The Role of Serum Vitamin D Levels in Solid Malignancy Risk: An Investigative Study

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Abstract

Background and objectives: Vitamin D involved in various conditions including signaling pathways that affects the numerous cellular processes. However, according to the recent observations, low level of serum vitamin D is associated with tumorogenesis.

Materials and Methods: The study includes 426 individuals of solid malignancies along with age and sex matched healthy controls (n= 426). The serum vitamin D level was estimated by electrochemiluminescence method and the data analyzed statistically.

Results: The mean of serum vitamin D in solid malignancies and control groups were 15.53ng/mL and 18.15ng/mL respectively. Vitamin D deficiency was found in the individuals of 380 cases of solid tumors (89.2%) and 355 of the control group (83.3%) and representing the risk association towards the disease (OR=1.65). The Sub group analysis also revealed that low vitamin D levels, i.e., less than 10 ng/mL was observed in all other categories of solid malignancies like breast, lung, gynecological, prostate, gastrointestinal, head & neck, sarcomas (bone & soft tissue) and various other solid malignancies.

Conclusion: The serum vitamin D deficiency is significantly associated with all the categories of solid tumors in comparison to control and maintaining the adequate levels may reduce the risk and their associated overall outcomes.

Introduction

Vitamin D and its metabolites have multitude of biologic effects like enhancement of cell adherence, intercellular communications and maintaining normal calcium gradient across the epithelium. Most tissues and cells in the body including heart, stomach, pancreas, brain, skin, gonads, and activated T and B lymphocytes, have nuclear receptors for 1,25(OH)2D, called vitamin D receptors [1]. Vitamin D inhibits proliferation and induces the terminal differentiation of normal and cancer cells that contain Vitamin D Receptors. However, recent studies elucidate its deficiency may be involved in the risk association of various malignancies. The complications of Vitamin D deficiency involved in both short and long term consequences of malignancies and maintaining the adequate serum levels of vitamin D is associated with reduced incidence and the death rates of colon, breast, prostate and ovarian cancer [2,3]. Apart from the regulation of cell proliferation, differentiation and function, the Vitamin D induces the expression of CYP27B1 (codes for 1α-hydroxylase) and extracellular calcium-sensing receptor (CaR) which controls the normal and cancer cell growth [4].

The vitamin D also involves in repressing the expression of the anti-apoptotic, pro-survival proteins BCL2 and BCL-XL, or inducing the expression of proapoptotic proteins (such as BAX, BAK and BAD) [5]. Solid malignancies are group of non-haematological (blood-borne) malignancies which includes carcinoma (adenocarcinoma, squamous cell carcinoma, neuroendocrine carcinoma, etc.), melanoma, sarcoma, glioma,

teratoma, mesothelioma etc. Studies reported that an increased uptake of vitamin D and to raise its blood levels up to >30ng/ml reduces the risk of developing colorectal, breast, and prostate cancer by 30 to 50% [6]. Certain Epidemiologic studies also have shown that higher levels of serum vitamin D are associated with reduced risk of cancer but there is no comprehensive data on its preventive role. Hence, there is a need to design the trials like the supplementation of specified doses of vitamin D along with its duration for the potential benefits which are still inconclusive. Therefore the purpose of this study was to determine the association of vitamin D deficiency and assess its possible risk in the influencing of various solid malignancies.

Materials and Methods

Study group and demographics

The study includes subjects of Indian origin comprises of 426 subjects of various solid malignancies, enrolled from January 2010 to August 2017. Age and gender matched 426 healthy controls were also included in the study after acquired the informed consent. The procedure to enroll the study group was in accordance with the ethical standards of responsible committees of the institute.

Inclusion and exclusion criteria

All newly registered cases of solid malignancies viz, breast, lung, gynecological, gastro intestinal, head and neck, sarcomas (bone and soft tissue), prostate cancer and other categories of solid malignancies (neuroendocrinal carcinoma, melanoma, chorionic carcinoma, Renal Cell Carcinoma and urothelial carcinoma). All low volume cases were included in the category of "other solid malignancies" for statistical purpose. All pre-treated and follow-up cases of malignancies were excluded from the study. Patients who were corrected for vitamin D deficiency followed by supplementation at the time of diagnosis were also excluded from this study.

