Introduction

The reduction in vitamin D concentration has been correlated with several disorders in the last decades, studies have found that deficiency of vitamin D is related to the development of many acute and chronic disorders, for instance deficiency of vitamin D lead to inadequate calcium and phosphate quantities and leading to secondary hypothyroidism. This vitamin is naturally available in some types of food and prescribed as a supplement to those with deficiency. It is a fat-soluble vitamin found in two forms, D2 (ergocalciferol) which can be obtained from nutrients like sea-food and vegetables, the other form is D3 (cholecalciferol) that has longer half-life and present in dairy products, also can be formed internally by exposure to ultraviolet light, which stimulate D3 formation under the skin, the later type constitute most of vitamin D produced in the body. Vitamin D rule against infection were detected centuries ago, historically tuberculosis patients were treated by exposure to sun-light to enhance eradication of the infection before the discovery of vitamin D and antibiotics. Presence of vitamin D in food is scarce, it can be found in fatty-fish, beef liver, cheese, egg, mushrooms, and milk. Dairy products if fortified can have measured amount of vitamin D for daily requirement. Following formation of both types of vitamin D in the body, it is metabolized in the liver and further hydroxylated in other tissues like kidneys and breast cells to become the most effective

Prevalence of vitamin D deficiency in early-diagnosed cancer patients: A cross-sectional study

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Abstract

Background: Vitamin D roles in human health and wellbeing have been extensively studied in the recent years. It has essential roles in homeostasis and maintaining many physiological functions. These roles are vital in immune system, respiratory system, cardiovascular system, and reproductive system. Deficiency in this vitamin has been correlated with many diseases in the body, and it has been correlated with developing cancer.

Objective: This study aimed to investigate levels of total vitamin D (25-hydroxycholecalciferol) in cancer patients.

Design: Retrospective.

Settings: Taif city- king Faisal Hospital (KFH).

Patients and methods: Serum levels of 25-hydroxycholecalciferol were classified into normal, insufficient, and deficiency group, patients were grouped according to these classes. 156 patients were included in this study, 128 females and 28 males, 100 healthy participants were included. Cancer patients were as follows, gastrointestinal tract cancer patients were 27, breast cancer patients were 73, female genital tract patients were 43, head and neck cancer patients were 6 and respiratory tract patients were 7.

Sample size: 256 participants were 100 healthy controls and 156 cancer patients.

Results: Deficiency was detected in most of the patients from both genders, and in both pre- and post-menopausal female patients.

Conclusion: These findings support the belief that deficiency in vitamin D is a risk factor leading to development of cancer.

Keywords: Vitamin D (25-hydroxycholecalciferol), breast cancer, gastrointestinal tract cancers, female genital tract cancers, respiratory tract cancers, head and neck cancer, menopause.

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form 1,25-hydroxy vitamin D the ligand for vitamin D receptor (VDR), furthermore, polymorphisms in VDR have been associated with obesity and breast cancer\(^1\)\(^{-}\)\(^9\). Moreover, binding of vitamin D and its metabolites to VDR can manifest vitamin D physiological effect\(^10\),\(^11\). The concentration of vitamin D in the serum should be monitored regularly, as several factors can affect vitamin D amount, for example less exposure to sun light can affect D\(_3\) formation which is the predominate endogenous formed vitamin D, and malnutrition or consumption of vitamin D free diet\(^12\). Immune system surveillance is essential to kill cancerous cells, patients with low vitamin D levels were exposed to high number of respiratory tract infection, autoimmune diseases, and development of several types of cancer\(^1\),\(^3\),\(^13\)-\(^16\).

The aim of this study was to investigate the prevalence of vitamin D deficiency in early-diagnosed cancer patients, also to evaluate the levels between patients age groups, and pre-menopausal female versus menopausal. The outcomes of this study can help to assess the probability of developing cancer due to vitamin D deficiency.

**Materials and Methods**

**Study design**

This retrospective cross-sectional study was approved by the directorate of health affairs in Taif city, IRN registration number HAP-02-T-067 for the period 2018 to May 2020, a consent form was provided prior using of data. All recruits in this study have to meet the following strict inclusion criteria to be included, firstly; diagnosed with any type of cancer at KFH between 2018 and 2020; secondly; only early-diagnosed cancer patients were included and patients who were previously diagnosed were excluded; thirdly; have not taken vitamin D supplement for at least 60 days and had measurement of vitamin D total (25-hydroxycholecalciferol) when they provided a biopsy sample to laboratory. The study aimed to obtain a total of 200 participants which are 100 patients and 100 healthy controls, however, the total number of participants reached 256 as follows 156 patients that have satisfied this study strict inclusion criteria, and 100 healthy participants were included free from cancer and debilitating disorders.

