Vitamin D and Ovarian Cancer

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Abstract
Ovarian cancer causes more deaths than any other cancer of the female reproductive system. The vitamin D receptor (VDR) is weakly to moderately expressed in normal ovarian cell, but is more strongly expressed in ovarian cancer line and tumor tissue. In vitro studies have reported that vitamin D administration inhibits cell growth and induces apoptosis in a dose dependent manner in both animal and human ovarian cancer cell lines. With available literature in the background, there is an urgent need to conduct a large case control trial to evaluate the association of vitamin D receptor gene polymorphism Fok1 with the risk of epithelial ovarian cancer. Also, we need to evaluate the levels of serum vitamin D in epithelial ovarian cancer patients.

Introduction
Ovarian cancer causes more deaths than any other cancer of the female reproductive system. Lifetime risk of women having ovarian cancer is 1% to 1.5% [1]. Epithelial ovarian cancer is the most common histological type of ovarian cancer. Approximately 90% of epithelial ovarian cancers are derived from the coelomic epithelium or mesothelium [1]. More than seventy percent of these patients present in advanced stage of this disease and have a cure rate of less than forty percent [2]. The high mortality in these cases is due to lack of highly sensitive and specific screening methods.

Vitamin D and its Metabolism
Vitamin D is a fat soluble secosteroid which is involved in a wide variety of biological processes like bone metabolism, modulation of immune response, cell proliferation and cell differentiation. There exists an inverse relationship between vitamin D levels in blood and incidence of many cancers [3,4].

Vitamin D is derived from the diet or by bioactivation of 7-dehydrocholesterol, is inert and must be activated to exert its biological activity. Vitamin D₃ is produced in the skin by an UV light induced photolytic conversion of 7-dehydrocholesterol to previtamin D₃ [5,6] followed by thermal isomerization to vitamin D₃ [7,8]. The first step in the metabolic activation of vitamin D is hydroxylation of carbon 25. This reaction primarily occurs in the liver. The second most important step in vitamin D bioactivation is the formation of 1,25(OH)₂D₃ from 25(OH)D₃ via 25(OH)D-1 alpha-hydroxylase which occurs mainly in kidney [8].

Role of Vitamin D Receptor
Most of the biological activities of 1,25(OH)₂D₃ are mediated by a high affinity receptor that plays a role in ligand binding, heteromerization with retinoid X receptor, binding of heterodimer to vitamin D response element and recruitment of other nuclear proteins into the transcriptional preinitiation complex. Thus, genetic alteration of the VDR gene could lead to important defects in gene activation, affecting calcium metabolism, cell proliferation, immune function, etc. which could be explained by changes in protein sequence.

The vitamin D receptor (VDR) is weakly to moderately expressed in normal ovarian cell, but is more strongly expressed in ovarian cancer line and tumor tissue [9-13]. In vitro studies have reported that vitamin D administration inhibits cell growth and induces apoptosis in a dose dependent manner in both animal [14] and human ovarian cancer cell lines [10,11,15-20].

VDR gene polymorphism, Fok I, (rs10735810/rs2228570) is reported to be in linkage disequilibrium with other VDR polymorphisms. A change in the sequence from C to T in the start codon translation site leads to generation of a polymorphic variant (TT) which is three amino acids longer and has decreased transactivation capacity as compared to the short CC allele [21].

Association of Vitamin D Receptor Gene Polymorphisms and Cancers
Several population based studies indicated that VDR gene polymorphisms are associated with human cancers [22,23]. A few studies tried to establish a relationship between vitamin D receptor gene polymorphism (Fok 1) and ovarian cancer. The odds ratio in these studies were observed to vary from 1.09 to 2.5 indicating that CT and TT genotypes of VDR gene polymorphism (Fok 1) are at increased risk of ovarian cancer [24,27].

Lurie et al. [24] studied the association of ovarian cancer risk with polymorphisms in the VDR gene, including Fok1,Cdx-
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2, Bsm1, Apa1, Taq1 and Bsm1-Apa1-Taq1 combined genotypes were examined among 313 women with epithelial ovarian cancer and 574 controls. This investigation provides some evidence that polymorphisms in the VDR gene might influence the ovarian cancer susceptibility.

Grant et al. [28] did a study to determine the association between seven VDR polymorphisms of functional significance and epithelial ovarian cancer in both Caucasians and African Americans. In follow-up analysis, associations were assessed between six single nucleotide polymorphisms (SNPs) in proximity of the Apa1 variant and a larger sample of African Americans. The authors found that African American women who carried at least one minor allele of Apa1 were at higher risk for invasive epithelial ovarian cancer, after controlling for age and admixture with an odds ratio for association under the log-additive model of 2.08. No association was observed between any of the VDR variants and epithelial ovarian cancer among Caucasians. A follow-up analysis in a larger sample of African American subjects revealed a nearly 2-fold increase in risk of invasive epithelial ovarian cancer.

Shelley et al. [29] examined whether three (SNPs) in the vitamin D receptor gene (Fok1, Bsm1, Cdx 2) were associated with risk of epithelial ovarian cancer in a retrospective case control study (New England Case Control studies, NECC), and a nested case control study of three prospective cohort studies: the Nurses Health Study (NHS), NHS11, and the Women’s Health Study (WHS). Data from the cohort studies were combined and analyzed using conditional logistic regression and pooled with the result from NECC, which were analyzed using unconditional logistic regression, using a random effects model. They obtained genotype data for 1,473 cases and 2,006 controls. They observed a significant positive association between the number of Fok1 f alleles and ovarian cancer risk in the pooled analysis (p-trend=0.03). The odds ratio (OR) for the ff versus FF showed significant association with ovarian cancer risk. Among the prospective studies, the risk of ovarian cancer by plasma vitamin D level did not clearly vary by any of the genotype. For example, among women with the Fok1 FF genotype, the OR comparing plasma 25-hydroxyvitamin D >32ng/mL versus 0-32ng/mL was 0.66, and among women with the Ff or ff genotype, the OR was 0.71. Their results of association with Fok1 VDR polymorphism further support a role of the vitamin D pathway in ovarian carcinogenesis.

Tamez et al. [30] did prospective cohort hospital based study to detect important gene mutation in ovarian cancer. He found that the VDR Fok1 C/C genotype was associated with better overall survival rate in patients with epithelial ovarian cancer than a combination of Fok1 C/T and Fok1 T/T.

Mohapatra et al. [31] studied the levels of serum vitamin D and occurrence of vitamin D receptor gene polymorphism (Fok1) in case of ovarian cancer. They found that serum vitamin D levels were significantly lower in ovarian cancer cases as compared to controls. The homozygous (TT) and heterozygous (CT) genotype predisposed to development of ovarian cancer in Indian population as compared to the homozygous (CC) genotype.

Conclusion

With this literature in the background, there is an urgent need to conduct a large case control trial to evaluate the association of vitamin D receptor gene polymorphism Fok1 with the risk of epithelial ovarian cancer. Also, we need to evaluate the levels of serum vitamin D in epithelial ovarian cancer patients. This can lead to identification of women at risk of epithelial ovarian cancer and preventive measures can be undertaken with appropriate counseling.

References


