Review

Epidemiology of Vitamin D Insufficiency and Cancer Mortality

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Abstract. *There is growing evidence that vitamin D exerts anticarcinogenic effects. Ultraviolet-B (UV-B) radiation, which is required for vitamin D production in the skin, was found to be inversely associated with cancer incidence and mortality. Recent studies have largely but not consistently shown that low 25-hydroxyvitamin D (25(OH)D) levels, which are considered to be the best indicator of vitamin D status, are a significant risk factor for cancer mortality. Circulating 25(OH)D levels were also associated with improved survival in colorectal and lung cancer patients and vitamin D insufficiency was observed in various other diseases such as autoimmune, infectious, musculoskeletal, neurological and cardiovascular diseases. In conclusion, we still need further studies to evaluate the association of vitamin D insufficiency and cancer incidence and mortality, but the multiple health benefits of vitamin D and the easy, safe and inexpensive way by which vitamin D can be supplemented should already guide current public health strategies to achieve 25(OH)D levels of at least 75 nmol/l (30 ng/ml) in the general population.*

Cancer research over the last three decades has produced accumulating evidence in favour of the hypothesis that a poor vitamin D status is associated with an increased cancer risk (1, 2). This is of particular importance for public health when considering the worldwide high prevalence of vitamin D insufficiency (3, 4). This pandemic of vitamin D insufficiency is mainly a consequence of lifestyle (*e.g.* reduced outdoor activities) and environmental factors (*e.g.* air pollution) that limit ultraviolet-B (UV-B) exposure of the skin, with subsequently reduced dermal vitamin D production (4). In general, UV-B-induced vitamin D production in the skin is the main source of vitamin D, whereas dietary vitamin D intake plays only a minor role (4).

Classification of the vitamin D status is usually carried out according to serum levels of 25-hydroxyvitamin D (25(OH)D) which is produced by hydroxylation of vitamin D in the liver (3). 25(OH)D is then converted to 1,25-dihydroxyvitamin (1,25(OH)$_2$D) by 1α hydroxylase activity in the kidney and various other tissues (1, 2, 5, 6). 1,25(OH)$_2$D activates the vitamin D receptor (VDR), which is nearly ubiquitously expressed and mediates its effects through binding to VDR response elements on the DNA that regulate approximately 3% of the human genome (7). Given this important role for the regulation of many different genes, it has been increasingly recognised that vitamin D exerts several molecular effects which are important to prevent the initiation and progression of cancer (1, 2). In this context, it has been shown that vitamin D and its metabolites play a central role in regulation of cell growth and the cell cycle, cellular differentiation, apoptosis, immune modulation, and in the integration of hormonal and cellular signalling pathways (1, 2). Molecular effects of vitamin D that are relevant for carcinogenesis have been excellently reviewed elsewhere (1, 2). In this brief review, we aim to provide an overview of the epidemiology of vitamin D insufficiency and overall cancer mortality, with a main focus on prospective follow-up studies and randomized controlled trials.

UV-B Radiation and Cancer Mortality

In 1941, Frank L. Apperly published data on an inverse association of solar radiation and cancer mortality (8). He concluded that exposure of suitable skin areas to sunlight might reduce cancer deaths, but his work did not significantly stimulate further research in this field at that time (8). About four decades later, in 1980, Garland and

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Garland were the first in modern literature to hypothesize that low UV-B radiation and subsequently reduced 25(OH)D levels were a risk factor for cancer mortality (9). Their hypothesis was based on the observation that colon cancer mortality in the US was significantly increased in populations with low exposure to solar UV-B radiation. Since then, the knowledge on UV-B radiation and cancer mortality has been extensively increased and was recently reviewed by Grant and Mohr (10). In brief, previous studies have shown that solar UV-B radiation was inversely associated with cancer incidence and mortality of up to 19 cancer sites (11). Importantly, the initial observations of inverse associations of UV-B and cancer mortality, which were largely made in the United States (US), have been further supported in various countries and at different latitudes (10). Furthermore, Grant *et al.* showed that even after considering the confounding factors of alcohol consumption, Hispanic heritage, urban/rural residence, poverty level and smoking (for lung cancer mortality), there still remained 13 cancer sites whose mortality rates were inversely associated with UV-B radiation: bladder, breast, colon, esophagus, gallbladder, stomach, ovary, pancreas, prostate, rectum, kidney and uterine corpus cancer, as well as Hodgkin's lymphoma (12).