Methodology

The diagnosis of solid tumors was confirmed by histopathological examination. Serum vitamin D levels were analyzed for all the cases and control after collecting the blood samples (5ml in Redtop vaccutainer) and analysed by Electrochemiluminescence (ECLIA) method on cobas e411 analyzer (Roche company). In this study, as per the manufactures recommendation the serum vitamin D is lower than 30ng/mL is considered as deficient and more than 100mg/mL is included in toxic range.

Statistical analysis

Data analysis was done by using the software Medcalc version 15.11 (Belgium) and graphical representation was done by Systat 13.1. The demographic variables and the descriptive measures in the cases and controls were presented as frequencies and percentages. The risk association of vitamin D deficiency in the experimental and control group comparison was done by using the odds ratio, Relative risk ratio and P value determination. The P-value ≤ 0.05, Odd's Ratio (OR) and Relative Risk ratio (RR) values of above 1.0 were considered as statistically significant. The Statistical representation was done with same sex control population for prostate and Gynecological malignancies to avoid gender bias during the data depiction.

Results

During the study period, 426 solid malignancy cases were considered, in which 148 cases were diagnosed as breast cancer, 74 Gastro intestinal (GI) cancers, 51 Gynecological malignancies (cervix, ovarian and endometrial), 46 lung cancer, 44 head and neck, 24 sarcomas (bone and soft tissue), 19 prostate cancer, and 20 other cases of solid tumors (5 Renal Cell Carcinoma, 4 urothelial carcinoma, 4 chorionic carcinoma, 2 Neuroblastoma, 2 neuroendocrinal carcinoma, 2 melanoma, and 1 Peritoneal Carcinoma) . It was noticed in the present study, the incidence of breast and gynecological cancers were more prevalent in females compared to other malignancies and represents about 46.7% of total cases. Mostly women aged 35yrs and above registered breast and gynecological malignancies whereas among the males, most of them present with lung and prostate cancers (43.6%) (Figure 1).

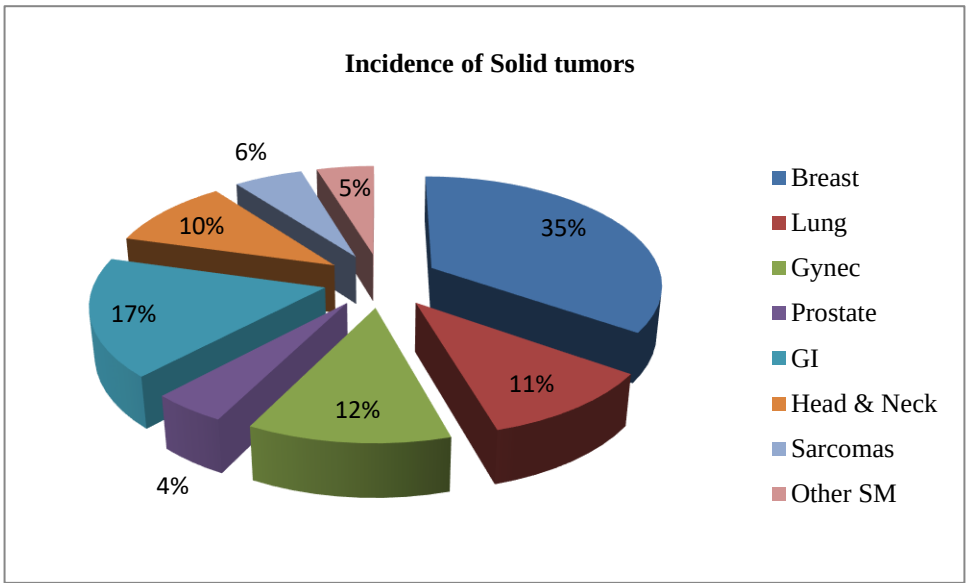
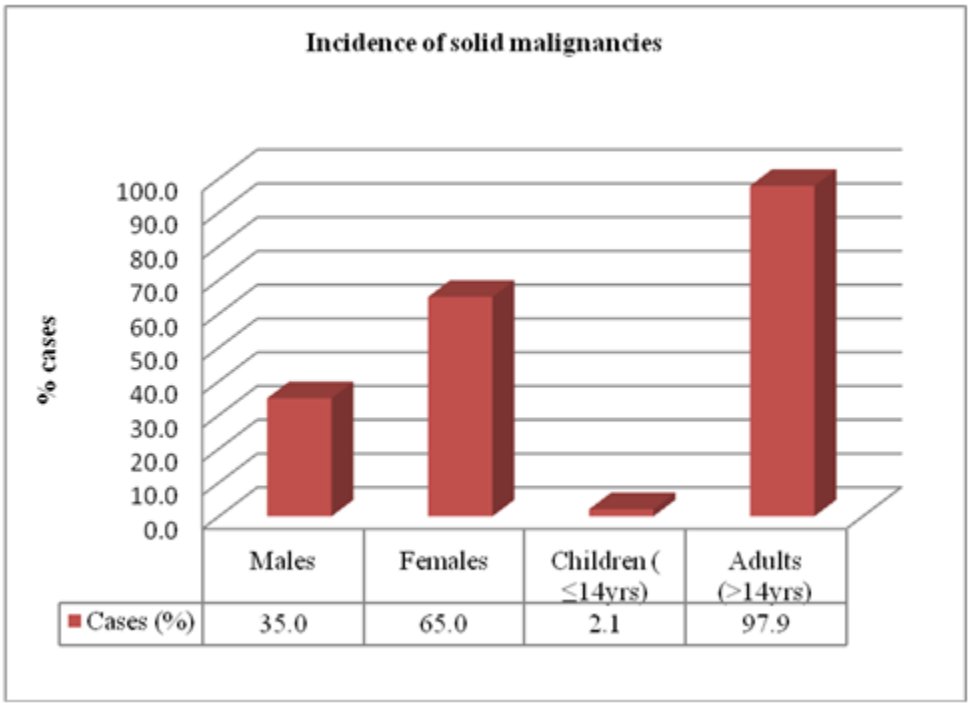


