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Vitamin D and Cancer: An overview on Epidemiological studies

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Abstract

In recent years, a rapidly increasing number of studies have investigated the relationship of vitamin D with total cancer and site-specific cancer obtaining diverse findings. In this chapter we provide an overview of epidemiological studies of vitamin D intake, 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D serum levels and vitamin D associated polymorphisms in relation to total and site-specific cancer risk. Overall, epidemiological evidence for total cancer is inconclusive. However, a large number of studies support a relationship of vitamin D with colorectal cancer and to a lesser extent with breast cancer. Findings are inconsistent for other cancers including all other gastrointestinal cancers and prostate cancer. Different vitamin D associated polymorphisms were found to be significantly associated to colorectal, breast and prostate cancer risk.

Keywords

Vitamin D, vitamin D intake, vitamin D supplements, 25-hydroxyvitamin D, 25(OH)D, 1,25-dihydroxyvitamin D, 1,25(OH)D, vitamin D receptor, VDR, polymorphism, SNP, neoplasms, colorectal neoplasms, prostatic neoplasms, breast neoplasms, lung neoplasms, gastric neoplasms, esophageal neoplasms, oesophageal neoplasms, hepatic neoplasms, pancreatic neoplasms.

Introduction

The first epidemiological studies on vitamin D and the risk of cancer appeared after ecological studies hypothesizing that geographical differences in cancer rates were to be attributed to variations in sunlight exposure and to vitamin D status, which is closely related to ultraviolet B (UVB) exposure [1]. Since then, several ecological studies have been conducted and associations between UVB, vitamin D and cancer have been suggested for as many as fifteen anatomical sites [2]. Plausible biological mechanisms have been proposed to explain in which way vitamin D could influence carcinogenesis. The biologically active vitamin D pathway metabolite $1,25(OH)_2D$ binds to the vitamin D receptor (VDR) regulating gene transcription and thereby influencing cancer development by reducing cell proliferation, angiogenesis and invasion, and by inducing cell differentiation and apoptosis [3]. Alternative mechanisms, such as anti-inflammatory effects, could also provide a basis for the influence of vitamin D in tumorigenesis [4,5]. The VDR has been found in human cancer cell lines throughout the body thus providing biological explanations to the associations between vitamin D and several types of cancer found in ecological studies. However, ecological studies are prone to potentially severe biases. In recent years a rapidly increasing number of individual level epidemiological studies have assessed the relationship between serum vitamin D levels and the risk of various forms of cancer. In this chapter, we provide an overview of current evidence on the association of vitamin D intake, serum vitamin D levels and vitamin D associated genetic polymorphisms with cancer risk from epidemiological studies.

Vitamin D and overall cancer risk

Few studies have assessed the association of 25-hydroxyvitamin D on the total burden of cancer. Most of these studies assessed the association with cancer mortality, whereas just three studies reported on cancer incidence. The earliest report on the association between 25(OH)D and the risk of all cancers dates from 2006. Investigators from the Health Professionals Follow-Up Study (HPFS), a large cohort study from the United States including more than 50,000 men, with 4,286 incident cancer cases and 2,025 cancer deaths during follow-up, reported increased cancer incidence and mortality for low levels of predicted 25(OH)D levels [6]. In a later analysis from the same population, it was also noted that the risk of cancer associated with low vitamin D was also modified by

ethnicity, with black men being at a higher risk of developing cancer as compared to white men [7]. Similarly, in the Uppsala Longitudinal Study of Adult Men (ULSAM), low 25(OH)D serum levels were also associated with increased risk of both cancer incidence and mortality [8]. On the contrary, in the “Cardiovascular Health Study”, a prospective, community-based cohort study of white older adults, low 25(OH)D was not significantly associated with cancer incidence [9].