**Sample analysis**

When patients were requested to provide biopsy sample according to physician request, minimum of 3 mL of venous blood were collected into plain tube, analyzed freshly and not stored through ROCHE COBAS\(^8\) platform e501. Patients were advised to fast for 10 hours prior collecting of the blood as the sample was used to diagnose other tests including vitamin D. This study has collected the following information, sex, age of the patient, type of diagnosed cancer, levels of vitamin D.

Vitamin D serum levels was categorized into three different categories, normal level for those who were ≥50 ng/mL, insufficiency for those who were 30 to 49 ng/mL, and deficiency for those who were ≤29 ng/mL.

**Statistical analysis**

Microsoft excel for office was used for sorting of data, calculating frequencies, percentage, chi-square analysis and standard deviation (σ), Pearson’s chi-square test was used to detect any significant frequency in a single category. For odds ratio (OR), relative risk (RR) and 95% confidence interval (95% CI) medcalc-website were used (www.medcalc.org), results when \( P \) value <0.05 were considered significant.

**Results**

**Demographic analysis**

This study has included 156 cases of early-diagnosed cancer patients (Table 1) and satisfied the strict inclusion criteria. Number of female cases was 128 and constitutes 82% of the study group, and number of male cases was 28 and constitutes 18% of the study group. Most of the cases were females for the age group 40–64 years which were 52% of total cases.

**Types of cancer**

After sorting of data of this study, the categories of cancer types are arranged as follows, breast cancer, respiratory tract cancer, head and neck cancer, and gastrointestinal tract cancer, and female genital tract cancer. The frequencies of these types are illustrated in Table 2.

**Prevalence of Vitamin D deficiency**

Analysis of the prevalence of vitamin D deficiency was assessed according to levels of the serum vitamin D into 3 groups normal, insufficient, and deficiency. Characteristics analyzed were age, sex, and menopausal status of female patients (Table 3) and according to type of cancer in (Table 4). Mean of vitamin D was higher in males than females for both healthy and patients. In males, mean levels were higher in healthy than patients (OR 2.95 and RR 2.0115) indicating increase frequency in patients than healthy of vitamin D deficiency. In females, same results were detected as mean levels were higher in healthy than patients (OR 1.26 and RR 1.118) indicating also high frequency in patients than healthy of vitamin D deficiency. Comparing levels by age showed high frequency and prevalence of cancer with vitamin D deficiency in ≤39 years, and higher mean levels in healthy than patients and high prevalence of vitamin D deficiency among patients (OR 17 and RR 3.4) as most of the healthy were in insufficient groups while patients were mostly having vitamin D deficiency. For 40 to 64 years mean levels were higher in healthy than patients.
### Table 1
Demographic analysis of the study including sex, frequency, mean and σ.

| Characteristics | Number of cases | Mean ± σ |
|-----------------|-----------------|----------|
| **Sex**         |                 |          |
| Male            | 28 patients     | 62 ± 15.4 |
| Female          | 128 patients    | 56.23 ± 13.86 |
| **Age**         |                 |          |
| ≥ 39            | Male            | 4 ± 7.14  |
| Female          | 32 ± 3.5        |
| 40–64           | Male            | 41 ± 5.8  |
| Female          | 115 ± 6.5       |
| ≥ 65            | Male            | 33 ± 6.4  |
| Female          | 31 ± 8.3        |
| **Total**       |                 | 256       |