Figure 1: Demographics of solid malignancies: Incidence of various solid malignancies in study group

Legends:
GI - Gastro intestinal cancers; Gynec - Gynecological malignancies (cervix, ovarian and endometrial); H&N - head and neck cancer; Sarcomas – Bone and Soft tissue; Other SM – Other Solid Malignancies

Out of the 426 cases, 277 (65%) were females and remaining 149 (34%) were males. The mean age of females was 50.1±12.6 (Mean±SD) and male was also 50.87±18.2 (Mean±SD). Hence the average age of the whole cohort was 50.4±14.85 (Mean±SD). Among 426 solid malignancies only 2.1% represents children of below 14 years and remaining 417 (97.9%) were adults (Figure 2).

Figure 2



Demographics of solid malignancies (gender and age based)

The Mean ± SE of serum vitamin D in solid tumor cases was 15.53 ± 0.582 ng/mL (95%CI= 13.0 - 16.7) with a median value of 12.59ng/mL and the control group mean ± SE was 18.34 ± 0.671 ng/mL (95%CI=17.0 - 19.6) with a median value of 15.13 ng/mL. The average and median values were significantly low in solid tumors when compared to the control group (P=<0.0001). Subgroup analysis of various solid tumors also showed low vitamin D levels when compared with control subjects (Table I).

Table 1: Risk association of Vitamin D ranges in various Solid malignancies

S.No	Contents	No. of samples	Range (ng/mL)	Mean ± SE (ng/mL)	95% CI for the mean
1	Control group	426	3 - 70	18.34 ±0.671	17.02 - 19.65
2	Total cases	426	3 - 70	15.53 ± 0.582	14.38 - 16.67
3	Breast cancer	148	3 - 70	17.36 ± 1.03	12.08 - 17.73
4	Lung cancer	46	3 - 41	13.94 ± 1.57	10.76 - 17.11
5	Gynecological malignancies	51	3 - 57.8	15.97 ± 1.78	12.40 - 19.55
6	Prostate cancer	19	3 - 28.38	14.29 ± 2.09	9.89 - 18.69
7	Gastro Intestinal malignancies	74	3 - 60	13.01 ± 1.3	7.42 - 13.47
8	Head and Neck cancer	44	3 - 70	19.10 ± 2.08	14.90 - 23.31
9	Sarcomas (Soft tissue and bone)	24	3 - 29.9	10.89 ± 1.57	7.64 - 14.14
10	Others solid malignancies	20	3 - 45.48	12.73 ± 2.42	7.65 - 17.81