In the Ludwigshafen Risk and Cardiovascular Health Study (LURIC), the association of 25(OH)D with total cancer mortality was assessed for patients referring to a coronary angiography [10]. The risk of dying from cancer was significantly decreased (HR, 0.45; 95%CI, 0.22-0.93) in the highest quartile of 25(OH)D (i.e., 25(OH)D concentration above 60 nmol/L) even after adjustment for relevant confounders. However, as the authors pointed out, the generalizability of the findings may be limited due to the specificity of the study population, being of Caucasian ethnicity, belonging to a small region of Germany, and referring to angioplasty [10]. In a population-based cohort study from Tromsø, Norway, serum 25(OH)D was measured separately for smokers and non-smokers, as the immunoassay seemed to overestimate 25(OH)D values for smokers [11]. In total 7,161 study participants had measured 25(OH)D serum levels. In contrast to the before-mentioned studies, 25(OH)D was not significantly associated with cancer mortality, neither in smokers nor in non-smokers [11]. Similarly, in the “InCHIANTI” study, another population-based cohort study of older men and women from Italy, quartiles of 25(OH)D were not significantly related to cancer mortality [12].

Melamed and colleagues assessed the relationship between serum concentration of 25(OH)D and cancer mortality in the Third National Health and Nutritional Examination Survey (NHANES III) [13]. The study population, which is representative of the US population, included adults above 20 years of age and belonging to different ethnic groups such as Hispanic blacks or Mexican Americans. Overall 25(OH)D was not associated with cancer mortality although a borderline increased risk of cancer was seen for the lowest quartile of 25(OH)D concentration (HR, 1.31; 95% CI, 0.96-1.81). In a more detailed analysis of the same study population with a particular focus on cancer [14], 25(OH)D serum levels and cancer mortality in men and women were not related. However, their data suggested an association of higher 25(OH)D concentrations with elevated risk of dying from cancer in men. On the other hand no association was observed among women [14]. Unexpectedly, an apparently protective effect of low 25(OH)D concentration with respect to cancer mortality was found in the “MrOS” study, a cohort of relatively

healthy community-dwelling men aged over 65 years of age from the US [14]. However, the number of cases was low and the risk estimate was on the borderline of statistical significance [15].

Overall, the evidence on the association between serum vitamin D and total cancer incidence and mortality remains inconclusive. Because it seems plausible that some cancers may be more vitamin-D-sensitive than others, we will in the following sections review the evidence for the association between serum vitamin D status and the risk of site-specific cancers.

Vitamin D and the risk of colorectal cancer

Colorectal cancer is the third most common cancer in the world and the first in developed regions [16]. In 2008, 1.2 million of new colorectal cancer cases were diagnosed (9.8% of all incident cancer) globally and more than 600,000 patients died from colorectal cancer (8.1% of the total cancer deaths) [16]. A large number of epidemiological studies have assessed the association of vitamin D with colorectal cancer. The risk of colorectal cancer has been assessed in relation to intake of vitamin D (total, dietary and from supplements), serum levels of 25(OH)D, a predicted 25(OH)D score, serum levels of $1,25(OH)_2D$, and polymorphisms of the VDR. Most of the studies focused on colorectal cancer incidence, except one study which addressed colorectal cancer mortality [17,18].

Vitamin D intake

The evidence on the association of vitamin D intake with colorectal cancer was summarized in two recent meta-analyses [19,20]. Although pooled risk estimates differed between both studies, due to different classification of the exposure to vitamin D (continuous or categorical), both studies consistently reported a significant reduction of risk of colorectal cancer overall, as well as of both colon and rectal cancer individually [19,20]. Moreover, the study by Touvier and colleagues distinguished between supplemental vitamin D and vitamin D from food, revealing a significant association of supplemental vitamin D, but not of dietary vitamin D with colon cancer risk [20]. Ma and colleagues observed stronger risk reductions for proximal and distal colonic segments [19].

25(OH)D levels and colorectal cancer

A number of meta-analyses of longitudinal studies have been conducted which consistently found an inverse relationship between

25(OH)D and colorectal cancer risk [17-21]. The most recent of these meta-analyses was conducted by Ma and colleagues [19] and included 9 studies with data from more than one million participants from several countries. Overall, 25(OH)D serum levels were significantly associated with a 33% reduction in colorectal cancer risk (HR, for the highest versus lowest 25(OH)D quartile: 0.67; 95% CI, 0.54-0.80). When stratifying by anatomical site, the risk reduction was similar for colon and rectum cancer. However, no significant risk reduction was observed for proximal and distal colon subsites. A stronger inverse association of 25(OH)D and colorectal cancer was noted in studies from the United States, as compared to European studies, whereas no significant association was observed in studies from Asia [19]. A more recent prospective study not included in the before-mentioned meta-analyses found no association between 25(OH)D and colon or rectal cancer in a population of male Americans participating in the Physicians' Health Study (PHS). However, when results from this newer investigation were pooled with previous studies of 25(OH)D and colorectal cancer, the authors still observed an inverse linear association [21]. Finally, high pre-diagnostic 25(OH)D levels have also been recently found to be associated with improved survival among colorectal cancer patients in the "European Prospective Investigation into Cancer and Nutrition" (EPIC) cohort [22].

