear	48 PCa patients 42 biopsy individuals 27 healthy controls	Case–control study	rs2070744

Abbreviations: BC, breast cancer; BLCA; bladder cancer; CRC, colorectal cancer; EMCA, endometrial carcinoma; GC, gastric cancer; LC, lung cancer; PCa, prostate cancer; OSCC, oral squamous cell carcinoma; UC, urothelial cell carcinoma; UCC, uterine cervical cancer; USA, United States of America.

3. Consequences of ED

As previously mentioned, ET-1, Ang II, and thrombin constitute EDCFs. Impaired vasodilation from ED implies the release and action of these vasoconstrictors inhibiting the anti-inflammatory and anti-coagulant attributes of healthy ECs [6]. Various genetic variations have been documented to influence the expression and/or activity of these molecules during ED. Consequently, investigating the role of these polymorphisms holds promise for elucidating the molecular mechanisms underlying ED and may offer novel therapeutic targets for managing ED and controlling cancer growth and progression (Table 2).

3.1. Endothelin-1 (ET-1)

ET-1, a potent vasoconstrictor peptide, is crucial in regulating vascular tone and endothelial function. Genetic variations within the ET-1 gene (*EDN1*) have been suggested to modulate the protein expression and/or activity, impacting vascular homeostasis and predisposing individuals to ED-related pathologies [58,59].

The association between *EDN1* and cancer has been documented with three distinct SNPs: rs5370 (C>A), a missense variation encoding an aspargine (N) instead of a lysine (K) [60]; rs1800541 (T>G), an alteration located at the gene promotor; and rs2070699 (G>T), an intronic variation [59]. Concerning rs5370, the presence of the A allele (forward strand) was associated with papillary thyroid cancer in individuals over 40 years, notably in men [61]. In contrast, the minor alleles of rs1800541 and rs2070699 seem to confer protection regarding osteosarcoma prognosis. Likewise, the rs1800541 G allele was associated with a reduced risk for pulmonary metastasis and chemoresistance. For the latter condition, the rs2070699 T allele was also related to a decreased risk [58,62]. Concordantly, a haplotype with a greater risk for hormone-refractory PCa was established with the ancestral alleles—rs1800541 T and rs2070699 G [63].

3.2. Angiotensin II (Ang II)

Ang II plays a pivotal role in vascular homeostasis. It is synthesized from angiotensinogen, encoded by the *AGT* gene, and further processed by the angiotensin-converting enzyme (ACE), encoded by a gene with the same name [64–68]. Variations in these genes may influence Ang II levels, impacting endothelial function.

An indel (I/D) polymorphism in *ACE* intron 16 is extensively documented in the literature. Current evidence indicates that the D allele carriers have increased ACE expression and activity [64,69]. Furthermore, this indel is referred to as influencing the risk of cancer [70–72]. Regarding GC, the DD genotype was associated with a higher risk of gastric tumorigenesis, lymph node metastasis and advanced clinical stages [64,69,73–75]. However, according to a 2015 meta-analysis, these associations are only observed in population-based studies, as the I allele seems to confer an increased risk to GC in hospital-based studies [76]. The *ACE* Indel is also referred to as contributing to the PCa risk in Latino and Asian ethnic groups [77,78]. Moreover, DD carriers also present more advanced stages of the disease and early-age diagnostics [79–83]. The same genotype seems to be related to an increased risk of oral precancerous lesions in betel quid chewers and OSCC and lymph node metastasis in men [84,85]. In disagreement, the II genotype was also associated with a three-fold risk of OSCC development [86–88]. The I allele could also be linked to the occurrence of EMCA (particularly in normotensive women under 63 years old), endometriosis and leiomyomas [67,89]. Regarding CRC, this indel is considered to have a gender-dependent effect. While D male carriers present larger tumours than those with the II genotype, females carrying the DD genotype have higher survival rates when compared to I carriers [90]. Another study showed an increased risk of early relapse and higher TNM stage for I allele carriers [91]. Contrariwise, the D allele correlates with poor differentiation and lymph node metastasis [92,93]. Regarding LC development, the I allele has a negative effect, particularly when combined with smoking habits in the older population [94–96]. In opposition, DD carriers have an increased susceptibility to squamous cell carcinoma development and smoking-related cancer death [97,98]. On the other hand, compared to the other genotypes, heterozygous individuals are suggested to have a raised non-small cell lung cancer (NSCLC) predisposition [99]. Moreover, the ID genotype seems to be related to adrenal incidentalomas compared to the controls [100]. Additionally, II and DD genotypes confer susceptibility to pancreatic cancer (PC) and chronic pancreatitis, respectively [101]. Regarding BC, the I allele carriers show a decreased risk [66,102–105]. Those with the I allele have a greater expression of HER2 [106], while DD genotype carriers present a better disease-free survival rate [106,107]. On the contrary, the DD genotype seems to be concomitant with worse prognostic factors in premenopausal women and decreased cancer-free survival in postmenopausal women [108–111]. Regarding hepatocellular carcinoma (HCC) progress, two different studies demonstrated conflicting results, showing decreased and increased risk for DD carriers, respectively [112,113]. Additionally, the ID genotype is also suggested to exert a protective role against BC [114]. The D allele presence is associated with an increased risk of uterine leiomyoma [115]; gall bladder carcinoma (GBC) [116], and glioma [117], while the homozygous D genotype is associated with increased susceptibility to glioma development and low overall survival [118,119]; renal cell carcinoma (RCC) [120]; BLCA [121]; basal cell carcinoma (BCC) [122–124]; poor leukaemia survival rates [125]; lymph nodes metastasis in laryngeal cancer (LaC) [126]; pituitary adenomas development and progression [127]; and EMCA [128]. Regarding cancer patients' prognosis, while a direct impact is not described, the *ACE* ID genotype was associated with higher haemoglobin levels and overall lower fat mass and muscle strength in patients at advanced stages compared to the II genotype [129].

The *ACE* rs4291 (T>A) is an alteration in the promoter region referred to confer susceptibility to cancer in the Asian and Caucasian ethnic groups and specifically to BC in Latino populations [68,103]. This SNP seems to be in linkage disequilibrium (LD) with the *ACE* indel among women. Those with the low-activity alleles (A and I of each polymorphism, respectively) showed decreased BC risk [66]. Moreover, women present a greater risk of BC when carrying the *ACE* rs4291 T allele and rs4343 (G>A) G allele concurrently [130].