An important aspect concerning the influence of UV-B exposure on vitamin D production and cancer is that due to their higher melanin content in the skin, black persons require more UV-B exposure than whites to produce similar amounts of vitamin D. Hence, blacks have a higher prevalence of vitamin D insufficiency than whites, raising the hypothesis that the higher cancer mortality rate among the US black population compared to US whites might partially be attributable to differences in vitamin D status. Indeed, data from the Health Professionals Follow-Up Study (HPFS), a cohort study among 47,800 men, showed that black men with risk factors for vitamin D insufficiency had a significantly increased risk of cancer mortality compared to white men (relative risk (RR) 2.27; 95% confidence interval (CI) 1.57-3.28) (13). On the other hand, there was no significant difference in cancer mortality when blacks with few risk factors for hypovitaminosis D were compared with whites.

Vitamin D Insufficiency and Cancer Mortality

In 2006, Giovannucci *et al.* were the first to present results of a prospective study on 25(OH)D levels and cancer mortality by analyzing data from the HPFS (14). 25(OH)D levels were measured in 1,095 out of 47,800 study participants and determinants of 25(OH)D levels, including vitamin D intake, skin pigmentation, geographic residence, sunlight exposure and body mass index, were used to estimate/predict 25(OH)D levels in the remaining study cohort. During the follow-up period from 1986 to January 31, 2000, 4,286 incident carcinomas and 2,025 cancer deaths occurred. After adjustments for possible confounders, an increment of 25 nmol/l in these predicted 25(OH)D levels was associated with a 17% reduction in total cancer incidence (RR 0.83; 95% CI 0.74-0.92) and a 29% reduction in total cancer mortality (RR 0.71; 95% CI 0.60-0.83). Significant inverse associations per increment of 25 nmol/l were also observed for colorectal (RR 0.63; 95% CI 0.48-0.83), pancreatic (RR 0.49; 95% CI 0.28-0.86), esophageal (RR 0.37; 95% CI 0.17-0.80) and oral or pharyngeal cancer mortality (RR 0.30; 95% CI 0.11-0.81).

In 2007, Freedman *et al.* published results from the Third National Health and Nutrition Examination Survey (NHANES-III), a study among 16,818 participants from the noninstitutionalized US population (15). The investigators of NHANES-III recorded 526 cancer deaths during follow-up. There was no significant association of 25(OH)D levels and total cancer mortality after adjustments for age, sex, race/ethnicity and smoking history. Colorectal cancer mortality was, however, reduced by 72% (95% CI 32-89%) when comparing persons with 25(OH)D levels above 80 nmol/l with those having 25(OH)D levels below 50 nmol/l. Breast cancer mortality was not significantly associated with vitamin D status when using 25(OH)D levels as a continuous variable but was significantly reduced in participants with 25(OH)D levels ≥62.5 nmol/l when compared to those with lower 25(OH)D concentrations (RR 0.28; 95% CI 0.08-0.93).

We also addressed the issue of vitamin D status and cancer mortality in 3,299 patients form the Ludwigshafen Risk and Cardiovascular Health (LURIC) study, a prospective cohort study from Germany among patients referred for coronary angiography (16). In that study, 95 cancer deaths occurred during a follow-up period of 7.75 years. The risk of total cancer mortality was reduced by 55% (RR 0.45; 95% CI 0.22-0.93) in the fourth *versus* the first 25(OH)D quartile.