$1,25(OH)_2D$ levels and colorectal cancer

The relationship of $1,25(OH)_2D$ and colorectal cancer has also been examined within the PHS but overall no significant association was observed [21]. The authors of this study also conducted a meta-analysis of prospective studies on the association of $1,25(OH)_2D$ and colorectal cancer risk. None of the four identified studies supported an association.

Vitamin D polymorphisms and colorectal cancer

A potential role of single nucleotide polymorphisms (SNPs) of the VDR for the risk of colorectal cancer has also been assessed in multiple studies [20,23]. A recent review and meta-analysis by Bai and colleagues identified 23 studies analyzing the risk of colorectal cancer in relation to several VDR polymorphisms [23]. In this study, among the five most commonly assessed VDR polymorphisms (BsmI, TaqI, FokI, ApaI and Cdx2), only the BsmI allele B was significantly associated with colorectal cancer risk (BB vs. bb: OR, 0.87, 95%CI, 0.80-0.94; BB vs. Bb + bb: OR, 0.90, 95%CI, 0.84-0.97). Further analyses indicated that this association was restricted to colon cancer and not seen for rectum cancer. Although the BsmI polymorphism is not functional, it has been reported to be in

linkage disequilibrium with the FokI polymorphism, which is thought to shorten the VDR protein and alter its transcriptional activity [23]. However, in a recent report from the EPIC study [22], neither BsmI, nor FokI genotypes were associated with the risk of dying from colorectal cancer or modified the association of 25(OH)D levels and colorectal cancer. Several limitations have to be kept in mind in the interpretation of genetic association studies of the relationship between vitamin D and colorectal cancer [24]. First, the majority of VDR polymorphisms are restriction fragment length polymorphisms (RFLPs) which are measured by rather insensitive techniques confined to small areas of the VDR gene and hence account for only a small variation in the DNA sequence of the VDR. Second, RFLPs are in most cases non-functional polymorphisms, although they are in some cases in linkage disequilibrium with other functional polymorphisms that could explain an association with cancer. Finally, the most commonly studied polymorphisms only address genetic variability in the VDR. It may also be of interest to account for genetic variability linked to vitamin D levels and vitamin D anticancer activity.

In summary, there is substantial and consistent evidence for an inverse association between 25(OH)D and colorectal cancer risk and for a potential protective effect of vitamin D. The possible mechanisms deserve further clarification.

Vitamin D and the risk of prostate cancer

Among men, prostate cancer is the second most frequently diagnosed cancer and the most prevalent cancer in the world. In 2008, more than 3 million patients had prostate cancer (23% of all prevalent cancers), almost 900,000 new prostate cancer cases were diagnosed (7.1% of all incident cancers) and more than 250,000 men died from prostate cancer (3.4% of the total cancer deaths) [16]. Prostate cancer is less fatal than other cancers (mortality/incidence ratio=0.29 [16]) but its treatment often substantially impairs quality of life. Efforts of prevention should particularly aim for reduction of aggressive disease which is associated with detriments in quality of life and lower survival. A common definition of aggressive prostate cancer is a combination of advanced stage (T3-T4) and high-grade (Gleason score >7).

Vitamin D intake

A large number of studies have aimed to address the role of the vitamin D pathway metabolites and vitamin D intake in the occurrence of

total and advanced prostate cancer [17,25,26]. For vitamin D intake, 13 observational studies were included in a recent review and meta-analysis conducted by Gilbert and colleagues [25]. For total prostate cancer, no association was observed in prospective and retrospective studies alone or in combination. Similarly, no statistically significant association with vitamin D intake was found for aggressive prostate cancer.