The D allele carriers aged between 36 to 54 years old are reported to present a greater risk of BC, whereas a reduced risk was associated with the II/AG and II/CC of *ACE* indel/*AGT* rs699 (A>G) and *ACE* indel/*AGT* rs4762 (G>A) haplotypes, respectively [131].

The *AGT* rs699 and rs4762 are two missense variants. The first one implicates a replacement of methionine by threonine in exon 2, whereas rs4762 represents a substitution of threonine with methionine at position 174 in the amino acid sequence [130]. Furthermore, nodal spread in intestinal-type GC correlates with the combined expression of this Indel and angiotensin II receptor type I (AT1R) [132]. Also, regarding *Helicobacter pylori* (HP) status, negative individuals seem to present a decreased risk of GC [133], whereas, in the HP-positive group with atrophy, the ID genotype seems to confer an increased risk [134].

The G allele of *AGT* rs699 was suggested to be associated with an increased risk of BCC [135], BLCA [136] and CRC [137]. However, in a 2023 study of the same population, the heterozygous genotype was significantly more frequent in the BCC patient group than in the controls [122]. The AA genotype was associated with decreased disease-free survival of BC [138]. Furthermore, the rs699 in the *AGT* gene showed reduced prevalence in Australian EMCA women [65]. Moreover, several *AGT* SNPs, namely rs7539020 (C>T), rs3889728 (C>G), rs3789662 (A>G), rs1326889 (C>T), and rs2493137 (T>C), are suggested to modulate renal cell cancer susceptibility among hypertensive or overweight individuals [139]. Regarding CRC, a greater prevalence of the AG/AG haplotype for rs699/rs5051 (C>T) was found in men [140].

3.3. Thrombin

Thrombin, a serine protease originating from prothrombin (its inactive precursor, encoded by *coagulation factor 2* (*F2*)), is a key player in haemostasis, coordinating platelet aggregation and blood coagulation. Its impact extends to diverse cellular functions, including chemotaxis, proliferation, extracellular matrix remodelling, and cytokine release. Just as Factor V Leiden, *F2* rs1799963 (G>A) is well-established as a risk factor for VTE [141,142]. This SNP is located at nucleotide position 20210 within the promoter region. The A allele leads to elevated levels of prothrombin, consequently increasing thrombin generation and favouring thrombogenesis [3,143]. Female carriers of the *F2* rs1799963 A allele with gynaecological malignancies are suggested to show advanced cancer stages at the time of surgery [144]. The rs1799963 AG genotype was also associated with a five-fold increased risk for HCC in subjects with *hepacivirus* [145]. Regarding CRC, whereas an increased susceptibility was correlated with the AA genotype, the AG genotype presented 30% less predisposition for its development [146,147].

Table 2. Epidemiological studies on the role of polymorphisms in vasoconstrictors-encoding genes on cancer susceptibility and progression.

First Author (Year)	Country/Ethnic Background	Population Characteristics	Study Design	Studied Polymorphisms
Hajek et al. (2003) [125]	Czech Republic/ Unclear	25 leukaemia patients	Cohort study	*ACE* indel
Koh et al. (2003) [66]	Singapore/Singaporean	189 BC patients 671 healthy controls	Nested case–control study	*ACE* indel *ACE* rs4291
Tormene et al. (2003) [144]	Italy/Unclear	52 women operated for gynaecological malignancy 198 women operated for gynaecological non-malignant disease	Case–control study	*F2* rs1799963
Freitas-Silva et al. (2004) [67]	Portugal/Portuguese	70 EMCA patients 101 healthy controls	Case–control study	*ACE* indel
Medeiros et al. (2004) [80]	Portugal/Portuguese	170 PCa patients 30 healthy controls	Case–control study	*ACE* indel
Chung et al. (2005) [84]	Taiwan/Taiwanese	61 OPL betel quid chewers 61 asymptomatic betel quid chewers	Case–control study	*ACE* indel

Table 2. *Cont.*

First Author (Year)	Country/Ethnic Background	Population Characteristics	Study Design	Studied Polymorphisms
Ebert et al. (2005) [73]	Germany/Caucasian	88 GC patients 145 healthy controls	Case–control study	*ACE* indel
González-Zuloeta Ladd et al. (2005) [111]	Netherland/Unclear	4878 female postmenopausal total participants 114 BC patients	Cohort study	*ACE* indel
Goto et al. (2005) [134]	Japan/Japanese	454 GC patients 202 healthy controls	Case–control study	*ACE* indel
Röcken et al. (2005) [75]	Germany/Unclear	113 GC patients 189 healthy controls	Case–control study	*ACE* indel
Arima et al. (2006) [98]	Japan/Japanese	937 total participants 176 subjects died of malignant neoplasm	Cohort study	*ACE* indel
Yaren et al. (2006) [109]	Turkey/Turkish	44 BC patients 46 healthy premenopausal women	Case–control study	*ACE* indel
Carl-McGrath et al. (2007) [69]	Germany/Unclear	45 GC patients	Cohort study	*ACE* indel
González-Zuloeta Ladd et (2007) [138]	Netherlands/Unclear	203 BC cases 3323 controls	Case–control study	*AGT* rs699
Hsieh et al. (2007) [89]	Taiwan/Taiwanese	120 UL patients 125 endometriosis patients 128 healthy controls	Case–control study	*ACE* indel
Röcken et al. (2007) [132]	Germany/Unclear	100 GC patients	Cohort study	*ACE* indel
Röcken et al. (2007) [90]	Germany/Unclear	141 CRC patients 189 healthy controls	Case–control study	*ACE* indel
Vairaktaris et al. (2007) [86]	Greece/Greek and German	60 OSCC patients 153 healthy controls	Case–control study	*ACE* indel
Yaren et al. (2007) [108]	Turkey/Turkish	57 BC patients 52 healthy controls	Case–control study	*ACE* indel
Yigit et al. (2007) [83]	Turkey/Turkish	48 PCa patients 51 healthy controls	Case–control study	*ACE* indel
van der Knaap et al. (2008) [110]	Netherland/Unclear	7679 participants *	Cohort study	*ACE* indel
Alves Corrêa et al. (2009) [114]	Brazil/Brazilian	101 BC patients 307 healthy controls	Case–control study	*ACE* indel
Harman et al. (2009) [100]	Turkey/Turkish	50 adrenal mass patients 30 healthy controls	Case–control study	*ACE* indel *NOS3* rs1799983
Loh et al. (2009) [71]	Mixed/Asian and Caucasian	203 case–control studies	Meta-analysis	*ACE* indel
Vairaktaris et al. (2009) [88]	Mixed/Greek and German	162 OSCC patients 168 healthy controls	Case–control study	*ACE* indel
Vasků et al. (2009) [140]	Czech Republic/Czech	102 CRC patients 101 healthy controls	Case–control study	*AGT* rs699 *AGT* rs5051
Vigano et al. (2009) [129]	Canada/Unclear	72 GC and NSCLC advanced cancer patients	Cohort study	*ACE* indel
Andreotti et al. (2010) [139]	Mixed	1035 RCC patients 777 controls	Case–control study	*AGT* rs7539020 *AGT* rs3889728 *AGT* rs3789662 *AGT* rs1326889 *AGT* rs2493137

