MINI-REVIEW

Do VDR Gene Polymorphisms Contribute to Breast Cancer?

Fouzia Shaikh*, Saeeda Baig, Qamar Jamal

Abstract

Breast cancer is the first or second leading cancer among females across the globe. A large number of studies have been conducted to assess any relationship between vitamin D receptor (VDR) gene polymorphisms and breast cancer development. Epidemiological studies have indicated that ethnic traits exhibited by a group of people with a common ancestry and culture, alter the link between VDR gene and breast cancer. It has been hypothesized that VDR polymorphisms have the capacity to impact both on incidence of breast cancer occurrence and to predict its outcome. A survey was here conducted to assess and compare the impact of vitamin D receptor gene polymorphisms Fok1, Bsm1, Taq1, Apa1 and poly (A) on development of breast cancer. Information was obtained from electronic databases including PubMed and Google Scholar for articles published during the period from 1996 to 2015. This search was achieved by using the terms "genetics", "breast cancer", "VDR gene", "polymorphisms". However, due to inconsistent results, no conclusive statements could be presented about the significance of the VDR genotype as far as the development of breast carcinoma is concerned'

Keywords: Breast cancer - VDR gene - polymorphisms - impact on development

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Introduction

Breast cancer stands the second most leading cancer among females around the globe (Du et al., 2014). It is the most frequently diagnosed cancer in Pakistan, with highest mortality rate in Asian population after the Jews from Israel. Karachi, has the maximum rate of breast carcinoma (38%) in female among the registered cancer cases (Iqbal MuN, 2015). The incidence rate of carcinoma of breast is comparable with highest risk regions in the world (Bhurgri et al., 2006). The overall risk of developing carcinoma of breast makes it the most frequent malignancy among the white females with estimates of 1 in 12 British and 1 in 8 American women (Khan et al., 2014).

The risk of breast cancer has been evaluated in relation to vitamin D receptor gene polymorphisms in number of studies because of evidence of regulatory effects on angiogenesis in malignancy (Banerjee, 2003; Giovannucci, 2005). The VDR was discovered in 1969 (Norman, 2008). Discovery of VDR expression in diverse normal human tissues cells has widened the perceived scope of the vitamin D. Vitamin D endocrine system is involved in several processes besides bone formation, like innate immunity, apoptosis, cell proliferation and differentiation, and mediates the anticancer activities of vitamin D via the Vitamin D Receptor (VDR) (Raimondi et al., 2009).

Female breast cancer occurrence is strongly age related, suggesting a link with hormonal status. Contrary to international studies, Pakistani women between 20 to 35 years of age are frequently reported in Karachi hospitals with advanced stages of breast cancer with large lesions, and are prone to develop metastasis with bad prognosis (Bhurgri et al., 2006; Naveed et al., 2014). In the UK between the years 2009 and 2011, approximately 80% of breast cancer cases were diagnosed above the age of 50 years, and about 24% in women aged 75 years and above, based on Breast cancer incidence statistics (2013).

The objectives of this search were to determine the effect of polymorphisms of the frequent SNPs in VDR (Fok1, Bsm1, Taq1, Apa1, Poly A) and the evolution of the breast carcinoma.

Discussion

Breast carcinoma is the cumulative result of various environmental and genetic alterations. Mechanism of breast cancer development is still not well established, but published data has identified the anti-cancerous functions of 1, 25 (OH)2 vitamin D3 in some malignancies (Iqbal MuN, 2015).

VDR Receptors in Mammary Glands: The calcitriol receptor also known as vitamin D receptor (VDR) is an intracellular hormone receptor, and a member of the nuclear class II receptor family of broadly known two groups and peculiarly binds to biologically effective form of vitamin D, 1,25-dihydroxyvitamin D (Raimondi et al., 2009). One family comprises of the estrogen, androgen, progesterone and mineralocorticoid receptors, while the other has thyroid (THR), vitamin D (VDR), retinoic acid (RAR), peroxisome proliferator-activated, and retinoid X receptors (RXR) (Ditsch et al., 2012). More than 36