25(OH)D levels and prostate cancer

The review of Gilbert and colleagues also identified 14 prospective studies focusing on 25(OH)D and total prostate cancer risk (4,353 cases); 6 of these studies also included information on aggressive prostate cancer (871 cases) [25]. Despite the large number of cases, no association was found between 25(OH)D concentrations with either total or aggressive prostate cancer [17,25]. More recently, a case-control study nested within the Malmö Diet and Cancer study (943 prostate cancer cases, 943 controls) suggested a weak nonlinear association between 25(OH)D levels and the risk of prostate cancer [27]. Moreover, a recent analysis from the "Prostate Testing for cancer and Treatment" (ProtecT) study did not find an association of 25(OH)D with overall prostate cancer risk, but suggested that a decrease in 25(OH)D concentrations may be associated with occurrence of aggressive prostate cancer [28].

$1,25(OH)_2D$ levels and prostate cancer

Growth-inhibitory effects of $1,25(OH)_2D$ on prostate cancer cells have been reported [5]. The meta-analysis of Gilbert and colleagues also analyzed the risk of prostate cancer in relation to $1,25(OH)_2D$ [25]. Seven studies (of which only 2 had information on aggressive prostate cancer) were identified with a total number of 1,361 prostate cancer cases. Overall, no association was observed with neither total nor aggressive prostate cancer risk. Shortly after their meta-analysis, Gilbert and colleagues published a report on the association of circulating $1,25(OH)_2D$ and prostate cancer diagnosis, stage and grade within the ProtecT study [29]. No evidence of an association of circulating $1,25(OH)_2D$ and total prostate cancer risk was observed. However, lower $1,25(OH)_2D$ levels (<83.2 pmol/L) were associated with an increased risk of aggressive prostate cancer.

Vitamin D polymorphisms and prostate cancer

Associations of VDR gene polymorphisms with the risk of prostate cancer risk have been examined in several studies. A systematic review

and meta-analysis of 26 studies published in 2006 did not find any significant association for the most commonly assessed SNPs [30]. Most recently, Shui and colleagues conducted an investigation on the association of 97 polymorphisms related to the vitamin D pathway with the risk of prostate cancer [31]. Overall, variation in vitamin D related polymorphisms was significantly associated to lethal prostate cancer [31]. Furthermore, variants in the VDR and in the CYP27A1 gene (which encodes the enzyme involved in the hydroxylation of cholesterol to 25-hydroxyvitamin D) were also independently related to lethal prostate cancer.

In summary, no agreement hitherto has been reached on whether vitamin D is associated to prostate cancer risk. However, there are indications that vitamin D might play a more important role for the development of aggressive prostate cancer and ultimately prostate cancer mortality. These indications should be followed up in further epidemiological studies.

Vitamin D and the risk of breast cancer

Breast cancer is the most common cancer of women globally. More than 1.3 million of breast cancer cases were diagnosed in 2008 (11% of all incident cancers), with nearly 500,000 breast cancer deaths [16].

Vitamin D intake

A meta-analysis by Chen and colleagues published in 2010 included data from 5 case-control and 6 cohort studies examining the association of vitamin D intake and breast cancer risk [32]. The pooled relative risk showed a significant decrease in breast cancer risk for high vitamin D intake as compared to low vitamin D intake (HR, 0.91; 95%CI, 0.85-0.97). Further stratification by study type yielded a non-significant association for case-control studies and a significant association for cohort studies. The authors also investigated whether there were differences between pre-menopausal and post-menopausal populations. An inverse association was noted in premenopausal women whereas in post-menopausal women the association was not statistically significant. Interestingly, a statistically significant reduction of breast cancer risk was found in studies assessing vitamin D supplementation (3 studies), whereas for dietary vitamin D (10 studies), no significant association was observed [32].

25(OH)D levels and breast cancer

A meta-analysis by Yin and colleagues published in 2010 included 10 studies on the association of 25(OH)D serum levels and breast cancer risk [33]. Overall, a significant inverse association was found (HR for an increase of serum 25(OH)D by 20 ng/ml, 0.73; 95% CI, 0.60-0.88). Stratification by type of study indicated that the association was much stronger and statistically significant only in case-control studies with measurement of 25(OH)D levels close to the time of diagnosis whereas no significant association was found in cohort studies or nested case-control studies assessing 25(OH)D levels years before diagnosis.