Table 2. *Cont.*

First Author (Year)	Country/Ethnic Background	Population Characteristics	Study Design	Studied Polymorphisms
Nacak et al. (2010) [95]	Turkey/Turkish	25 LC patients 165 healthy controls	Case–control study	*ACE* indel
Namazi et al. (2010) [106]	Iran/Iranian	70 BC patients 70 healthy controls	Case–control study	*ACE* indel
Srivastava et al. (2010) [116]	India/North Indian	233 GBC patients 260 non-cancer controls	Case–control study	*ACE* indel
Liu et al. (2011) [92]	China/Chinese	241 CRC patients 299 non-cancer controls	Case–control study	*ACE* indel
Lukic et al. (2011) [101]	Serbia/Unclear	45 PC patients 55 chronic pancreatitis patients 128 healthy controls	Case–control study	*ACE* indel
De Martino et al. (2011) [120]	Austria/Unclear	10 RCC patients 173 healthy controls	Case–control study	*ACE* indel
Mendizábal-Ruiz et al. (2011) [104]	Mexico/Mexican	65 BC patients 40 benign breast disease patients	Case–control study	*ACE* indel *AGT* rs699
Vossen et al. (2011) [147]	Germany/German	1801 CRC patients 1853 healthy controls	Case–control study	*F2* rs1799963
Dević Pavlić et al. (2012) [97]	Croatia/Croatian	308 LC patients 353 healthy controls	Case–control study	*ACE* indel
Correa-Noronha et al. (2012) [128]	Brazil/Brazilian	74 EMCA patients and 228 controls 83 EOC patients and 297 controls	Case–control study	*ACE* indel
Huhn et al. (2012) [137]	Mixed/Czech and German	1025 Czech cancer cases and 787 Czech controls 1798 German cancer cases and 1810 German controls	Case–control study	*AGT* rs699
Liu et al. (2012) [85]	Taiwan/Taiwanese	205 male oral cancer patients 88 Oral precancerous lesions patients 120 healthy controls	Case–control study	*ACE* indel
Wang et al. (2012) [79]	China/Han Chinese	189 PCa patients 290 non-cancer controls	Case–control study	*ACE* indel
Altas et al. (2013) [127]	Turkey/Unclear	21 hypophyseal adenoma patients 20 healthy controls	Case–control study	*ACE* indel
Fishchuk et al. (2013) [131]	Ukraine/Ukrainian	131 BC patients 102 healthy women	Case–control study	*ACE* indel *AGT* rs699 *AGT* rs4762
Namazi et al. (2013) [107]	Iran/Iranian	110 BC patients	Prospective study	*ACE* indel
Vylliotis et al. (2013) [87]	Mixed/Greek and German	160 OSCC patients 168 healthy controls	Case–control study	*ACE* indel *F2* rs1799963 *AGT* rs699
Yapijakis et al. (2013) [123]	Greece/Greek	92 BCC patients 103 healthy controls	Case–control study	*ACE* indel
Yuan et al. (2013) [112]	China/Chinese	293 HCC patients 384 healthy controls	Case–control study	*ACE* indel *NOS3* rs869109213

Table 2. *Cont.*

First Author (Year)	Country/Ethnic Background	Population Characteristics	Study Design	Studied Polymorphisms
Zang et al. (2013) [62]	China/Han Chinese	260 pulmonary metastatic stage III osteosarcoma patients 260 matched pulmonary metastatic stage IIB osteosarcoma patients	Case–control study	*EDN1* rs1800541 *EDN1* rs2070699 *EDN1* rs5370
Phukan et al. (2014) [94]	India/Northeast Indian	151 LC patients 151 controls	Case–control study	*ACE* indel
Xie et al. (2014) [82]	Mixed	7025 cancer cases 34,911 controls	Meta-analysis	*ACE* indel
Zhang et al. (2014) [70]	Mixed	5007 cancer cases 8173 controls	Meta-analysis	*ACE* indel
Zhou et al. (2014) [58]	China/Han Chinese	350 Paediatric osteosarcoma patients with <90% tumour necrosis 350 matched osteosarcoma patients with ≥90% tumour necrosis	Case–control study	*EDN1* rs1800541 *EDN1* rs2070699 *EDN1* rs5370
Ding et al. (2015) [130]	China/Han Chinese	606 BC patients 633 healthy controls	Case–control study	*ACE* rs4291 *ACE* rs4343
Gan et al. (2015) [133]	Mixed/Asian and Caucasian	1480 GC cases 3773 non-cancer controls	Meta-analysis	*ACE* indel
Lian et al. (2015) [119]	China/Chinese	800 glioma patients 800 healthy controls	Case–control study	*ACE* indel
Pabalan et al. (2015) [74]	Mixed	1459 cancer cases 2581 controls	Meta-analysis	*ACE* indel
Wei et al. (2015) [64]	Mixed	1392 cancer cases 2951 controls	Meta-analysis	*ACE* indel
Yang et al. (2015) [76]	Mixed/Asian and White	2903 GC cases 10,833 controls	Meta-analysis	*ACE* indel
Zha et al. (2015) [113]	China/Dai Chinese	210 HCC patients 206 healthy controls	Case–control study	*ACE* indel
Hanafy et al. (2016) [145]	Egypt/Egyptian	280 HCV-infected patients 100 healthy controls	Case–control study	*F2* rs1799963
Pringle et al. (2016) [65]	Australia/Mixed	184 type 1 endometrioid cancer women 153 healthy controls	Case–control study	*AGT* rs699 *ACE* rs4291
Ali et al. (2017) [121]	Pakistan/Pakistani	200 BLCA patients 200 healthy controls	Case–control study	*ACE* indel
Baghad et al. (2017) [146]	Morocco/Moroccan	76 CRC patients 182 healthy controls	Case–control study	*F2* rs1799963
Marques et al. (2017) [91]	Brazil/Admixed Brazilian	140 CRC patients 140 non-cancer controls	Case–control study	*ACE* indel
Xu et al. (2017) [63]	China/Han Chinese	234 PCa patients with HRPC within six years after androgen deprivation therapy 234 matched PCa patients without HRPC within six years after androgen deprivation therapy	Case–control study	*EDN1* rs1800541 *EDN1* rs2070699 *EDN1* rs5370
Zheng et al. (2017) [93]	China/Chinese	146 CRC patients 106 healthy controls	Case–control study	*ACE* indel
Moghimi et al. (2018) [102]	Mixed	2846 BC cases 9299 controls	Meta-analysis	*ACE* indel
Pandith et al. (2018) [118]	India/Indian	12 glioma patients 141 non-cancer controls	Case–control study	*ACE* indel
Peddireddy et al. (2018) [99]	India/South Indian	246 NSCLC patients 250 healthy controls	Case–control study	*ACE* indel *NOS3* rs869109213