Out of 426 solid tumor cases, 380 cases were (89.2%) showed vitamin D deficiency and only 46 (10.8%) cases had sufficient serum vitamin D levels. Whereas, in the control group of total 426 cases, 355 cases registered serum vitamin D deficient (83.3%) and 71cases had sufficient vitamin D levels (16.7%). Vitamin D deficiency percentages in subgroup analysis too showed much higher deficiency rates compared with control group subjects. Vitamin D deficiency percentages in various categories solid tumors were observed in the following order Prostate (100%)>Sarcomas (95.83%)>others (95.0%)>GI (93.24%)>Lung (86.96%)>Breast (86.49)>Head & Neck (86.36%)>Gynecological malignancies (86.27%)>Controls (82.17%). (Figure 3).

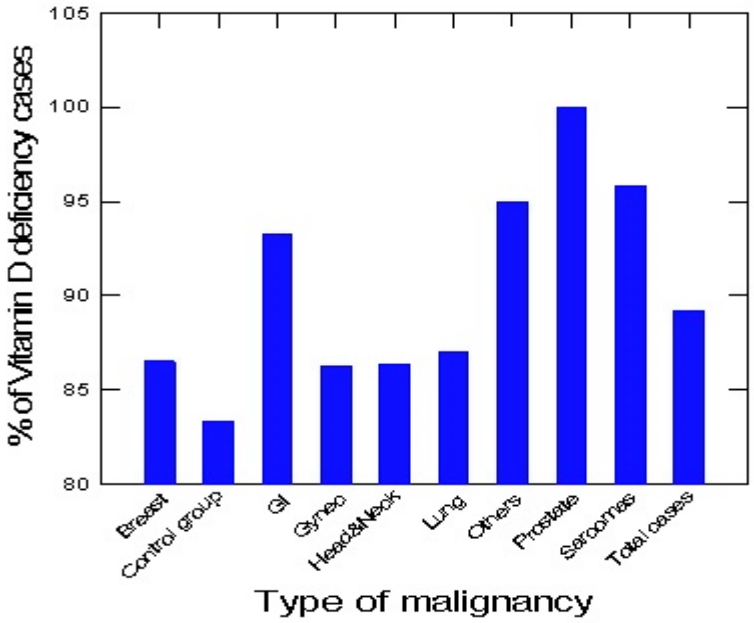


Figure 3:

Vitamin D deficiency percentage in various solid malignancies

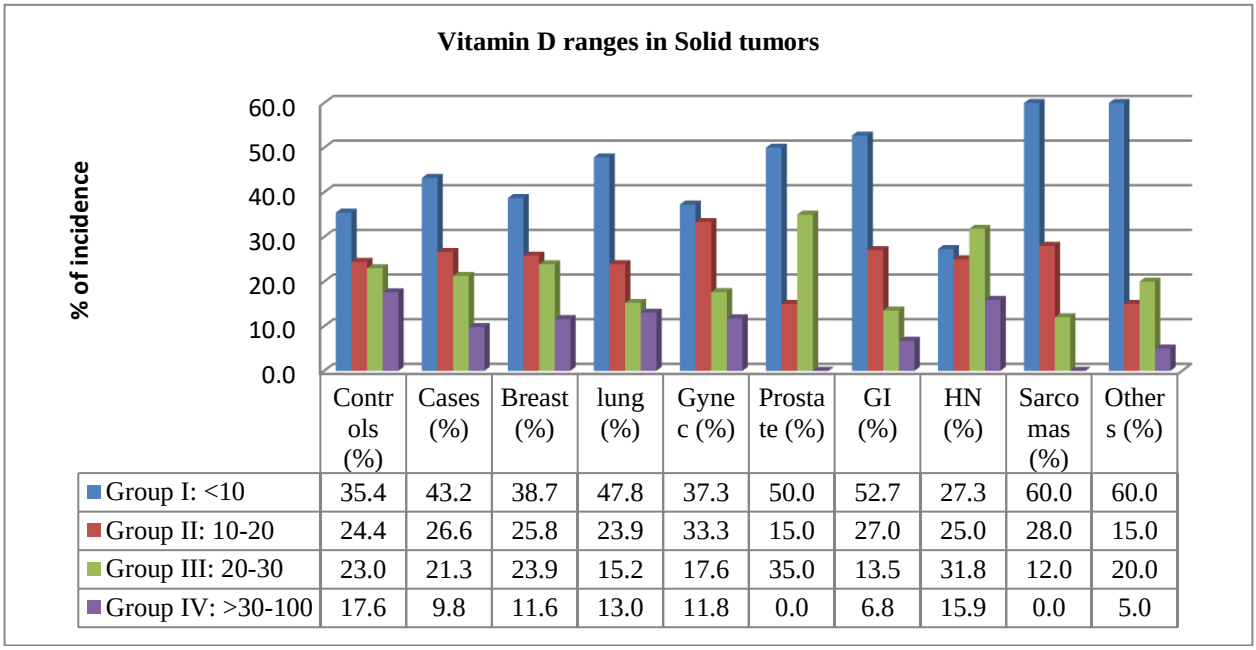
Despite an increased number of controls having deficiency of Vitamin D, solid malignancies had more higher deficiency rates with statistically significant representing the risk association towards the disease (Odds ratio, OR of 1.65; 95% CI=1.109 - 2.460, P value 0.013 and Relative risk ratio, RR 1.070). The Sub group analysis also revealed that low vitamin D levels were significantly associated with disease incidence in all subsets of solid tumors, especially in prostate cancer, GI and sarcomas. In prostate cancer, all 19 cases were vitamin D deficient and showing significant association when compared with male control samples (OR=8.30; 95% CI=0.487-141.49, P-value =<0.0001 and RR=1.21). Similarly in sarcomas, 95.83% cases were vitamin D deficient with statistically significant risk association (OR=4.6; 95%CI=0.611-34.6, P-value=0.138 and RR=1.15), followed by other solid tumors (OR=3.8; 95%CI=0.500-28.8, P-value=0.018 and RR=1.14,), GI (OR=2.76; 95%CI=1.075-7.085, P-value=0.034 and RR=1.12), lung (OR=1.25; 95%CI= 0.544-2.904; P-value=0.528 and RR=1.043), breast (OR=1.280; 95% CI=0.749-2.187, P-value=0.366 and RR=1.037), Head and Neck (OR=1.266; 95% CI= 0.5161-3.1091, P-value=0.605 and RR=1.0364) and Gynecological malignancies (OR=1.216; 95%CI=0.513-2.884, P-value=0.0348 and RR=1.029) (Table 2).

Table 2: Association of Vitamin D deficiency in Solid malignancies

S.No	Contents	Odds ratio (OR)	95% CI	z statistic	P value	Relative risk ratio (RR)
1	Control Vs Cases	1.652	1.10 to 2.46	2.471	0.0135	1.07
2	Breast cancer	1.28	0.749 to 2.187	0.903	0.366	1.037
4	Lung cancer	1.3333	0.5447 to 3.2635	0.63	0.528	1.0435
5	Gynecological malignancies	1.257	0.544 to 2.904	0.536	0.5922	1.0353
6	Prostate cancer	7.843	0.468 to 131.4	1.432	0.152	1.2
7	Gastro Intestinal malignancies	2.76	1.075 to 7.085	2.111	0.0348	1.1189
8	Head and Neck cancer	1.2667	0.5161 to 3.109	0.516	0.6059	1.0364
9	Sarcomas (bone &Soft tissue)	4.6	0.6113 to 34.617	1.482	0.1383	1.15
10	Others solid malignancies	3.8	0.5006 to 28.84	1.291	0.196	1.14