$1,25(OH)_2D$ levels and breast cancer

Four studies assessing the association of $1,25(OH)_2D$ and breast cancer risk were included in the meta-analysis of Chen and colleagues [32]. Overall no association was observed between $1,25(OH)_2D$ and breast cancer risk.

Vitamin D polymorphisms and breast cancer

Associations of the most commonly assessed VDR polymorphisms with breast cancer risk have been examined in 21 case-control studies included in a meta-analysis by Tang and colleagues published in 2009 [34]. Overall, they found only the FokI polymorphism to be significantly associated with increased risk of breast cancer in European populations (ff vs. FF genotype: HR, 1.15, 95%CI, 1.03-1.28), with no evidence of high heterogeneity among studies. The “ff” genotype of the FokI polymorphism has been associated to a shift in the length of the VDR protein that could influence its transcriptional activity. However, a limitation of the studies included in the meta-analysis was an insufficient confounder adjustment (i.e., age, sun exposure and vitamin D intake were not included as covariates) which could explain the association observed for the FokI polymorphism [34]. More recently, in the “Shanghai Breast Cancer Study”, the FokI polymorphism and other common variants in the vitamin D pathway were not associated with breast cancer risk [35]. Furthermore, vitamin D related variants identified in a genome-wide association study were also not associated to breast cancer risk in this study.

Overall, the evidence for a protective role of vitamin D against breast cancer remains inconclusive. However, some promising findings from studies on vitamin D intake and on case-control studies on 25(OH)D levels suggest a potential role of vitamin D in breast cancer prevention that should be clarified in further research.

Vitamin D and the risk of lung cancer

Lung cancer is the most common cancer and the most common cancer cause of death globally. More than 1.6 million new lung cancer cases were diagnosed in 2008, with almost 1.4 million lung cancer deaths in the same year [16]. The biological plausibility of a potential association of vitamin D and lung cancer is supported by the effect of vitamin D on anti-inflammatory processes in the lung [36]. These mechanisms could not only have an influence on inflammatory lung diseases such as asthma or COPD but could also ultimately influence carcinogenesis [4,5,37]. Lung cancer, as other cancer sites, has also been related to low sunlight exposure [38]. In an ecological study comprising more than 111 countries, low UVB radiation, considered by the authors a marker of vitamin D deficiency, was associated with higher incidence rates of lung cancer [38].

To our knowledge no study has yet reported on the association of vitamin D intake with occurrence of lung cancer. However, improved survival has been reported for early-stage non-small-cell lung cancer patients with high vitamin D intake and high serum vitamin D levels [39,40].

In contrast to other major cancers, only few epidemiological studies have assessed the association of serum 25(OH)D levels with lung cancer risk, and none of the few studies did find an association in the overall population [6,14,41-44]. Looking at specific population subgroups, however, a significant inverse association with lung cancer incidence has been noted among women and young subjects in a Finnish cohort [42], an increased lung cancer mortality for higher 25(OH)D concentrations was found in men in the NHANES III study [14], a lower risk of lung cancer was found among Finish smokers whose blood was drawn during darker months in the Alpha-Tocopherol, Beta-Carotene (ATBC) Cancer Prevention Study [43], and a decreased lung cancer mortality was observed among smokers with high serum 25(OH)D concentrations also in the NHANES III study [44].

A recent in vitro study reported that the cellular mechanisms of $1,25(OH)_2D$ in lung cancer cells differ from those in other cancers [45]. For example in the prostate, $1,25(OH)_2D$ has an effect in apoptosis whereas in the lung the effect noted was a decrease in cell proliferation. Moreover, increased VDR expression correlated with increased $1,25(OH)_2D$ levels and was associated with improved survival in patients with lung adenocarcinoma [45]. We did not identify any epidemiological study on $1,25(OH)_2D$ and the occurrence of lung cancer. However, findings from in vitro studies suggest a role of this vitamin D metabolite in cancer

prevention. Other factors involved in the vitamin D pathway such as enzymes CYP27B1 and CYP24A1 have also been linked to the development of lung cancer [46].

