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Human papilloma virus profiles in breast cancer in correlation with Vitamin D

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ABSTRACT

The major roles of vitamin D in the genesis of breast cancer and as an immunomodulator against acute and chronic infections have been the subject of much research in recent years. A low vitamin D status could decrease the function of blocking the cell multiplication cycle of the cancer process and weaken the immune system. In this context, we were interested in the implication of vitamin D status in women with human papilloma virus (HPV)-induced breast cancer. Our study included 63 women, 53 with breast cancer and 10 healthy women, and we measured the plasma 25(OH)D3 level and looked for the presence of HPV by PCR in our population. 90.6% had low serum 25(OH)D3 levels and HPV was found in 41% of cases. In this regard, the data in the literature are discordant. Vitamin D status could explain the concomitance of the two conditions, breast cancer and HPV; it would be desirable to broaden the sample in order to better define its impact.

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Introduction

Vitamin D is one of the major components of phosphocalcic metabolism. The relatively low plasma levels of calcium and phosphorus will be accurately adjusted from inputs, outputs and bone stock to maintain phosphocalcic homeostasis and skeletal mineralization. Vitamin D contributes to this balance (1). Vitamin D has a double exogenous origin: food, including supplements, provides D2 and D3, and endogenous: skin synthesis of the form D3 only. Only 10% to 20% of circulating vitamin D comes from the diet (apart from any supplementation) (2). It contains vitamin D2 and vitamin D3 which will be absorbed at the intestinal level.

The vitamin D content in food or drugs can be expressed in International Units (IU) or micrograms (µg): 1 IU = 0.025 µg or 1 µg = 40 IU (3).

1,25(OH) 2 D must bind to the vitamin D receptor (VDR) to perform its functions. VDR is a nuclear receptor that belongs to the family of nuclear steroid receptors. It binds to 1.25(OH) 2 D, with a very high affinity, which is consistent with the low levels of hormones found in the circulation. The affinity of 25(OH)D and other metabolites for VDR are two orders of magnitude lower, and 25(OH) D binds to VDR only if it is present at levels high enough to compensate for its low affinity. (4).

VDR is a nuclear receptor, whose general structure is characteristic of other steroid receptors in the superfamily, such as the glucocorticoid receptor and the estrogen receptor.

Many epidemiological studies have found a significant association between low serum levels of 25(OH)D and the development of some cancers. The hypothesis of a potential relationship between vitamin D and cancer was first suggested by geographical observations

The cancer diagnosis supports the hypothesis of an inverse correlation between serum vitamin D levels and breast neoplasia. (5).

The level of vitamin D plays a role in maintaining the functioning of the immune system which can promote another risk of cancer by a viral infection, especially DNA viruses, especially HPV (6).

Materials and Methods

Blood samples

This study included a total of 63 people in two groups: 53 breast cancer patients and 10 control women. The patients are women with breast cancer diagnosed at the National Institute of Oncology (INO) in Rabat, during the period from November 2021 to February 2022. Blood samples were taken before the start of any treatment (surgery, chemotherapy or radiation). Required Ethical approval was obtained from the committee of biomedical research ethics in Morocco (No. 3/2018/30 April/2018-Morocco).

Determination of vitamin D

The blood samples are collected on dry tubes with sep-

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arating gel and sent from Rabat to the biology center of Casablanca certified iso 9001V 2015. The determination of total vitamin D is carried out on the VIDAS-3 automat on the luminescence chemistry technique.

DNA extraction

DNA extraction from breast cancer fresh biopsies was performed by using the Kit PureLinkTM Genomic DNA (Invitrogen). Aliquots of 25 mg of samples were digested with 20 µl of proteinase K and 180 µl of Digestion buffer at 55ºC, for 1 to 4 hours. DNA precipitation was performed by adding 200 µl of ethanol (90%). DNA was eluted in 25 to 50 µl of Elution buffer and stored at -20ºC until further use. DNA was quantified using the Nanodrop spectrophotometer. Samples with a DNA concentration of 20–50 ng/µl or above were selected to perform the polymerase chain reaction.

Internal control

The samples were checked by internal control for the β-globin gene by PCR. Using the primers PCO4(5'CAACTTCATCCACGTTCACC3') and GH20 (5'GAAGAGCCAAGGACAGGTAC 3') which flanks a sequence of about 300 bp. Only the samples that were positive for the human ß-globin gene are the subject to research the DNA.