Summarizing the results of these three studies we have inconsistent results, with two studies (HPFS and LURIC) which found a significant association of compromised vitamin D status and total cancer mortality and one study (NHANES-III) which observed significant associations only for colorectal and breast cancer mortality but not for 25(OH)D levels and total cancer mortality. Underlying differences of the study populations and study designs may account for these inconsistent results. In particular, the study cohorts of LURIC and NHANES-III were significantly different, with the LURIC cohort being 2 decades older with much lower 25(OH)D levels and a more homogeneous study population compared to the very

heterogeneous study cohort of NHANES-III which included various ethnicities from different geographic regions in the US. Of note is that after the LURIC data were published, Freedman *et al.* performed a reanalysis of NHANES-III for non-Hispanic whites by using a reference group (lowest 5%) with similar 25(OH)D concentrations as the reference group (lowest quartile) in the LURIC study. The risk of cancer mortality was non significantly reduced by 22% in the lowest 5% in NHANES-III (RR 0.78; 95% CI 0.42-1.43), when compared to the highest quartile (17). Hence, this latter analysis might suggest that the association of vitamin D insufficiency and increased cancer mortality is particularly apparent for persons with very low 25(OH)D levels. However, according to the conclusion by Freedman *et al.*, the small numbers with depressed 25(OH)D levels in NHANES-III limit the power of that study to discern effects at very low 25(OH)D levels (17).

Importantly, both the LURIC and NHANES-III studies considered the seasonal variations in 25(OH)D levels in their statistical analyses, because the seasonal changes in UV-B exposure are responsible for circannual differences of the vitamin D status (16, 17). This is well illustrated by observations that 25(OH)D levels are up to twice as high at the end of the summer when compared to winter levels (16, 18-20). To reduce possible confounding by these seasonal variations in 25(OH)D levels, we and others classified the vitamin D status of an individual according to the percentile distribution of 25(OH)D levels within the respective month in which blood was drawn (17, 18). We therefore suggest that in the future the vitamin D status of an individual be classified not only according to absolute 25(OH)D levels but also according to percentiles of population-based 25(OH)D levels for each month of the year. Another issue which is important to consider when interpreting or analyzing data on vitamin D and cancer is the fact that low physical activity is related to both vitamin D insufficiency and increased cancer risk and may therefore be a possible confounder (20). This problem is, however, complex because reduced physical activity with subsequent reduced outdoor activities and lower UV-B exposure is not only a cause of vitamin D insufficiency but might also be a consequence of vitamin D insufficiency. In this context, it has been demonstrated that vitamin D exerts beneficial effects on musculoskeletal health and reduces fractures and falls thereby preventing immobilisation (2, 4). Given that the assessment of physical activity is not trivial, it was not measured and adjusted for in most of the aforementioned studies but the LURIC study did show that the association of cancer mortality and vitamin D insufficiency remained significant even after adjustment for physical activity level (16).

Vitamin D Insufficiency and Mortality Among Cancer Patients

Observations that cancer patients who were diagnosed in summer had a better survival compared to those diagnosed in winter, and findings that the associations of low UV-B radiation and indices of a poor vitamin D status were stronger for cancer mortality than for cancer incidence, stimulated further studies to evaluate whether 25(OH)D levels are related to mortality in cancer patients (10, 21). Towards this, Ng *et al.* studied 304 participants from the Nurses' Health Study (NHS) and the HPFS who were diagnosed with colorectal cancer during the respective study periods (21). Participants in the highest quartile of 25(OH)D levels had a 48% lower risk of total mortality (RR 0.52; 95% CI 0.29-0.94) when compared to patients within the lowest quartile. In addition, among 447 participants with early stage non-small cell lung cancer (NSCLC), the risk of mortality was non-significantly reduced by 26% in the highest *versus* the lowest 25(OH)D quartile (RR 0.74; 95% CI: 0.50-1.10; P for trend 0.07) (20). This latter association was statistically significant for patients with stage IB-IIB (RR 0.45; 95% CI 0.24-0.82) but not for those with stage IA cancer (22).

Apart from this, it is important for us to point out that a poor vitamin D status has also been associated with increased total mortality in two population-based studies (23, 24). Furthermore, Autier and Gandini published a recent meta-analysis of randomized controlled trials which showed that vitamin D supplementation was associated with a statistically significant reduction of total mortality (RR 0.93; 95% CI 0.87-0.99) (25). These data underline that beyond cancer, vitamin D exerts multiple effects that are relevant for overall health resulting in an increased lifespan (2, 4).