Only two studies addressed the association of vitamin D related SNPs with the risk of lung cancer. In a case-control study comprising 137 lung cancer patients, the TaqI genotype “TT” was associated with a two-fold increase in the risk of lung cancer as compared to the “tt” genotype. In the same study the haplotype “baT” (BsmI, ApaI and TaqI) was associated with increased lung cancer risk as compared to the most common “BAt” haplotype [47]. VDR polymorphisms Cdx2, FokI and BsmI have been studied in American lung cancer patients. The “CC” genotype of the FokI polymorphism was associated with improved survival, whereas the haplotype “GTC” (Cdx2, FokI and BsmI) went along with worse survival [48].

In summary, evidence for the role of vitamin D in lung cancer risk is rather limited and inconclusive. However, indications of associations between 25(OH)D and lung cancer risk observed in subgroups of the general population and associations with vitamin D related SNPs deserve further study. In addition, there is a need of studies assessing the influence of vitamin D intake on lung cancer risk.

Vitamin D and the risk of other digestive tract cancers

Whereas the evidence for an inverse association of vitamin D and colorectal cancer risk is quite robust and supported by a large number of studies, available evidence is much more limited for the remaining digestive tract cancers. In the NHANES III study population, a combined endpoint of digestive cancers (esophageal, gastric, hepatic and pancreatic) was not significantly associated with 25(OH)D serum levels [14]. On the other hand, in the ULSAM cohort of Swedish men very strong multivariate-adjusted associations with a combined endpoint of pancreas, liver and biliary duct cancer mortality were observed for high (HR, 10.30; 95%CI, 1.81-58.56) and low (HR, 5.71; 95%CI, 1.81-18.03) 25(OH)D serum levels [8]. Next, we will review the epidemiological evidence for single digestive tract cancers other than colorectal cancer.

Gastric cancer

According to the estimates from the IARC, gastric cancer was the fourth most common cancer worldwide with about 1 million new gastric cancer cases diagnosed in 2008 (8% of the total). This cancer is highly

associated to economic status as nearly 70% of all incident cases occur in less developed countries where it is the second most common cancer and the third most common cancer cause of death. Incidence is particularly high in Eastern Asia. Major risk factors include *Helicobacter pylori* infection, smoking, alcohol drinking and consumption of processed meat, salty food and pickled vegetables [49].

In a case-control study conducted in an Italian population including 723 gastric cancer cases and 2024 controls and published almost 20 years ago, higher intake of vitamin D was associated to a higher risk of gastric cancer, with a statistically significant trend across quintiles of vitamin D intake [50]. To our knowledge, no further study has assessed the risk of gastric cancer according to intake of vitamin D.

A larger number of studies have analyzed the risk of gastric cancer in relationship to 25(OH)D. Two early studies did not find gastric cancer to be associated to predicted [6] and measured circulating vitamin D levels [51]. In the Cohort Consortium Vitamin D Pooling Project of Rarer Cancers" (VDPP), data were pooled from 10 prospective cohort studies from the US, China and Finland [52]. Overall, 784 gastric cancer cases were included in this consortium of which 135 were located in the gastric cardia. Overall, no association with total gastric cancer was observed. However, an increased risk of gastric noncardia cancer was observed for the highest vitamin D concentrations. Unexpectedly, among several population subgroups (Asians, never smokers and subjects with low alcohol consumption) low vitamin D levels (<50 nmol/L) as compared to normal vitamin D levels (50-75 nmol/L) were associated with a decreased risk of upper gastrointestinal cancer (no separate analyses were reported for gastric cancer) [53]. In addition, low 25(OH)D serum levels have also been associated with worse gastric cancer survival in Chinese patients [54]. In summary, the association of vitamin D and gastric cancer is still unclear and inconclusive and requires further study.

Esophageal cancer

Esophageal cancer is the eighth most common incident cancer worldwide with nearly half a million new cases in 2008 and the sixth most common cancer cause of death with over 400,000 deaths in 2008. Esophageal cancer is also more frequent in developing countries and especially in Southern and Eastern Africa [16].