Table 2. *Cont.*

First Author (Year)	Country/Ethnic Background	Population Characteristics	Study Design	Studied Polymorphisms
Singh et al. (2018) [105]	India/North Indian	161 BC patients 152 healthy women	Case–control study	*ACE* indel
Wang et al. (2018) [77]	Mixed	1098 PCa cases 12,960 controls	Meta-analysis	*ACE* indel
Aydin et al. (2019) [61]	Turkey/Unclear	113 PTC patients 185 healthy controls	Case–control study	*EDN1* rs1800541 *EDN1* rs5370
Benenemissi et al. (2019) [117]	Algeria/Algerian	36 glioma patients 195 healthy controls	Case–control study	*ACE* indel
Keshavarzi et al. (2019) [115]	Iran/Iranian	202 UL patients 211 healthy controls	Case–control study	*ACE* indel
Papaggelopoulos et al. (2019) [135]	Greece/Greek	190 BCC patients 99 healthy controls	Case–control study	*AGT* rs699
Xiao et al. (2019) [68]	Mixed	8 case–control studies	Meta-analysis	*ACE* rs4291
Banerjee et al. (2021) [96]	India/North Indian	154 LC patients 205 healthy controls	Case–control study	*ACE* indel
Dastgheib et al. (2021) [103]	Mixed	35 case–control studies	Meta-analysis	*ACE* indel *ACE* rs4291
Koronellos et al. (2021) [124]	Greece/Greek	104 BCC patients 111 healthy controls	Case–control study	*ACE* indel
Samara et al. (2021) [136]	Greece/Caucasian	73 BLCA patients 73 healthy controls	Case–control study	*AGT* rs699
Du et al. (2022) [81]	Mixed	817 PCa patients 917 controls	Meta-analysis	*ACE* indel
Said et al. (2022) [78]	Tunisia/Tunisian	124 PCa patients 143 healthy controls	Case–control study	*ACE* indel
Kumbul et al. (2023) [126]	Turkey/Unclear	44 LaC patients 61 healthy controls	Case–control study	*ACE* indel
Yapijakis et al. (2023) [122]	Greece/Greek	100 BCC patients 103 healthy controls	Case–control study	*AGT* rs699 *ACE* indel

* Cancer specification not available. Abbreviations: BC, breast cancer; BCC, basal cell carcinoma; BLCA, bladder cancer; CRC, colorectal cancer; EMCA, endometrial cancer; EOC, epithelial ovarian cancer; GBC, gall bladder cancer; GC, gastric cancer; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HRPC, hormone-refractory prostate cancer; LaC, laryngeal cancer; LC, lung cancer; NSCLC, non-small cell lung cancer; OSCC, oral squamous cell carcinoma; OPL, oral precancerous lesions; PC, pancreatic cancer; PCa, prostate cancer; PTC, papillary thyroid cancer; RCC, Renal Cell Carcinoma; UL, uterine leiomyoma.

4. Adhesion Molecules

The ability of ECs to induce vasodilation mediated by NO is the most common way to measure endothelial function using the flow-mediated vasodilation (FMD) test. However, this ultrasound imaging-based test has poor reproducibility due to operational and patient cardiac function variability [6,8,148]. In this context, the use of ED-circulating biomarkers may present a more reliable alternative [7,26].

In addition to endothelial permeability, decreased NO bioavailability induces the expression of important adhesion molecules, namely P-selectin, E-selectin, vWF, ICAM-1 and VCAM-1, which facilitate cell-to-cell interaction, promoting the migration and adhesion of leucocytes [149]. These molecules are indicative of the pro-thrombotic environment that precedes the development of cardiovascular conditions, with the extent of ED serving as a

valuable prognostic indicator [7,8,26]. These well-characterized markers can be measured in circulation with readily available commercial immunoassays, exceeding at least four indicative criteria of an ideal marker/test [149]. Specifically, they demonstrate ease of use, cost-effectiveness, operator independence, and superior reproducibility. Nevertheless, as not all markers exhibit high sensitivity, combining various methodologies, such as microparticles and CECs, would be advocated [150].

Given the implications of ED in cancer pathways, exploring genetic polymorphisms within genes encoding for adhesion molecules takes on paramount significance (Table 3).