The present study also showed an inverse association between the disease incidence and vitamin D levels in all solid malignancies. We observed an increased incidence of disease in the cases where vitamin D levels were less than 10ng/mL (43.2%) in comparison to control group (35.4%). The disease prevalence was noticed in the subjects with the increased levels of vitamin D in all categories of solid malignancies. To understand the disease risk association with vitamin D levels, we have categorized all solid malignancy cases in to four groups viz, Group I (Vitamin D levels of below 10ng/mL), Group II (Vitamin D levels between 10.01-20.00 ng/mL), Group III (Vitamin D levels between 20.01-30.00 ng/mL) and Group IV (Vitamin D of >30.01 and <100 ng/mL). In breast cancer, the majority of the cases (38.7%) were presented with very less vitamin D levels, i.e, less than 10 ng/mL, and the prevalence decreased with increased levels of vitamin D i.e., 25.8% cases were in the range of 10-20 ng/mL and 23.9% cases in the range of 20-30 ng/mL and only 11.6% cases had sufficient vitamin D levels at the time of disease presentation. Similar findings were observed in all other categories of solid malignancies except head & neck cancer where more cases were observed in the range of Vitamin D levels >20-30ng/mL. This is followed by group I, II and IV and however only 15.9% cases had sufficient vitamin D levels and remaining 84.1% showed vitamin D deficiency (Figure 4).

Figure 4



	Controls (%)	Cases (%)	Breast (%)	lung (%)	Gynec (%)	Prostate (%)	GI (%)	HN (%)	Sarcomas (%)	Others (%)
Group I: <10	35.4	43.2	38.7	47.8	37.3	50.0	52.7	27.3	60.0	60.0
Group II: 10-20	24.4	26.6	25.8	23.9	33.3	15.0	27.0	25.0	28.0	15.0
Group III: 20-30	23.0	21.3	23.9	15.2	17.6	35.0	13.5	31.8	12.0	20.0
Group IV: >30-100	17.6	9.8	11.6	13.0	11.8	0.0	6.8	15.9	0.0	5.0

Association of Vitamin D levels and Incidence of solid tumors

Details of vitamin D ranges in various solid malignancies are represented in the below mentioned order.
Breast cancer: Group I (38.7%)>Group II (25.8)>Group III (23.9%)>Group IV (11.6%)
Lung carcinoma: Group I (47.8%)>Group II (23.9)>Group III (15.2%)>Group IV (15.2)
Gynecological malignancies: Group I (37.3%)>Group II (33.3)>Group III (17.6%)>Group IV (11.8%)
Prostate cancer: Group I (50.0%)>Group III (35.0%)>Group II (15.0%)>Group IV (0.0%)
Gastrointestinal cancers: Group I (52.2%)>Group II (27.0%)>Group III (13.5%)>Group IV (6.8%)
Head & Neck cancers: Group III (31.8%)>Group I (27.3%)>Group II (25.0%)>Group IV (15.9%)
Sarcomas (bone & soft tissue): Group I (60.0%)>Group II (28.0%)>Group III (12.0%)>Group IV (0.0%)
Other solid malignancies: Group I (60.0%)>Group III (20.0%)>Group II (15.0%)>Group IV 50%

Discussion

On an average 25% to 50% of the malignancies seen in routine clinical practice have serum vitamin D levels below the optimal range and estimated that up to 1 billion people have vitamin D deficiency globally. Several reports suggested that serum vitamin D deficiency leads to an increased incidence and poor outcomes in colorectal, breast, lung, melanoma and prostate cancers [7]. Despite of growing evidence of relationship between vitamin D levels and solid tumors, more data and research is to be needed to know about the risk and therapeutic outcomes in all malignancies. So far, most of the studies were focused on breast, prostate, and gastric cancers instead of

comprehensive studies on solid tumor subtypes. The present study focused on the importance of optimized serum vitamin D levels for healthy human physiology by determining serum vitamin D levels in various solid tumors along with the possible risk association between the disease and serum vitamin D deficiency status. Our results showed high percentage of vitamin D deficiency rates in all subtypes of solid tumors with an average deficiency of 89.2%, where as in controls it was 82.17%. Despite an increased number of controls having deficiency of Vitamin D, solid tumor cases showed more deficiency rates than control samples and found statistically significant risk association towards the disease. This study also revealed that the low levels of vitamin D is directly associated with higher risk of developing the disease in comparison to control group.