*Ziauddin University, Karachi, Pakistan *For correspondence: fouziashaikh@live.com*

types of tissue in the body have expression of Vitamin D Receptor like breast, bone, prostate, gut, activated B and T lymphocytes, monocytes, and keratinocytes with distinct mitochondrial, membrane, cytosol and peri-nuclear localization (Gombart, 2006; Silvagno et al., 2010). In normal mammary gland VDR is expressed in epithelial, stromal, and immune cells and is controlled in the epithelial compartment during hormonal changes during puberty and pregnancy (Zinser, 2004). Figure1

Several studies show that genetic variance can affect an individual receptivity to dietary or pharmacological interventions (Welsh, 2007). SNPs are widely dispersed through the human genome and because of great levels of inconsistency, have gained reputation as genetic markers helpful in attaining disease vulnerability in complicated genetic characteristics (Collins et al., 1997).

VDR Gene and Breast Cancer: The molecular location of VDR receptor gene is on the long arm of chromosome 12 (12q12-q14) and includes not less than 11 exons that stretch 60 kb of DNA with five promoter regions (Zhou, 2009). Figure 2

VDR Genotypes and Polymorphisms: VDR gene has more than 470 single-nucleotide polymorphisms (SNPs) (Zmuda et al., 2000; Mc Cullough et al., 2009). The important and intensively studied single nucleotide polymorphisms (SNPs) of VDR are, FokI (rs2228570), VDR-BsmI (rs1544410), VDR-TaqI (rs731236), VDR-ApaI (rs7975232) and Poly(A) (Alimirah et al., 2011). Over the years, most of The molecular epidemiological studies have been done to relate the associations of important VDR polymorphisms with breast cancer (Curran et al., 1999; Ingles et al., 2000; Bretherton et al., 2001; Hou et al., 2002; Buyru et al., 2003; Guy et al., 2004; Sillanpaa et al., 2004; Chen et al., 2005; Lowe et al., 2005; John et al., 2007; Mc Cullough et al., 2007; Trabert et al., 2007; Abbas et al., 2008; Barroso et al., 2008; Sinotte et al., 2008; Chakraborty et al., 2009; McKay et al., 2009; Rollison et al., 2011; Huang et al., 2012; Mishra et al., 2013; Du et al., 2014

Ethnic Variation in VDR Gene Polymorphisms: VDR gene show sequence level dissimilarity in the different populations, both at the 5' and 3' termini (Trabert et al., 2007). Epidemiological studies have frequently reported that the fundamental features of the population with varying ethnicities can alter the links between VDR gene polymorphisms and carcinoma. The ethnic groups were categorized into (Caucasian, Asian, and African-American) by Wang et al., 2013. Review by Uitterlinden AG et al. (2004) and Kostner et al. (2009) showing ethnic variation. Indian subcontinent where populations/ethnicity are quite different, not much information regarding the allelic variations of VDR (Fok1) gene is available (Bid, 2003). Figure 3

The VDR gene FokI polymorphism and breast cancer risk: The Fork1 restriction enzyme occupies a polymorphic site in exon 2 of the VDR gene (Yang B et al., 2014). Genotypes are identified as FF, Ff and ff for the VDR-FokI polymorphisms. The capital letter indicates the absence and small letter the existence of the restriction site (Uitterlinden et al., 2004). The alliance of Fok1 polymorphism with breast cancer reveals that Fok1 is the most controversial SNP. VDR FF allele in combination with long-Poly A was reported to be a possible risk factor in the UK in the study by Guy et al. (2004), whereas Chen et al (2005) found VDR ff to be a risk factor in the Nurses' Health study in the USA. In the year 2009, the meta-analysis was done by Tang et al, which shows a strong connection between VDR ff and raised risk of breast cancer in European females. Study by Shahbazi et al. (2013) on Iranian breast cancer patients could not establish statistically significant affiliation between Fok1 genotypes and breast carcinoma. However in 2013, Mishra et al, proposed that VDR FokI f allele may share in the evolution of breast carcinoma in young age and F allele in tumor progression and patient prognosis.