4.1. P-Selectin

P-selectin is a product of *SELP*, and a member of the selectin protein family found on the outer membrane of activated ECs. The crucial function of P-selectin in facilitating leukocyte recruitment to the site of inflammation has been proposed as a driver of tumour aggressiveness and a contributing factor to the onset of cancer cachexia [151]. Two *SELP* SNPs are highlighted in this context: the intergenic variant rs3917647 (G>A) and the missense SNP rs6136 (T>G). Regarding the former, the GG and AA genotypes were linked to high and low P-selectin plasma levels, respectively. The unfavourable nature of the rs3917647 GG genotype in patients with head and neck cancer (HNC) suggests this alternation as a protective factor against cancer malnutrition and potential cachexia [151]. Likewise, the rs6136 T allele was linked to increased expression of *SELP* mRNA, while the G allele was associated with reduced serum P-selectin levels. The evidence pinpoints the rs6136 T allele as a protective factor for cancer cachexia in HNC patients, as well [151,152]. These findings were concordant in locally advanced and metastatic PC [153].

4.2. E-Selectin

E-selectin, encoded by *SELE*, is another significant member of the selectin family. This protein plays a fundamental role in promoting tumour angiogenesis and cancer progression, facilitating interactions between cancer cells and endothelial monolayers, especially during the metastatic process, underlining its importance in early metastasis stages [154]. Concordantly, some tumours, particularly BC and CRC, were found to express E-selectin ligands [155,156].

Four SNPs of *SELE* are described in the literature. Starting with rs5361 (T>G), this missense polymorphism causes the exchange of an uncharged serine with a positively charged arginine within the epidermal growth factor domain. This alteration possesses the capability to alter ligand affinity [156]. The ancestral T allele was demonstrated to be a protective factor against BC [157,158]. The negative impact of the SNP G allele is confirmed among GC patients, with the allele being associated with disease development and poor prognosis [159,160]. The same allele was also associated with an increased risk of PC and ovarian cancer (OC) and a worsened prognosis for BC patients [161–163]. Likewise, this allele was also linked to an elevated risk of relapse, metastasis and mortality among CRC patients [154–156]. A meta-analysis suggested rs5361 as an overall cancer risk factor among Caucasian and Asian ethnic groups [164]. In the same fashion as rs5361, rs5362 (A>G), rs5367 (A>G), and rs5368 (G>A) variant alleles were demonstrated to be associated with an increased risk of BC. Among them, only rs5368 causes a change in the amino acid sequence from histidine to tyrosine [154].

4.3. Von Willebrand Factor (vWF)

Besides P-selectin, vWF emerges as one of the molecules meeting the criteria for robust biomarkers of ED [148]. Only one *VWF* polymorphism is identified to influence cancer pathways, namely the intronic SNP rs73049469 (C>A). The variant A allele is linked to lower *VWF* expression at the transcription levels, and it is shown to be associated with worse overall survival among NSCLC patients [165,166].

4.4. ICAM-1

This cell adhesion molecule, a member of the Ig-superfamily, serves as a crucial factor in the recruitment, activation, and facilitation of leukocyte functions at inflammatory sites. As a result of proteolytic cleavage, its soluble form becomes notably elevated in both inflammatory and malignant conditions [167,168]. Six polymorphisms within *ICAM1* have been associated with tumorigenic roles: rs5498 (A>G), rs1799969 (G>A), rs281437(C>T), rs1437 (A>G), rs923366 (C>T) and rs3093030 (C>T).

The rs5498 polymorphism represents a missense variant within exon 6, giving rise to an amino acid substitution from glutamine (E) to lysine (K). This shift affects the splicing of *ICAM1* mRNA, leading to a higher concentration of the soluble protein [168–170]. Beyond its well-established association with atherosclerosis, this SNP has garnered attention for its diverse implications in various cancer types. However, its effects remain the subject of debate, as it can either confer risk or protection depending on the tumour [171]. Namely, the homozygous minor allele (G allele) genotype was associated with an increased risk of cancer in the Asian ethnic group but decreased risk in Europeans [172,173]. The G allele was also related to an increased risk of OSCC but diminished for CRC and melanoma [168,173,174]. Furthermore, this allele seems to increase the susceptibility to CRC, especially for older individuals [175–178]. When in homozygosity, the presence of the lysine correlates with well-differentiated CRC [179]. The G variant allele is also suggested to be a protective factor for cervical adenocarcinoma [169]. In GC, the AA genotype was associated with an augmented risk and a higher likelihood of metastasis compared to the G allele [168,180]. Likewise, the A allele showed an association with advanced stages and poorer survival rates among NSCLC patients [181]. In opposition, the G allele was related to the risk of OC (especially for those with first-degree hereditary tumours or precocious menarche), UC development and invasive stages, HCC in smokers, PCa development, precancerous lesions in uterine cervical carcinogenesis and gliomas development [182–187].

The rs1799969 SNP results in an exchange of a glycine for an arginine in exon 4, at codon 241, with the ability to alter the functional activity of ICAM-1 and consequently grant the capacity to recruit and activate immune cells. The variant A allele was shown to be associated with higher cancer risk [172,188]. The presence of the A allele was linked to gliomas and CRC and the GA genotype to BC [168,177]. The A/G haplotype for rs1799969/rs5498 is associated with an increased risk of BC, while it is suggested to exert a protective effect on primary brain tumours [167,168].

The variant T alleles of rs281437 and rs923366 *ICAM1* SNPs, two 3′ UTR variants, were associated with increased and reduced risk of primary HCC, respectively [189]. Nonetheless, the CC genotype of rs281437 seems to be related to a higher risk of BC development when compared to the other genotypes [190]. As for rs1437, a 3′ UTR located SNP, the variant G allele was linked to OC augmented risk [191].

Although the functional consequence of rs3093030 is unknown, a protective effect of the variant T allele was found for UCC and primary HCC [169,189]. In contrast, in a different population, women seem to be more susceptible to invasive uterine cervical carcinogenesis when the variant allele is in homozygosity. The C/G, T/A and T/G haplotypes of rs3093030/rs5498 were shown to increase the risk of precancerous lesions and invasive UCC [186]. For UCC, a reduced risk C/T/G haplotype of rs281432(G>C)/rs3093030/rs5498 was discovered [169].

4.5. VCAM-1

Similarly to ICAM-1, VCAM-1 acts in the immune-endothelial communication system, contributing to inflammatory and immune processes and cancer metastasis [192]. Numerous *VCAM1* polymorphisms have been linked to cancer. The intronic variation rs3176861 (C>T) currently has an unknown functional consequence. Nevertheless, the presence of the T allele relates to a substantial decrease in the odds of developing lymphedema after BC surgery [193]. The polymorphism rs1041163 (T>C) is an intergenic variant located within exon 9. The SNP C allele was deemed a protective factor for non-Hodgkin lym-

phoma (NHL) [194]. In opposition, for the synonymous variant rs3176879 (G>A), the variant allele seems to confer susceptibility to recurrent BLCA in patients submitted to immunotherapy [195,196].