Abnet and colleagues have repeatedly assessed the association of 25(OH)D levels with esophageal cancer in a high-risk Chinese rural population with unclear findings [51,55]. An increased risk of esophageal squamous dysplasia for high 25(OH)D concentrations [55] and an

increased risk of esophageal squamous cell carcinoma for low 25(OH)D concentrations were observed [51]. Moreover, Giovannucci and colleagues observed a strongly decreased esophageal cancer risk (RR, per increase by 25nmol/L: 0.37; 95%CI, 0.17-0.80) with increasing levels of predicted 25(OH)D [6]. On the other hand, in the VDPP study no association was observed between circulating 25(OH)D serum concentration and risk of total esophageal cancer (n=265 cases), adenocarcinoma (n=104) or small cell carcinoma (n=142 cases) [53]. Current evidence for esophageal cancer seems conflicting and more studies are needed to clarify these contradictory results.

Pancreatic cancer

With a mortality/incidence ratio of 0.96 [16], pancreatic cancer is one of the most fatal malignancies, with little if any improvement in survival during the past decades. Given the essential lack of effective treatment new approaches to prevention would be particularly relevant to reduce the burden of this cancer.

The association of vitamin D intake with pancreatic cancer risk has been assessed in two studies with conflicting results. In the HPFS and Nurses' Health Study (NHS) cohorts, higher intake of vitamin D was associated with lower risk of pancreatic cancer, with stronger associations among men (HPFS) than among women (NHS) [56]. Conversely, in a population from the San Francisco Bay Area, currently recommended dietary vitamin D intake was associated to higher odds of pancreatic cancer among male but not among female participants [57].

Results of studies analyzing the relationship of predicted 25(OH)D levels and pancreatic cancer are more consistent. In both the HPFS and the NHS, higher predicted 25(OH)D levels were associated with significantly lower pancreatic cancer risk [6,58].

Stolzenberg-Solomon and colleagues have repeatedly analyzed pancreatic cancer risk in relation to 25(OH)D levels in diverse populations with diverse findings. In the ATBC study population of Finnish smokers, higher vitamin D levels were associated with an increase in pancreatic cancer risk [59]. This finding was confirmed in the VDPP study, which included nearly 1,000 pancreatic cancer cases [60]. However, this apparent increment in pancreatic cancer risk with higher vitamin D concentration has recently been attributed to a statistical artifact by critics [61]. In the "Prostate, Lung, Colorectal and Ovarian Screening Trial" (PLCO), Stolzenberg and colleagues did not find an association between vitamin D and pancreatic cancer [62]. More recently, a pooled analysis of five large American cohorts (HPFS, NHS, PHS, WHI and WHS; 451

pancreatic cancer cases, 1,167 controls) found a significantly decreased pancreatic cancer risk for the higher versus lower plasma 25(OH)D levels [63]. Overall, the evidence remains conflicting and further investigations are needed to clarify the association between vitamin D and pancreatic cancer risk.

Liver cancer

Liver cancer is the sixth most common cancer worldwide with most of the burden occurring in developing countries (85% of the cases in 2008). Liver cancer is highly fatal, with a ratio of mortality to incidence of 0.93, making it the third most common cause of death from cancer in the world [16]. Liver cancer occurs mainly as a consequence of liver cirrhosis which in most cases is caused by hepatitis B and C, viral infections that are common in developing countries, or excessive alcohol consumption.

While no study on the association of 25(OH)D levels with liver cancer has been reported to date, several studies have indicated an antiproliferative/apoptotic effect of $1,25(OH)_2D$ and analogues on hepatocellular carcinoma (HCC) cell lines [2]. Furthermore, common VDR polymorphisms at restriction enzyme sites FokI, BsmI, ApaI and TaqI have been studied in relation to HCC in patients with liver cirrhosis. The genotypes bb (BsmI) and TT (TaqI) were associated with significantly increased risk of HCC [64]. Given the small number of studies conducted until now, and plausible biological mechanisms for a protective effect of vitamin D, further research is particularly important for this highly fatal cancer.

Vitamin D and rare cancers

Vitamin D levels have also been related to the risk of bladder cancer with diverse findings: a significant inverse association among male smokers in the ATBC study [65], a non-significant inverse association among men in the HPFS [6] and no association in the PLCO for non-smokers and women [66].

A systematic review published in 2008 assessed the association of vitamin D intake with endometrial cancer risk. Strong heterogeneity between studies and overall no association was found [67]. The VDPP study reported in 2010 did also not find an association between serum 25(OH)D levels and endometrial cancer [68].