### Table 2
Types of cancer included in this study according to sex, tissue type, diagnosis, and frequencies.

| Sex             | Tissue Type                              | Cancer Type          | n cases | Percentage % |
|-----------------|------------------------------------------|----------------------|---------|--------------|
| Male            | Gastrointestinal tract                   | Sigmoid              | 10      | 35.7         |
|                 | Caecum                                   | 1                    | 3.5     |
|                 | Ascending colon                           | 1                    | 3.5     |
|                 | Descending colon                          | 1                    | 3.5     |
|                 | Rectal mass                               | 5                    | 17.8    |
|                 | Colon mass, Rectum polyp                  | 3                    | 10.7    |
|                 | Gastric and liver tumor                   | 1                    | 3.5     |
| Head and Neck   | Nasopharyngeal carcinoma                  | 1                    | 3.5     |
| Respiratory tract| Lung                                     | 1                    | 3.5     |
|                 | Nose                                     | 4                    | 14.28   |
| Female          | Breast cancer                             | Invasive Duct Carcinoma| 55    | 42.18        |
|                 | Invasive Lobular Carcinoma                | 9                    | 7       |
|                 | Invasive micropapillary carcinoma         | 1                    | 0.78    |
|                 | Mucinous adenocarcinoma                   | 1                    | 0.78    |
|                 | Invasive pleomorphic lobular carcinoma    | 1                    | 0.78    |
|                 | Invasive mammary carcinoma                | 1                    | 0.78    |
|                 | Infiltrating lobular carcinoma            | 1                    | 0.78    |
|                 | Infiltrating Duct carcinoma               | 1                    | 0.78    |
|                 | Solid papillary carcinoma breast          | 2                    | 1.5625  |
|                 | In situ duct carcinoma                    | 2                    | 1.5625  |
| Female Genital tract | Endometrial cancer                 | 26                  | 20.31   |
|                 | Cervical cancer                           | 11                   | 8.59    |
|                 | Anterior vaginal wall                     | 1                    | 0.78    |
|                 | Uterus, cervix, and fallopian tube        | 3                    | 2.34    |
|                 | Ovarian cyst                              | 1                    | 0.78    |
|                 | Uterine carcinoma                         | 1                    | 0.78    |
| Head and Neck   | Tongue carcinoma                          | 1                    | 0.78    |
| Respiratory tract| Bronchus                                  | 1                    | 0.78    |
| Gastrointestinal tract | Tubulovillous Adenoma               | 2                    | 0.78    |
|                 | Rectal mass                               | 1                    | 0.78    |
|                 | Esophageal                                | 1                    | 1.56    |
| **Total**       |                                          | 156                  |

### Table 3
Evaluation of serum levels of vitamin D between healthy and cancer patients according sex, age and menopause status.

| Characteristics | Serum level Vit-D ng/mL (σ) | Normal ≥ 50 | insufficiency 30–49 | Deficiency ≤ 29 | P value | Odds ratio (P-value, CI 95%) | Relative risk (P-value, CI 95%) |
|-----------------|----------------------------|-------------|---------------------|-----------------|---------|----------------------------|--------------------------------|
| **Sex**         |                            |             |                     |                 |         |                           |                                 |
| Male            | Patients                   | 30.51 (12.49)| 2 (7.15%)           | 13 (46.42%)     | 0.01328 | 2.9 (0.0295, 1.1142 to 7.84) | 2.0115 (0.02734, 0.8103 to 3.7417) |
|                 | Healthy                    | 38.68 (14.03)| 8 (16%)             | 30 (60%)        | 0.01624 | 1.26 (0.4828, 0.6561 to 2.4387) | 1.118 (0.4945, 0.8198 to 1.5) |
| Female          | Patients                   | 29.4 (12.51)| 10 (7.8%)           | 44 (34.37%)     | 0.00000 | 17 (0.009, 3.202 to 90.25)   | 3.4 (0.0057, 1.4267 to 8.1)    |
|                 | Healthy                    | 53 (13.6)  | 4 (8%)              | 20 (40%)        | 0.02065 | 17 (0.4828, 0.6561 to 2.4387) | 1.118 (0.4945, 0.8198 to 1.5) |
| **Age groups**  |                            |             |                     |                 |         |                           |                                 |
| ≥ 39            | Male                       | 23.02 (13.7)| 1 (5%)              | 2 (10%)         | 0.00001 | 17 (0.009, 3.202 to 90.25)   | 3.4 (0.0057, 1.4267 to 8.1)    |
|                 | Female                     | 38.625 (16.06)| 12 (5.25%)        | 10 (62.5%)      | 0.19691 | 17 (0.009, 3.202 to 90.25)   | 3.4 (0.0057, 1.4267 to 8.1)    |
| 40–64           | Male                       | 55.93 (14.34)| 8 (13%)             | 30 (48.4%)      | 0.04751 | 1.96 (0.0434, 1.020 to 3.766) | 1.4291 (0.0533, 0.995 to 2.05) |
|                 | Female                     | 31.81 (10.81)| 5 (6.9%)            | 20 (46.5%)      | 0.00121 | 1.0435 (0.0434, 1.020 to 3.766) | 1.0233 (0.0533, 0.995 to 2.05) |
| ≥ 65            | Male                       | 33.45 (12.17)| 2 (9%)              | 10 (45.5%)      | 0.23351 | 0.9355 (0.9353, 0.3721 to 2.9264) | 0.9503 (0.0533, 0.995 to 2.05) |
|                 | Female                     | 54.38 (14.11)| 7 (8.1%)            | 31 (36.04%)     | 0.00042 | 1 (0.0001, 2.14 to 7.5)      | 0.8421 (0.0743, 0.7 to 1.017)  |
| **Menopause**   |                            |             |                     |                 |         |                           |                                 |
| Pre             | Patients                   | 28.67 (14.2)| 3 (7.14%)           | 13 (30.9%)      | 0.00007 | 5.14 (0.0001, 2.374 to 11.15) | 1.44 (0.725, 0.97 to 2.15)    |
| Healthy         | Patients                   | 34.38 (14.11)| 2 (8%)              | 14 (53.5%)      | 0.01346 | 1 (0.0001, 2.374 to 11.15) | 1.44 (0.725, 0.97 to 2.15)    |