Among all the solid tumors, the prostate cancer had shown more positive association and high relative risk towards the disease than other malignancies. Studies reported that an increased incidence and mortality of prostate cancer was associated with limited exposure to sunlight and vitamin D deficiency [8]. Several studies on various GI cancers revealed that serum vitamin D levels have an inverse relationship with the disease status and progress. Bao et al found that the direct usage of 1,25-dihydroxy vitamin D3 induces cellular apoptosis in gastric cancer cells and also increased the expression of VDR and CYP24A1 supporting the anti-tumoral role that vitamin D may activate in gastric cancer. A recent cohort study found that paricalcitol (an analog to calcitriol) suppresses the growth of gastric cancer cells by regulating cell cycle, apoptosis and inflammation without inducing the hypercalcemia effects seen by calcitriol [3,9]. In another study by Yu et al demonstrated that calcitriol, in combination with the chemotherapy drug like gemcitabine increases caspase-dependent apoptosis of human pancreatic cancer cells both in vitro and in vivo [3,10]. The Meta-analysis has shown a clear inverse association between Vitamin D status risk of colorectal cancer and adenoma [11]. The polymorphisms in CYP24A1 and CYP27B1 can regulate and alter the vitamin D metabolism in colon cancer and supports the concept of further studies to determine the exact mechanism of vitamin D effects in colorectal cancer [3, 12, 13].

Our study showed 93.2% deficiency rate with significant risk association between the vitamin D levels and its possible risk in all the gastro intestinal malignancies (OR=2.76). It was observed that out of all the GI malignancies with the deficient of vitamin D levels, 31% of cases registered colorectal cancers. One study by Pourgholami et al showed that Vitamin D decreases the hepatocellular carcinoma proliferation in vitro and in vivo [3, 14]. The Meta-analysis of total 12 studies showed that high vitamin D status was associated with the decreased risk of lung cancer but the high vitamin D intake was not associated with decreased lung cancer risk [15, 16]. Though there is no statistically significant association in the meta-analysis study, there was a tendency of low risk of lung cancer in individuals with high levels of vitamin D intake. Their data suggest an inverse association between serum vitamin D and lung cancer risk, and its preventive role**.** Our study supports the meta-analysis of Liqun Zhang and substantiates the high deficiency rates at the time of disease presentation with significant risk towards the disease (OR=1.25). Thus, more focused studies are needed to investigate the effect of vitamin D intake on lung cancer risk. Compared to other cancer types, head and neck carcinomas have received a lesser attention and the data availability is limited so far. Rita et al observed an elevation in the immune cells and decreased tumor cells activity within the Head and neck squamous cell carcinoma (HNSCC) tissue followed by the treatment of 1,25 (OH)2D3. However, an interesting observation in the same study that the cancer recurrence was augmented by over 3-fold in the group receiving 1, 25(OH) 2D3 followed by the surgical treatment as opposed to the group of untreated patients [17].

These observations are leading to the debate of the extent of anti-tumor effectiveness of vitamin D metabolites and the variability in the levels that are used in studies to assess its anti-cancer potential in head and neck cancers. Our data presented with increased vitamin D deficiency and significant risk association in head neck cancers (OR=1.266) with an average deficiency of 87%. In our study the common cancers in females were breast (35%) and gynecological malignancies (11%) and of these 85% were found to have deficient levels. Among the six hospital based case control studies, four reported an inverse association between the dietary calcium intake and breast cancer risk whereas, the remaining two studies reported a non significant risk in the reduction of breast cancer up on consumption of high dietary calcium [18,19,20]. Our study showed 86.5% deficiency with statistically significant risk association with Odd,s risk ratio of 1.280. To further confirm the potential protective effects of calcium and vitamin D on breast cancer, well-designed studies are warranted. The Women's Health Initiative clinical trial of calcium and vitamin D supplementation may provide us with valuable information.