Table 3. Epidemiological studies on the role of ED-related adhesion molecules gene polymorphisms on cancer susceptibility and progression.

First Author (Year)	Country/Ethnic Background	Population Characteristics	Study Design	Studied Polymorphisms
Chen et al. (2006) [185]	USA/African-American	286 PCa patients 391 healthy controls	Case–control study	*ICAM1* rs5498
Theodoropoulos et al. (2006) [177]	Greece/Greek	222 CRC patients 200 healthy controls	Case–control study	*ICAM1* rs5498 *ICAM1* rs1799969
Alessandro et al. (2007) [156]	Italy/Caucasian	172 CRC patients 80 healthy controls	Case–control study	*SELE* rs5361
Arandi et al. (2008) [167]	Iran/southern Iranian	276 BC patients and 235 healthy controls 264 BC patients and 200 healthy controls	Case–control study	*ICAM1* rs1799969 *ICAM1* rs5498
Burim et al. (2009) [187]	Brazil/Unclear	158 astrocytoma patients and 162 controls	Case–control study	*ICAM1* rs5498 *ICAM1* rs1799969
Wang et al. (2009) [179]	China/Chinese	87 CRC patients 102 non-CRC controls	Case–control study	*ICAM1* rs5498 *ICAM1* rs1799969
Wang et al. (2009) [194]	Jamaica/Jamaican	395 NHL patients 309 non-NHL controls	Case–control study	*VCAM1* rs1041163
Panoussopoulos et al. (2010) [161]	Greece/Unclear	80 PC patients 160 healthy controls	Case–control study	*SELE* rs5361
Naidu et al. (2011) [157]	Malaysia/Malaysian	387 BC patients 252 healthy controls	Case–control study	*SELE* rs5361
Tan et al. (2012) [152]	Scotland and Canada/Unclear	775 cancer patients 101 validation cohort patients	Cohort study	*SELP* rs6136 *ICAM1* rs281432
Thanopoulou et al. (2012) [181]	Greece/Unclear	203 NSCLC patients 175 healthy controls	Case–control study	*ICAM1* rs5498
Tian et al. (2012) [180]	China/Chinese	332 GC patients 380 healthy controls	Case–control study	*ICAM1* rs5498
Xia et al. (2012) [159]	China/Chinese	311 GC patients 425 controls	Case–control study	*SELE* rs5361
Kontogianni et al. (2013) [163]	Greece/Unclear	261 BC patients 480 healthy controls	Case–control study	*SELE* rs5361
Liarmakopoulos et al. (2013) [160]	Greece/Greek	88 GC patients 480 healthy controls	Case–control study	*SELE* rs5361
Lin et al. (2013) [174]	Taiwan/Unclear	595 OSCC patients 561 healthy controls	Case–control study	*ICAM1* rs5498
Miaskowski et al. (2013) [193]	Mixed	155 BC patients with lymphedema 387 BC patients without lymphedema	Case–control study	*VCAM1* rs3176861
Yilmaz et al. (2013) [168]	Turkey/Turkish	92 primary brain tumour patients 92 healthy controls	Case–control study	*ICAM1* rs5498 *ICAM1* rs1799969
Avan et al. (2014) [153]	Italy/Unclear	303 locally advanced or metastatic PC	Cohort study	*SELP* rs6136
Cai et al. (2014) [182]	China/Northern Han Chinese	408 OC patients 520 healthy controls	Case–control study	*ICAM1* rs5498

Table 3. *Cont.*

First Author (Year)	Country/Ethnic Background	Population Characteristics	Study Design	Studied Polymorphisms
Cheng et al. (2014) [164]	Mixed/Asian and Caucasian	1675 cancer patients 2285 controls	Meta-analysis	*SELE* rs5361
Wang et al. (2014) [183]	Taiwan/Taiwanese	279 UC patients 279 healthy controls	Case–control study	*ICAM1* rs5498
Andrew et al. (2015) [196]	USA/Caucasian	783 UC patients	Cohort study	*VCAM1* rs3176879
Cheng et al. (2015) [172]	Mixed	4844 cancer patients 5618 healthy controls	Meta-analysis	*ICAM1* rs5498 *ICAM1* rs1799969
Tang et al. (2015) [173]	Mixed	5528 cancer patients and 6173 controls for rs5498 3138 cancer cases and 3699 controls for rs3093030	Meta-analysis	*ICAM1* rs5498 *ICAM1* rs3093030
Chen et al. (2016) [184]	Taiwan/Taiwanese	305 HCC patients 613 healthy controls	Case–control study	*ICAM1* rs5498
Ghazy et al. (2016) [191]	Egypt/Unclear	60 mixed-type OC patients 20 healthy controls	Case–control study	*ICAM1* rs1437
Golnarnik et al. (2016) [158]	Iran/Northern Iranian	100 BC patients 120 healthy controls	Case–control study	*SELE* rs5361
Lu et al. (2016) [162]	China/Chinese	687 OC patients 687 healthy controls	Case–control study	*SELE* rs5361
Novikov et al. (2016) [178]	Russia/unclear	49 CRC patients 30 BC patients 33 controls	Case–control study	*ICAM1* rs5498
Sun et al. (2016) [186]	Taiwan/Taiwanese	91 UCC patients 63 patients with precancerous lesions 290 healthy controls	Case–control study	*ICAM1* rs5498 *ICAM1* rs3093030 *ICAM1* rs281432
Zhang et al. (2016) [188]	Mixed	4608 cancer patients 4913 controls	Meta-analysis	*ICAM1* rs1799969 *ICAM1* rs3093030
Liu et al. (2017) [175]	China/Chinese	195 CRC patients 188 healthy controls	Case–control study	*ICAM1* rs5498
Powrózek et al. (2019) [151]	Poland/Unclear	62 HNC patients	Cohort study	*SELP* rs3917647 *SELP* rs6136
Qian et al. (2019) [166]	Mixed European/Caucasian	948 NSCLC patients	Cohort study	*VWF* rs73049469
Ghazy et al. (2020) [190]	Egypt/Egyptian	40 BC patients 40 healthy controls	Case–control study	*ICAM1* rs281437
Feng et al. (2021) [169]	China/Northern Chinese Han	488 UCC patients 684 patients with cervical precancerous lesions 510 healthy females	Case–control study	*ICAM1* rs5498 *ICAM1* rs3093030 *ICAM1* rs281432
He et al. (2021) [189]	China/Unclear	290 HCC patients 290 healthy controls	Case–control study	*ICAM1* rs281437 *ICAM1* rs923366 *ICAM1* rs3093030
Qiu et al. (2021) [176]	Mixed	1003 CRC patients 1303 healthy controls	Case–control study	*ICAM1* rs5498 *ICAM1* rs3093030
Zakariya et al. (2022) [154]	Iraq/Iraqi	60 BC patients 40 healthy controls	Case–control study	*SELE* rs5361 *SELE* rs5368 *SELE* rs5362