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and most patients showed vitamin D deficiency, and healthy having insufficient of vitamin D (OR 1.96 and RR 1.4291). And for more than 64 years mean levels were higher in healthy than patients, and equal percentage of patients in insufficient and deficient group (OR 1.0435 and RR 1.0233) but with insignificant P value. Prevalence of vitamin D deficiency in females were further studied according to menopause state, and high prevalence of vitamin D deficiency in postmenopausal females in both healthy and patients (OR 4 and RR 0.8421), also in premenopausal females patients were highly having vitamin D deficiency and healthy mostly having insufficient vitamin D (OR 5.14 and RR 1.44).

For gastrointestinal tract cancer patients, high prevalence of vitamin D deficiency was detected (OR 3.41 and RR 0.6823), and sigmoid cancer patients have shown high prevalence of vitamin D deficiency (OR 3.17 and RR 0.6925). In head and neck high frequency of vitamin D deficiency detected (OR 3.17 and RR 0.65). In respiratory tract cancer patients, no normal level of vitamin D was detected (OR 3.51 and RR 0.69), and sigmoid cancer patients have shown high prevalence of vitamin D deficiency (OR 3.41 and RR 0.6823), and breast cancer patients have shown high prevalence of vitamin D deficiency (OR 3.55 and RR 0.69).

**Table 4 Evaluation of serum levels of vitamin D between cancer patients according to different characteristics (All; all patients).**

| Type of cancer | Characteristics | Serum level Vit-D ng/mL (0) | Normal ≥ 50 | insufficiency 30–49 | Deficiency ≤ 29 | P value | Odds ratio (P-value, CI 95%) | Relative risk (P-value, CI 95%) |
|----------------|----------------|-----------------------------|------------|---------------------|----------------|--------|-----------------------------|-------------------------------|
| Gastrointestinal tract | All | 27.81 (13.63) | 11 (40.74%) | 14 (51.85%) | 0.01312 | 3.17 | (0.087, 0.85 to 11.9) | 0.6679 (0.1924, 0.35 to 1.23) |
| | Sigmoid | 29.4 (13.68) | 4 (40%) | 5 (50%) | 0.00022 | 3.17 | (0.087, 0.85 to 11.9) | 0.6679 (0.1924, 0.35 to 1.23) |
| Head and neck | All | 34.5 (10.71) | 0 | 3 (50%) | 0.2231 | 3.17 | (0.0175, 0.6 to 16.7) | 0.65 (0.2096, 0.2933 to 1.475) |
| | Invasive duct carcinoma | 31.5 (14.24) | 8 (14.8%) | 17 (31.5%) | 0.0021 | 3.55 | (0.0005, 1.75 to 7.2) | 0.69 (0.0101, 0.527 to 0.9172) |
| | Invasive lobular carcinoma | 40.44 (14.9) | 3 (33.3%) | 4 (44.4%) | 0.90484 | 1.75 | (0.6752, 0.325 to 5.66) | 0.4 (0.0559, 0.1522 to 1.0239) |
| Respiratory tract | All | 31.57 (14) | 10 (13.15%) | 26 (34.21%) | 0.00014 | 3.17 | (0.0001, 1.85 to 6.7) | 0.6975 (0.0027, 0.5447 to 0.8804) |
| | Invasive duct carcinoma | 31.5 (14.24) | 8 (14.8%) | 17 (31.5%) | 0.0021 | 3.55 | (0.0005, 1.75 to 7.2) | 0.69 (0.0101, 0.527 to 0.9172) |
| | Endometrial carcinoma | 27.61 (8.5) | 0 | 10 (38.5%) | 0.00055 | 5.07 | (0.0005, 2.03 to 12.63) | 0.8097 (0.2006, 0.5861 to 1.1187) |
| Female genital tract | All | 26.49 (8.79) | 0 | 14 (34.14%) | 0.00001 | 6.1 | (0.0001, 2.76 to 13.5) | 0.87 (0.2542, 0.677 to 1.0886) |
| | Cervical cancer | 23.75 (9.99) | 0 | 3 (27.2%) | 0.01163 | 3.5 | (0.0029, 2.07 to 34.4) | 0.95 (0.812, 0.66 to 1.4) |