In a meta-analysis of 10 studies of 25(OH)D levels and ovarian cancer reported in 2011, a tentative, statistically non-significant inverse

association was observed [69]. Additional analyses from the VDPP consortium likewise did not find evidence for an association [70].

A number of further studies have assessed associations of vitamin D with head and neck cancer [71,72], kidney cancer [73], non-Hodgkin lymphoma [74,75], brain cancer [6,76] and thyroid cancer [77] with diverse findings.

Methodological considerations

Investigating the association of vitamin D and cancer is subject to several methodological challenges. The use of a single measurement of 25(OH)D has been referenced in many studies on the association of vitamin D and cancer as a limitation. Fair correlations between measurements taken years apart, ranging from 0.77 to 0.42 and decreasing with time intervals between measurements have been reported in several cohort studies [78]. The decrease in correlation over time has been used to argue that studies with measurement of serum 25(OH)D close to the time of diagnosis might provide more valid estimates of association than studies with blood samples many years before diagnosis. However, as the vitamin D measurement becomes closer to the diagnosis of cancer, reverse causality becomes a potential concern. That is, low vitamin D status might be a consequence of the cancer or cancer associated changes in lifestyle habits. This issue is of special concern in case-control studies in which blood samples are usually taken at the time of diagnosis of patients.

Seasonal variation in 25(OH)D levels is substantial, especially in Northern latitudes, since UVB is the major contributor to vitamin D synthesis in the body and increasing differences in sunlight exposure across seasons are observed with increasing distance from the equator. Accounting for season of blood draw is therefore essential for studies on the association of vitamin D levels and cancer risk. Wang and colleagues evaluated the use of different methods to account for seasonal variation: adjusting for date of sample collection, matching on date of collection and using season-specific cut-off points to categorize subjects according to exposure. Not accounting for seasonality resulted in bias towards the null whereas adjusting for season in the model resulted in bias away from the null. The best approach was to create season-specific categories since it minimized bias toward the null and did not cause bias away from the null [79].

A variety of laboratory methods have been used for measuring 25(OH)D levels and discrepancies have been observed among them. This

source of variability severely impedes comparisons of studies using different 25(OH)D measurement methods. Therefore, standardization of measurements is needed. Liquid chromatography-Tandem Mass Spectrometry (LC-MS/MS) analysis is generally considered as the most reliable measurement method. In the past, the majority of studies have measured serum 25(OH)D levels by immunoassay (IA) analyses whose results substantially differed from those obtained by LC-MS/MS in studies where both methods were employed [80,81]. Both substantially higher and substantially lower values of IA measurements have been observed [80-82], which may lead to substantial bias in estimates of prevalence of vitamin D deficiency and thresholds of vitamin D levels below which cancer risk may be increased [82]. Standardization of 25(OH)D measurements will be crucial to overcome these potential problems in future studies.

Some studies have measured 25(OH)D only in a sample of participants and derived an algorithm for predicting 25(OH)D levels from this sample which was then applied to study participants for whom 25(OH)D measurements were not available [6,83]. Despite good agreement between predicted and measured 25(OH)D levels, use of predicted values will inevitably induce some imprecision which is expected to attenuate true associations with cancer risk. Therefore, true measurements should be used whenever feasible.

Finally, many previous studies have assumed a linear association between 25(OH)D and cancer risk in their models of analysis. By this approach, possibly non-linear associations e.g., increased risk at both the lower and the upper end of the 25(OH)D distribution, may have been missed. Given repeated reports of “U-shaped” associations [8,60], future studies should aim for careful dose-response analyses of potential association between vitamin D status and cancer.

Conclusion

In the past few years, a rapidly increasing number of studies have assessed a potential role of vitamin D for cancer risk and survival. Despite a large heterogeneity in study designs, settings and results, there is increasing evidence that low levels of vitamin D may increase the risk of several cancers, the evidence being strongest for colorectal cancer. Given the high prevalence of low vitamin D levels in many populations and easy, non-interventional possibilities to increase exposure (moderate, well-dosed sun exposure, ideally combined with outdoor physical activity or supplementation) a possible role of vitamin D in cancer prevention should

be followed-up with high priority in both epidemiological and intervention studies.

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