Detection of HPV

Detection of HPV sequences was performed using a nested PCR approach (Tawe *et al.,* 2018). DNA was first amplified with MY09 (CGTCCMARRGGAWACTGATC) MY11 (GCMCAGGGWCATAAYAATGG) primers that were used as a template for the second PCR amplification using GP5+ (TTTGTTACTGTGGTAGATACTAC) and GP6+ (CTTATACTAAATGTCAAATAAAAA) primers. For PCR, the mixture contained 200 ng of DNA for the first PCR and 2 µl of PCR product for the second PCR, 12.5 µl of Master Mix (Vazyme Green Taq Mix), 6.5 µl of distilled water. The mixture was initially denatured at 94°C for 3 minutes followed by 35 cycles with denaturation at 94°C for 1 minute, primers' hybridization at the corresponding annealing temperature 55°C for 1 minute and extension at 72° for 1 minute. At the end of the last cycle, the mixture was further incubated at 72°C for 10 min. PCR products were visualized by electrophoresis on 2 % agarose gels after staining with ethidium bromide (10 mg/ml) and visualized in UV light. Standard PCR precautions and procedures were used to avoid contamination.

Statistical analysis

Statistical analysis is performed on IBM SPSS Statistics version 20. The association between vitamin D levels with the molecular prevalence of HPV in breast cancer and the different parameters was tested by the chi-square and Fischer exact test. A p-value below 0.05 is considered statistically significant.

Results

Overall, 53 patients whose HPV DNA testing and 10 healthy patients are defined as a control group. 22 patients were considered as study groups according to their HPV status. The mean ages of the participants in the study and control groups were 55 years old. The HPV-type distribution of the study group is demonstrated in Table 1.

Among the studied population, 22 (41 %) were infected by HPV. Hypovitaminosis D represents 22(41.5 %), while the proportion of women with insufficient status present 26(49.1 %) and just 5(9.4 %) of them had a normal vitamin D level.

The association between vitamin D status and infection by HPV was presented in Table 2. Among the HPV-infected women with breast cancer, 12 (36.4%) had low vitamin D levels although just 4 (12.1%) had a normal status. The results show a lack of significance between vitamin D and

Table 1. Clinicopathological parameters.

Parameters	Number (percentage)
Age	
< 50	26 (49 %)
> 50	27(51 %)
weight	
< 66	27(51%)
> 66	26(49 %)
Size	
< 160	28(53 %)
> 160	25(47 %)
Vitamin D Dosage	
> 30	5(9.4 %)
between 12 et 29	26(49.1 %)
< 12	22(41.5 %)
IMC	
< 25	29(55%)
> 25	24(45 %)
HPV infection	
Positive	22 (41 %)
Negative	31 (59%)

Table 2. Association between vitamin D analysis and HPV infection and other parameters.

		Vitamin D analysis			p-value
		< 12 ng/mL	12< VIT D< 30 ng/mL	> 30ng/mL	
		22 (41.5 %)	26 (49.1 %)	5 (9.4 %)	
Age	**< 50 years**	12 (33.3 %)	20 (55.6 %)	4 (11.1 %)	0.211
	> 50 years	10 (58.8 %)	6 (35.3 %)	1 (5.9 %)	
HPV infection	**Positive**	12 (36.4 %)	17 (51.5 %)	4 (12.1 %)	0.513
	Negative	10 (50 %)	9 (45 %)	1 (5 %)	
Weight	**< 66 Kg**	14 (56 %)	10 (40 %)	1 (4 %)	0.097
	> 66 Kg	8 (28.6 %)	16 (57.1 %)	4 (14.3 %)	
Size	**< 166 cm**	11 (50 %)	11 (50 %)	0	0.122
	> 166 cm	11 (35.5 %)	15 (48.4 %)	5 (16.1 %)	
BMI	**< 25**	13 (56.5 %)	9 (39.1 %)	1 (4.3 %)	0.126
	> 25	9 (30 %)	17 (56.7 %)	4 (13.3 %)	

BMI: Body Mass Index; P-value by chi-square test.

this infection with a P-value of 0.513.

The majority of women under the age of 50 years old have a deficiency of vitamin D 12 (33.3 %), 26 (49.1 %) have an insufficiency, Meanwhile 4 (11.1 %) present a normal rate of this prohormone. For women over 50 years of age, 10 (58.8%) were vitamin D deficient and only one patient (5.9%) had a normal level. No association was found between age and the level of vitamin D.

Our results show no significance between vitamin D and Weight, size and body mass index among these women with a p-value of respectively 0.097, 0.122 and 0.126.

Discussion

Vitamin D and HPV

Regarding the association between vitamin D and HPV, a study of 82 patients with a positive Papanicolaou test found low serum 25(OH)D3 levels in this group, not found in the group of women with a negative Papanicolaou test (7). Work on 67 patients followed up for systemic lupus erythematosus showed that a high prevalence of HPV infection in the cervix was associated with a plasma 25(OH) D level below 20 g/l, whereas those with serum 25(OH) D levels greater than or equal to 20 g/l had a lower prevalence of infection (30.7% vs 25.8%) (8).

A study of 4343 women aged 18-59 years found that high-risk HPV prevalence was correlated with a serum 25(OH)D level of 20 g/l (9). Furthermore, Shim J., et al, reported in 2016 that there is an association between the high prevalence of vaccine-preventable HPV and low serum 25(OH)D (10).