**Discussion and Conclusion**

This study aimed to investigate the prevalence of vitamin D deficiency among early-diagnosed cancer patients between 2018 to May 2020. 156 patients were recruited into this study, shared between 28 males and 128 females. The serum level of vitamin D was classified into three groups, the objective of this classification was to investigate the variation of serum vitamin D levels. Vitamin D deficiency is clearly detected in most of this study patients, obviously most of patients’ groups have deficiency of vitamin D (Table 3 and 4).

Vitamin D is effective against cancer prevention, and deficiency in vitamin D have been associated with several diseases1, 4, 7, 15, which explain the results of this study. However, an inconsistent study to ours and the rest studies established this point1, 4, 7, 15-18. In this study, an association was clear between vitamin D deficiency and different types of cancer. High percentage of gastrointestinal tract cancer patients have vitamin D deficiency (OR 3.41, 95% CI 1.4 to 8.25) which is consistent with several studies established this point19. Several studies have stated that vitamin D deficiency is a risk sign of developing breast cancer, and another study have stated that most of their study group were vitamin D deficient which is consistent to our findings (OR 3.51, 95% CI 1.4 to 8.25). Invasive duct carcinoma was the common type of breast cancer in our study, and 53.7% (OR 3.55, 95% CI 1.75 to 7.2) of those patients already have vitamin D deficiency. Female genital tract patients also showed vitamin...
D deficiency (OR 6.1, 95% CI 2.76 to 13.5), and further analysis of cervical cancer (OR 8.5, 95% CI 2.07 to 34.4) and endometrial cancer patients (OR 5.07, 95% CI 2.03 to 12.63) have showed the same feature. For endometrial cancers a study have showed no relation between serum levels of vitamin D and developing endometrial cancer which contrast our finding.\(^2\) In cervical cancer, according to many studies is developed due to human papilloma virus (HPV) infection and lack of knowledge is established, cervical cancer is common in patients who have showed low levels of vitamin D, these finding can suggest that deficiency of this vitamin can weaken the immune response leading to HPV infection and development of cancer due to HPV.\(^2,4,24\)

Vitamin D deficiency can lead to several health complications which can increase in post-menopausal females.\(^2\) Mean of serum vitamin D in post-menopausal female was 29.75 (11.86) and pre-menopausal was 28.67 (14.2) which almost equivalent, both show deficiency in vitamin D and this finding contrast other study stated postmenopausal have higher levels of vitamin D moreover, both groups have more patients with deficiency in vitamin D. Several studies have detected cancer even with supplementation of vitamin D in breast cancer patients.\(^2,4,20\)

In conclusion, this study has detected high prevalence of vitamin D deficiency among different cancer patients. This study revealed high prevalence of vitamin D deficiency with high OR which associate between the frequency and developing cancer. According to many previous studies, this deficiency is common among healthy and patients, however, in healthy people if not maintained by improving diet, absorbing sun light, practicing sport and prescribing high-quality supplements of vitamin D can impact health and lead to several complications. Promoting and providing health education have helped in increasing knowledge of the importance of vitamin D. Screening among public should be performed to all age groups especially that show signs of deficiency. Due to its essential role in maintain healthy body, healthy immune system, and regulating many other functions in the body.

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