Abbreviations: BC, breast cancer; CRC, colorectal cancer; GC, gastric cancer; HCC, hepatocellular carcinoma; HNC, head and neck cancer; OC, ovarian cancer; OSCC, oral squamous cell carcinoma; PCa, prostate cancer; PC, pancreatic cancer; NHL, non-Hodgkin lymphoma; NSCLC, non-small cell lung carcinoma; UC, urothelial cell carcinoma; UCC, uterine cervical cancer.

5. ED-Related Proteins and Cancer Hallmarks

Overall, despite data inconsistencies, ED-related genetic polymorphisms appear to impact the tumorigenic process. Literature suggests a complex relationship between ED and cancer, with the former playing a multifaceted role in the risk and progression of the latter [11,197,198]. By examining the specific contributions of proteins associated with ED to different hallmarks of cancer, the molecular mechanisms underlying tumour formation and dissemination can be further dissected. This knowledge lays the groundwork for validating the role of ED-related genetic polymorphisms (Table 4) in cancer biology, enriching our comprehension of the intricate interplay between the two conditions.

From a protein standpoint, as already discussed, NO can exert a dual role in cancer, modulating cell proliferation and apoptosis in a concentration-dependent manner, with low concentrations promoting cell proliferation and anti-apoptotic responses and vice versa [12]. Furthermore, NO dysregulation can foster a pro-thrombotic and pro-inflammatory environment, which promotes tumour proliferation, limits immune response and facilitates angiogenesis and metastasis [199]. Impaired vasodilation raises the action of vasoconstrictors, such as ET-1, Ang II and thrombin. Besides thrombosis, these molecules play a role in tumorigenesis by promoting cellular proliferation, angiogenesis, and metastasis. Regarding ET-1, it triggers sustained proliferative signalling, apoptosis evasion, and migration and invasion, through its receptor ET_A [61,200]. Additionally, it promotes angiogenesis by fibroblast stimulation, resulting in remodelling and deposition of the extracellular matrix (ECM) and consequent release of angiogenic factors [200]. Similarly to ET-1, Ang II is a mitogenic and pro-angiogenic vasoconstrictor that promotes tumour angiogenesis and inflammation through the upregulation of vascular endothelial growth factor (VEGF) and prostaglandins [201]. Moreover, upon binding to its receptors, AT1R and AT2R, Ang II activates signalling pathways of cell proliferation. Interestingly, AT1R (unlike AT2R) exhibits anti-apoptotic properties [202,203]. Lastly, thrombin can stimulate DNA synthesis and upregulate several growth and angiogenesis-related genes by activating the protease-activated receptor 1 (PAR-1) pathway [204,205]. Furthermore, by promoting the overexpression of adhesion molecules, these vasoconstrictors may facilitate immune evasion and tumour invasion and metastasis [206,207]. Indeed, the levels of selectins and CAMs in the serum of cancer patients correlate with tumour dissemination [208]. Furthermore, vWF, in combination with thrombin, contributes to the formation of tumour-platelet aggregates, enabling tumour cell survival and their successful metastasis [198]. In summary, proteins associated with ED play a pivotal role in cancer initiation and progression, contributing to various hallmarks of the disease (Figure 3). Thus, polymorphisms within their coding genes may contribute to alterations in cancer susceptibility and progression in patients carrying these variants. Understanding the impact of these DNA variations might enhance our comprehension of cancer development and open avenues for targeted interventions to disrupt these pathways and hinder disease development and progression.

Table 4. Characterization of ED-related Genetic Polymorphisms via Ensembl.

Gene	Polymorphism	Substitution	Ancestral Allele	Global MAF (MA)	Most Severe Consequence
NOS3	rs2070744	C>G	C	23% (C)	Intron variant
	rs1799983	T>G/A	G	18% (T)	Missense variant
	rs869109213	VNTR	NA	NA	Intron variant
EDN1	rs5370	G>T	G	25% (T)	Missense variant
	rs1800541	T>G	T	28% (G)	Regulatory region variant
	rs2070699	G>C/T	G	36% (T)	Intron variant

Table 4. *Cont.*

Gene	Polymorphism	Substitution	Ancestral Allele	Global MAF (MA)	Most Severe Consequence
ACE	Indel	Indel	NA	NA	-
	rs4291	T>A/G	A	35% (T)	Regulatory region variant
	rs4343	G>A	A	36% (G)	Synonymous variant
AGT	rs699	A>G	G	29% (A)	Missense variant
	rs4762	G>A	G	10% (A)	Missense variant
	rs1326889	C>T/A	T	22% (C)	Intron variant
	rs281432	C>G	G	48% (C)	Intron variant
	rs2493137	T>C	T	48% (T)	Intron variant
	rs5050	T>C/G	G	18% (G)	5 prime UTR variant
	rs5051	C>G/A/T	T	29%(C)	5 prime UTR variant
	rs7539020	C>T	C	49%(C)	Intron variant
	rs3889728	C>G/T	C	30%(T)	Intron variant
	rs3789662	A>G	A	34%(G)	3 prime UTR variant
F2	rs1799963	G>A	G	<1% (A)	3 prime UTR variant
SELP	rs3917647	G>A	G	46% (A)	Intergenic variant
	rs6136	T>C/G	T	4% (G)	Missense variant
SELE	rs5361	T>G/A	T	5% (G)	Missense variant
	rs5362	A>G	G	5% (G)	Non-coding transcript exon variant
	rs5367	A>G	A	5% (G)	Splice region variant
	rs5368	G>A	G	15% (A)	Missense variant
VWF	rs73049469	C>A	C	13% (A)	Intron variant
ICAM1	rs1437	A>G/T	G	37% (G)	3 prime UTR variant
	rs5498	A>G	A	36% (G)	Missense variant
	rs1799969	G>A	G	6% (A)	Missense variant
	rs281437	C>G/T	C	26% (T)	3 prime UTR variant
	rs923366	C>T/A	T	35% (T)	3 prime UTR variant
	rs3093030	C>T	C	32% (T)	Non-coding transcript exon variant
VCAM1	rs3176861	C>T	C	20% (T)	Intron variant
	rs3176879	G>A	A	13% (G)	Synonymous variant
	rs1041163	T>C	T	18% (C)	Intergenic variant