The sarcomas and other solid tumors like neuroblastoma, renal cell carcinoma, chorio carcinoma showed more than 95% of vitamin D deficiency with statistically significant risk association. Overall our study determined the increased incidence of Vitamin D deficiency in all the subgroups of solid malignancies. Subgroup analysis of

prostate, breast, gynecological, gastrointestinal, lung, Head and Neck cancers, sarcomas and other solid tumor cases showed an average 90% of vitamin D deficiency with low levels at the time of diagnosis when compared to healthy control samples. In addition to the increased vitamin D deficiency rates, our study also proved that low levels of vitamin D are disease is directly associated disease incidence in various categories of solid tumors. Our study observations suggest the importance of further comprehensive studies on the anti-tumor role of vitamin D metabolites and its significance in the disease status and risk association. Further studies should focus in determining the role of Vitamin D in various pathways of tumorgenesis. This would give an insight into the pathogenic mechanism and help to evolve the strategies for risk reduction and improved survivals.

The International Agency for Research on Cancer (IARC) released a report in 2008 on Vitamin D and Cancer and concluded that there is a consistent inverse association between serum 25-hydroxyvitamin D levels and the incidence of colorectal cancer and sporadic colorectal adenoma. Results from randomised controlled trials to date have not demonstrated an effect of vitamin D supplementation on colorectal cancer risk. As per the report the evidence for breast cancer seems to be weaker and there is no beneficial role in the reduction of prostate and other cancers. However, due to several issues like doses, interaction and duration they cannot be judged as contradictory to the evidence from observational studies either. Results from the observational studies and randomised trials suggest that vitamin D supplements may lower all cause mortality due to malignancies, but remains to be established. There is no much data available on the health hazards of long term maintenance of high 25-hydroxyvitamin D serum levels in the healthy subjects over long periods. Past experiences with other compounds (e.g., several anti-oxidants and hormone replacement therapies) have shown serious adverse effects of the chronic use of supplements or long-term maintenance of high serum levels.

Hypotheses on vitamin D status and colorectal cancer, cardiovascular diseases and all-cause mortality should be tested in appropriately designed randomised controlled trials [21]. William Grant has critically analyzed the IARC report 2008 on Vitamin D and Cancer and commented that, with the overwhelming evidence on the enormous health benefits and limited adverse effects by increasing serum Vitamin D levels at the population level will do much to reduce the economic burden of disease. The same author concluded also that the evidence available till date is strong enough to recommend vitamin D to prevent and treat cancer and suggests an early change in health policies based on present-day evidence, for better prevention of the disease [22]. Several issues make it difficult to draw the firm conclusions about the relationship of vitamin D and cancer, first the difficulty of attributing outcomes to the effect of a single nutrient versus other nutrients or non-nutrient factors. Second, the development of most cancers is a multifactorial process, making it difficult to assign causality to a single potential risk factor. Third, randomized controlled trial data are lacking and results from observational studies are often mixed or inconclusive. Fourth, the use of serum 25-OH-D levels as a biomarker has not been validated and measurement methodologies have been variable. Finally, the relationship between levels of 25-OH-D and cancer risk or mortality is not consistent across tumor types or between males and females. Despite these limitations, the vitamin D data are interesting enough to warrant more rigorous scientific investigations [23].

Overall our study demonstrated an increased prevalence of Vitamin D deficiency in the newly diagnosed solid malignancies. Subgroup analysis also showed low levels across all the subtypes of malignancies during diagnosis. It is crucial to know whether the biological properties of Vitamin D as suggested by basic and animal research actually exist in humans. Further studies should focus on determining the role of Vitamin D in various pathways of tumor genesis, prevalence of genetic polymorphisms which would give an insight into the pathogenic mechanism and help to evolve strategies for risk reduction and improved survivals. However, to date no recommendations were made for set up an optimal vitamin D levels that eventually may contribute to reduce the tumerognenesis or other chronic diseases.

Conclusion

The vitamin D deficiency is highly prevalent in our population and there is a significant association with all categories of solid tumors. Diet and sun exposure are not sufficient to maintain adequate levels of the vitamin, hence food fortification policies should ensure to adequate daily replacements of Vitamin D. As estimation of vitamin D is not routinely advised except in symptomatic patients, it is worthwhile screening for Vitamin D levels at the time of initial diagnosis of cancer and in routine Health Checks. Maintaining the adequate levels of Vitamin D may reduce the risk of cancer and improve overall clinical outcomes. Therefore, the future research should emphasize on its therapeutic implications and considering the Vitamin D as a predictive biomarker for various cancers.

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Conficts of interest
No conflicts of interest declared

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