However, a recent study in 2020 did not find an association between high-risk HPV and plasma 25(OH)D concentration (11).

Vitamin D, known for its role in bone, also plays an anti-infective role. Indeed, it has been shown that there is a strong association between the development of active tuberculosis and low plasma 25(OH)D levels (12). A study by Yamshchikov AV, et al. in 2009 looked at the anti-infective effect of vitamin D in upper respiratory diseases, tuberculosis and immunodeficiency virus (13). A study in the ANRS COPANA cohort demonstrated the link between low CD4 counts, increased inflammatory markers and low serum 25(OH)D levels in newly diagnosed HIV+ patients (14).

Regarding the relationship between vitamin D and the influenza virus, a study in Norway showed that low serum vitamin D levels are closely associated with high mortality from seasonal influenza and pneumonia (15). A Japanese study of Japanese schoolchildren (6-15 years) between December and March demonstrated the benefit of vitamin D supplementation at 1200 IU/day on the incidence of influenza A, particularly in asthmatic children (16).

Regarding the relationship between vitamin D and COVID-19 disease, one work reported the link between COVID-19 deficiency (17).

In fact, the anti-infective effect of vitamin D is due to its immunomodulatory role: it prevents the proliferation of T cells (18), on the one hand, and macrophages have the capacity to produce vitamin D, on the other (19). It inhibits inflammation-inducing mediators and stimulates monocytes and macrophages.

When confronted with an infectious agent, the latter induces an over-expression of the "Toll-like receptor", the VDR (vitamin D receptor) and 1-α hydroxylase. Activated VDR leads to a decrease in pro-inflammatory cytokines (interleukin-1, interferon-γ, tumor necrosis factor-α) and an increase in anti-inflammatory cytokines (interleukin-10).

Locally produced calcitriol will stimulate macrophages leading to autophagy and synthesis of anti-microbial peptides (cathelicidin), and natural anti-infectives (20, 21).

Vitamin D and breast cancer

In addition, due to the presence of the vitamin D receptor on the surface of breast tissue, Holick reported in 2006 that this receptor is activated by vitamin D (22). This activation results in terminal differentiation and inhibition of cell growth (22). Studies have suggested that vitamin D receptors are present in more than 80% of breast tumours, giving them a protective role against tumour proliferation (23,24,25).

A study investigating the implication of vitamin D deficiency on cancer susceptibility found an association between low serum 25(OH)D3 levels and increased prevalence of breast cancer genesis, risk of recurrence and mortality (26). A meta-analysis of premenopausal women demonstrated the protective role of high serum vitamin D levels and the development of breast neoplasia (27). Another study found that in patients with a serum vitamin D

level below 50 nmol/l, the risk of developing breast cancer is higher in African American patients than in Hispanic patients (28). Work from randomised trials has emphasised that high vitamin D levels are associated with a reduced risk of breast cancer, with the most protective values being 150 nmol/l (29).

HPV and breast cancer

The risk factors incriminated in the genesis of breast cancer are well known: female gender, late puberty and menopause, use of oral contraceptives, smoking, etc. In addition, there is the involvement of certain oncogenic viruses, particularly HPV. Indeed, more than 40 studies conducted in 20 countries have discovered HPV gene sequences in breast neoplastic tissue (30, 31). In the USA, the prevalence of HPV in breast neoplasia was reported to be 86% in the study by Zur Hansen H. and Villiers EM (32). It would appear that HPV 16 and 18 are the most frequently found in breast cancer, but Chinese and Japanese studies have shown the frequent presence of HPV 33 and 58 (30,31). The study by Lawson J.S; et al. showed the presence of high-risk HPV on benign breast tissue that developed into HPV-positive breast cancer cells 1 to 11 years later after the initial discovery of HPV (33). Furthermore, the same study reported the occurrence of HPV-induced cervical lesions before the occurrence of breast cancer in the same patient (33).

The study by Dimri G., et al. demonstrated that mammary epithelial cells are immortalised and transformed by HPV (34). The work of Yasmeen A., et al. showed that non-invasive and non-metastatic breast cancer cells are transformed by HPV 16 E6 and E7 oncoproteins into invasive and metastatic cells (35). Ngan C., et al. report the hypotheses that HPV may indirectly influence breast cancer genesis as well as an act through the "hit and run" technique in that it triggers breast cancer genesis and subsequently disappears from tumour cells not found at the time of clinical breast cancer diagnosis (36). In addition, the APOBEC enzyme involved in cell cycle control appears to be influenced by HPV leading to genomic instability and ultimately to the occurrence of breast cancer (37,38).

Conclusion

Our study shows that the majority of women with breast cancer 90.6% present a deficiency or insufficiency of vitamin D, while just 9.4 % had a normal level. 22 of them were infected with HPV. We find no evidence for an association between vitamin D levels and infection by HPV among women with breast cancer.

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Conflict of interest

The authors declare that they have no conflict of interest

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