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COMMENTARY

Comment to "Vitamin D Receptor Poly(A) Microsatellite Polymorphism and 25-Hydroxyvitamin D Serum Levels: Association with Susceptibility to Breast Cancer"

Salvatore Chirumbolo

Department of Medicine-Unit of Geriatry, University of Verona, Verona, Italy

To the Editor,

The article by Colagar et al. [1], in the latest issue of this journal, showed the relationship between the genetic polymorphism of vitamin D receptor (VDR), as a VDR polyA allele L microsatellite variants, serum level of 25(OH)D_3 and risk of breast cancer. As in many other type of malignancies, low levels of 25(OH)D_3, the main circulating form of vitamin D following dietary intake, has been associated with higher breast cancer susceptibility, particularly with plasmatic levels of 25(OH)D_3 below 20 to 32 ng/mL [2]. Therefore, one of the major goal pursued by physicians endeavoured to prevent or fight cancer is to increase plasma bioavailability of 25(OH)D_3 by increasing vitamin D intake or ameliorating its gut adsorption, supplementation protocol or pharmacokinetics [3]. However, the paper by Colagar appears to raise the same concern that I addressed in some recent papers of mine [4], namely that the preventive effect of vitamin D on cancer depends on the wide collection of factors including genetic polymorphism for VDR [1], for example, for breast cancer the different ability of individuals to respond to 1,25$(OH)_2D_3$ might depend on the Taq1 VDR polymorphism [5]. The individual genetic endowment to respond to vitamin D, in such a fashion able to assess its presumptive chemopreventive potential against some important malignancies such as breast cancer, should be a fundamental hallmark to arrange any vitamin D supplementation protocol [4]. Other genetic polymorhisms may be involved in the chemopreventive role of 25(OH)D_3, for example those ones regarding P450 family of cytochromes [6], as interestingly CYP1A1 is involved in xenobiotic metabolism and is a VDR target [7], moreover CYP3A4 is a human microsomal 25(OH)D_3 hydrolase [8]. Because of the genetic variability of VDR exising within the Causasian population, the authors discussed the controversial issue that any variant in VDR may influence the activity of vitamin D against tumors and their prevalence in the population [1]. Yet, some correlation exists between low levels of circulating 25(OH)D_3 and frequency of breast cancer [2,9], which should suggest for an increase in vitamin D intake as a supplementation aid, but very few reports correlated positive outcomes for breast cancer incidence following vitamin D supplementation [3,10]. While several papers associated cancer risk with a low 25(OH)D_3 plasma level, the reason of this insufficient bioavalailability is far to be elucidated. Cancer cells can promote the 25(OH)D_3 enzymatic hydroxylation, contribuiting in the reduction of the level in the circulating form [11,12], The protective effect against breast cancer claimed by the authors [1] might derive from a wide panoply of variability, which may even involve P450 cytochromes and aryl hydrocarbon receptor polymorphism [13,14], though some contradictory evidence yet exists [15]. The conclusion which the authors reached assessed that breast cancer risk is related to low levels of the circulating metabolite 25(OH)D_3 and to a favorable assessment of a VDR genetic polymorphism, particularly with poly(A) long (LL+LS) microsatellite alleles [1]. Interestingly, this genetic polymorhism was associated with breast cancer also in a Northern Indian population, nearby the Iranian regions from which the authors recruited their patients [16]. Interestingly, Fok1 polymorphism is a poly(A) microsatellite polymorphism, which was recently closely associated to breast cancer [17], although yet Fok1 is also a VDR polymorphism that has been associated with many other types of cancers [18] and even with pulmonary tuberculosis susceptibility [19]. The au-

Correspondence to: **Salvatore Chirumbolo**
Department of Medicine-Unit of Geriatry, University of Medicine, LURM est Policlinico GB Rossi ple AL Scuro 10, Verona 37134, Italy
Tel: +39-0458128456, Fax: +39-0458027403
E-mail: salvatore.chirumbolo@univr.it

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thors did not clarify which kind of VDR polymorphism, previously described in the literature, they reported in their paper. The genetic association of VDR polymorphism to several types of cancer makes particularly puzzling the role of the genetic variability of vitamin D enzymes and receptors in the presumptive chemopreventive role of $1,25(OH)_2D_3$. HLA-aplotype genetic linkage may be a possible path to focus onto vitamin D action on tumors. Due to the strong association with tuberculosis (TB) susceptibility and Fok1 VDR polymorphism [19], a suggestion might come from the evidence that some HLA alleles, such as the aplotypes HLA-DRB1, HLA-DQB1 or more precisely DRB1*1101-1121-DQB1*05 are associated with TB as well as the polymorphic SNP variants Fok1, Bsm1, Apa1, and Taq1, some of which related to breast cancer [20]. The question is if some HLA aplotypes in linkage disequilibrium with VDR polymorphic genes may be used as genetic markers to evaluate the individual's vitamin D response against breast cancer [21]. This issue puts questions and concerns about the fundamental role of genetic determinants for ensuring vitamin D efficacy in counteracting cancer malignancy through its immune modulating and hormonal action.

CONFLICT OF INTEREST

The author declare that he has no competing interests.

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