Abbreviations: MA, minor allele; MAF, minor allele frequency; NA, no data available; VNTR, variable number tandem repeats.

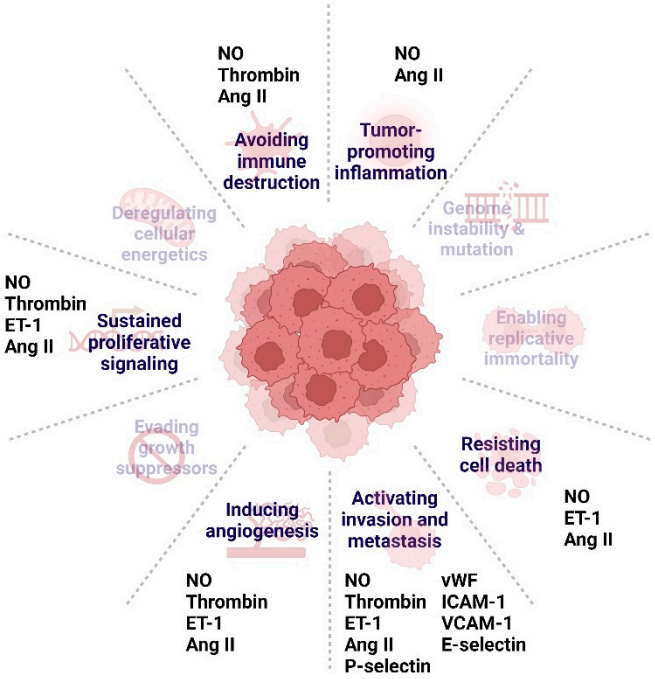

Figure 3. Endothelial dysfunction-related proteins and their respective contribution to cancer hallmarks. Hallmarks depicted with transparency denote the absence of documented endothelial dysfunction-related proteins contributing to them. Abbreviations: Ang II, Angiotensin II; ET-1, Endothelin-1; ICAM-1, intercellular adhesion molecule-1; NO, nitric oxide; VCAM-1, vascular cell adhesion molecule-1; vWF, von Willebrand factor. Figure created with Biorender.com (accessed on 13 April 2024).

6. Conclusions

In this comprehensive narrative review, genetic polymorphisms implicated in ED were evaluated for their impact on cancer susceptibility and progression among distinct ethnic groups. Briefly, our examination reveals a tendency for BC as a primary focus in studies concerning multiple ED-related genetic polymorphisms, closely followed by CRC. Notably, BC has garnered widespread attention across various countries, particularly in China, where research efforts have been particularly pronounced. China also stands out for its extensive study of distinct SNPs, a trend also observed in Turkey. Moreover, among the polymorphisms examined, the *ACE* indel distinguishes itself as a frequently studied variant, suggesting its potential relevance in the tumorigenic process. The polymorphisms under study exhibit a clear tendency to modulate cancer risk. The *ACE* indel stands out with over 50 risk associations for cancer, especially for BC, followed by PCa. Across all cancer models, the D allele commonly emerges associated with risk, while inversely the I allele is reported to confer protection. Additionally, as many risk associations for CRC were found for *ICAM1* rs5498 as for the *ACE* indel, despite being much less studied in the general population. Controversy surrounds this SNP, with the G allele being the most frequently associated with cancer risk and also the most frequently associated with protection. Protection against osteosarcoma was solely associated with *EDN1* SNPs, while PCa was mainly studied in relation to *NOS3* SNPs. Overall, BC, PCa, and CRC were the main tumour models in studies concerning ED-related genetic polymorphisms. Most of the variants seem to have a context-dependent role varying upon specific tumour and patient characteristics. It should be noted that many of the conducted studies exhibited significant flaws, such as failing to specify the risk/protection genotype, or not confirming the results with subsequent validation studies. Hence, future studies with larger sample sizes are warranted to elucidate these complexities. Since proteins associated with ED contribute to several hallmarks of cancer, a better understanding of these DNA variations holds promise for the development of precision medicine approaches to improve cancer patient care and

enhance clinical outcomes. Inclusively, as a wide range of molecules play relevant roles in ED, the implications of other downstream proteins in tumorigenesis should be dissected. Likewise, given the central role of ED in CAT, the influence of the studied polymorphisms in CAT pathogenesis needs to be clarified.

Author Contributions: Conceptualisation, I.G.d.M.; Methodology, I.G.d.M.; Writing—Original Draft Preparation, I.G.d.M.; Writing—Review & Editing, I.G.d.M., V.T., D.P. and R.M.; Supervision, V.T., D.P. and R.M.; Funding Acquisition, V.T. and R.M. All authors have read and agreed to the published version of the manuscript.

Funding: This study was funded by the Portuguese Oncology Institute of Porto (IPO Porto) (CI-IPOP-22-2015) and Fundação para a Ciência e Tecnologia (FCT). V.T. is a Ph.D. scholarship holder (Grant reference: 2020.08969.BD) supported by FCT, co-financed by European Social Funds (FSE) and national funds of MCTES. The institutions had no implications for writing and publishing this manuscript.

Data Availability Statement: The data presented in this study are available on request from the corresponding author.

Acknowledgments: The authors would like to thank Ministério da Saúde de Portugal, Portuguese Oncology Institute of Porto (IPO Porto), Portuguese League Against Cancer (NRNorte) and Fundação para a Ciência e Tecnologia (FCT).

Conflicts of Interest: The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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