The VDR gene BsmI polymorphism and breast cancer risk: The Bsm1 polymorphism is situated at the 3' end of the VDR gene. It does not affect the quality of the translated VDR protein (Raimondi Set al., 2009). Genotypes assigned are BB, Bb, bb for the BsmI polymorphisms. The second most frequent studied VDR polymorphism-BsmI, which after analysis showed mixed results. Some studies reported its association with breast cancer development (Guy et al., 2004; Shahbazi et al., 2013).The study by Lowe et al. (2005) shows strong association between the VDR bb genotype and breast cancer. Studies by other researchers did not reveal any significant difference in the prevalence of the BsmI polymorphism in breast cancer patients (Chen et al., 2005;

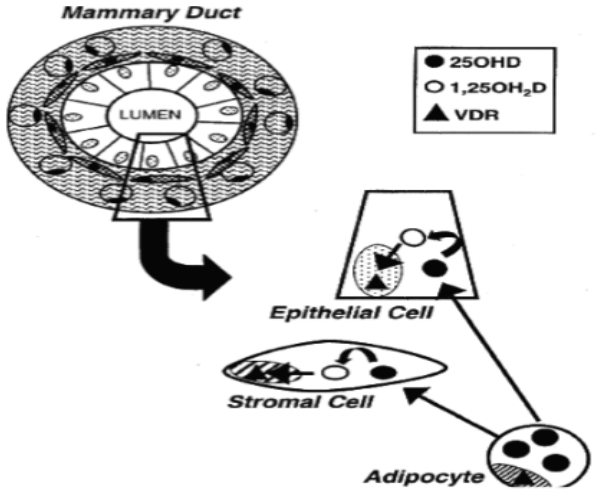

Figure 1. Localization of VDR in Mammary Gland

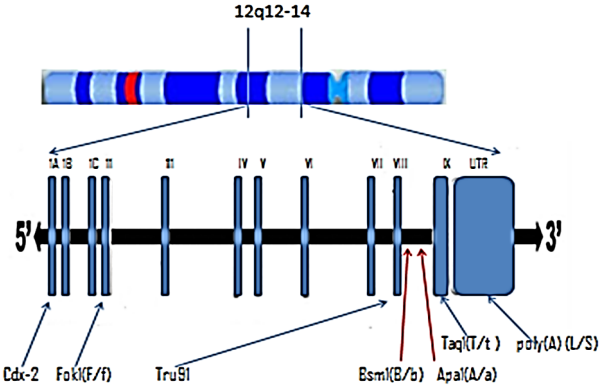

Figure 2. Human Vitamin D Receptor (VDR) Gene Polymorphic Sites

Wang et al., 2013; Zhang, 2014).

The VDR gene ApaI polymorphism and breast cancer risk: Apa1 restriction sites lies in an intronic region between exon VII and IX (Buyru N et al., 2003). Genotypes were designated as AA, Aa, aa for the ApaI polymorphisms. VDR Apa1polymorphisms were identified to have significant association with tumor differentiation. Anaplastic tumors are more inclined to express a polymorphic allele of VDR ApaI (Aa or aa). Alleles of VDR, ApaI confer an increased risk for breast cancer development in few studies (Guy et al., 2004; Engel et al., 2013; Fuhrman et al., 2013) ,but data from various other researches showed no associations between the VDR variants ApaI and breast cancer (Hou et al., 2002; Bhanushali et al., 2009; Chakraborty et al., 2009; Dalessandri et al., 2011; Mishra et ai., 2013).

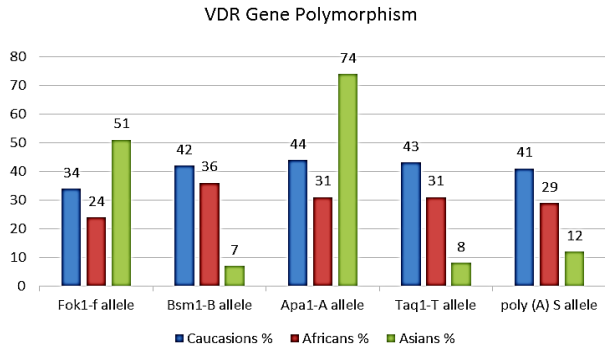

Figure 3. Ethnic Variation in VDR Gene Polymorphisms (after Kostner, 2009; Uitterlinden et al, 2004

VDR gene TaqI po lymorphism and breast cancer risk: The TaqI polymorphism is a T/C nucleotide substitution (ATT to ATC), an RFLP at codon 352 in exon 9 of the VDR gene. Individuals are generally designated as TT, Tt or tt. Taq1 shows a definite association with breast cancer in few researches. Study by Perna L et al (2013), points to a significant prognostic value of taq1in breast cancer patients. No significant increase in risk for breast cancer has been seen in women both heterozygous and homozygous for t allele in multiple studies (Wang et al., 2013).

The VDR gene poly(A) polymorphism and breast cancer risk: The poly (A) mononucleotide repeat occupies the 3'-untranslated region (3'-UTR) section of the gene, firmly interconnected with Bsm1, Apa1 and Taq1 has a strong influence on VDR mRNA integrity (Gombart, 2006). Individuals are categorized as having alleles with short (S, with <18 As) or long (L, with >18 As) poly (A) stretches. The S allele is considered to be the more effective VDR allele (Mishra et al., 2013).

Vitamin D receptor (VDR) poly (A), polymorphism has been implicated in the development of breast

Table 1. Analyses of Polymorphisms in Breast Cancer

Studies	Year	Polymorphism	Study Type	Study Population	Cases/Controls
Abbas et al	2008	Fok1, Taq1	PCCS*	German	1408/2612
Barroso et al	2008	Fok1,Taq1	CCS**	Spanish	549/556
Bretherton-Watt et al	2001	Fok1, Bsm1	CCS	Caucasian	181/241
Buyru et al	2003	Bsm1, Taq1	CCS	Turkish	78/27
Chakraborty et al	2009	Apa1, Taq1	CCS	North Indian	160/140
Chen et al	2005	Fok1, Bsm1	CCS	USA	1234/1676
Curran et al	1999	Fok1, Taq1, Apa1	CCS	Australian	135/110
Fuhrman et al	2013	Fok1, Bsm1	CCS	USA	484/845
Guy et al	2004	Fok1, Bsm1, poly(A)	CCS	Caucasian	398/427
Hou et al	2002	ApaI, TaqI, and BsmI	CCS	Taiwanese	80/169
Huang et al	2012	Bsm1, Apa1, Taq1	CCS	Han Chinese	146/320
Ingles et al	2000	Fok1, Bsm1	CCS	Latinas	143/300
John et al	2007	Fok1, Taq1, Bgl1	CCS	Mixed	814/910
Lowe et al	2005	Bsm1	CCs	Caucasian	179/179
MacKay	2008	Fok1, Bsm1	CCS	Caucasian	6300/8100
McCullough et al	2007	Fok1, Bsm1, Taq1, Apa1, poly (A)	NCCS***	Caucasian	500/500
Mishra DK et al	2013	Fok1, Bsm1, Taq1, Apa1	CCS	Mixed	232/349
Rollison et al	2012	Fok1, Bsm1	PCCS	Hispanic, non-Hispanic	2,325/2,525
Sillanpaa et al	2004	Apa1, Taq1	CCS	Finnish	483/482
Sinotteet al	2007	Fok1,Bsm1	CCS	French Canadian	718/1596
Trabert et al	2007	Bsm1	PCCS	Caucasian& African American	1631/1435
Yang et al	2014	Fok1, Bsm1, Apa1 and Taq1	CCS	Caucasian	38,151/47,546
Yingying Du	2014	Bsm1	CCS	Mixed	10,212/12,808

*Population-based case-control study; **Case-Control study; ***Nested Case-Control Study

carcinoma. In 2000, Ingles et al, reported a remarkably elevated probability of breast malignancy among Latina females of different cultural groups with the SS genotype as compared to the LL poly (A). However, meta-analysis of studies by Jinjiang et al. (2014) showed no interconnection of VDR poly (A) polymorphism with chance of developing breast cancer.

Conclusion

Insight into the role of VDR polymorphisms imparts idealistic vision or perception which can expedite the development of up to date prophylactic approaches for breast malignancies.

The evaluation of data regarding the VDR gene polymorphisms, most prevalent in breast carcinoma of various ethnic populations shows diverse results. This might be due to the limitation of individual studies or genetic variations due to racial or cultural diversity.

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