Vitamin D Supplementation and Cancer Mortality

The impact of a daily supplementation of 400 IU vitamin D plus 1,000 mg calcium on cancer mortality was evaluated in the Women's Health Initiative (WHI), a randomized, double-blind, placebo-controlled trial among 36,282 women (26, 27). During an average follow-up period of 7 years, 726 patients died due to cancer. There was a non-significant reduction of cancer mortality of 11% in the vitamin D and calcium *versus* the placebo group (RR 0.89; 95% CI 0.77-1.03; *p*=0.12) (26). When interpreting these statistically non significant results of the WHI, it should be underlined that there is a general consensus that daily vitamin D doses of 400 IU (as used in the WHI) are too low to sufficiently raise the vitamin D status to 25(OH)D levels which significantly improve health outcomes and which should be at least as high as

Table I. *Associations of vitamin D and cancer risk.*

Study (ref)	Study design	Outcome measure	Risk reduction of cancer per increase of 25 nmol/l (10 ng/ml) in 25(OH)D level
Lappe *et al.* (31)*	Randomized controlled trial	Cancer incidence	60%
Lappe *et al.* (31)**	Prospective follow-up	Cancer incidence	35%
LURIC (16)	Prospective follow-up study	Cancer mortality	34%
HPFS (14)	Prospective follow-up study	Cancer mortality	29%
WHI (26)***	Randomized controlled trial	Cancer mortality	23%
Trivedi *et al.* (30)****	Randomized controlled trial	Cancer mortality	17%
NHANES-III (15, 17)	Prospective follow-up study	Cancer mortality	Data not available

*Risk reduction of cancer was calculated according to the difference of 24.9 nmol/l in 25(OH)D levels after 12 months of treatment between the vitamin D plus calcium and the placebo group, and the risk reduction of cancer incidence in the calcium plus vitamin D group of 60% (31).
**Predictive value of baseline 25(OH)D levels for cancer incidence (31).
***Risk reduction of cancer was calculated according to the estimated increase of 25(OH)D of 11.8 nmol/l and the risk reduction of cancer mortality in the intervention group of 11% (14 and 26).
****Risk reduction of cancer was calculated according to the difference of 20.9 nmol/l in 25(OH)D levels between the vitamin D and placebo group, and the reduction of cancer mortality in the intervention group of 14% (30).

75 nmol/l (30 ng/ml) (28). This notion is in line with other vitamin D-related health outcomes because a recent meta-analysis showed that vitamin D intake had no significant effect on fracture risk in randomized, placebo controlled trials with a daily supplementation of 400 IU vitamin D (29). The incidence of fractures was, however, significantly reduced by vitamin D supplementation in studies using daily vitamin D doses >400 IU (29). Furthermore, in addition to the WHI study, another randomized, double-blind, controlled trial involving a four-monthly supplementation with 100,000 IU vitamin D was performed among 2,686 people aged 65-85 years living in the general community of Great Britain (30). In that study, risk of total cancer mortality was non significantly reduced by 14% in the vitamin D *versus* the placebo group (RR 0.86; 95% CI 0.61-1.20) (30).

Moreover, Lappe *et al.* performed a randomized controlled trial among 1,179 healthy community-dwelling postmenopausal women (31). This trial included three groups: placebo, calcium (1,400-1,500 mg) and calcium (1,400-1,500 mg) plus 1,100 IU vitamin D. Fifty women developed cancer during the study duration of 4 years including 13 incident cases diagnosed in the first year of the study. Compared to the placebo group, the risk of incident cancer was reduced by 60% in the vitamin D plus calcium group (RR 0.40; 95% CI 0.20-0.82). This latter analysis was repeated for women free of cancer after 1 year of follow-up in order to reduce possible bias by occult cancer that was already present but not diagnosed at baseline. In this analysis, risk of incident cancer was reduced by 77% in the calcium plus vitamin D *versus* the placebo group (RR 0.23; 95% CI 0.09-0.60). For both these analyses there was no significant difference for cancer incidence between the placebo and the calcium group. This

study by Lappe *et al.* does not provide data on cancer mortality but the findings of this trial with regard to cancer incidence are of great importance because this was the first study to show to vitamin D supplementation significantly reduced the risk of cancer in a randomized placebo-controlled trial.

Conclusion

Epidemiological data from prospective follow-up studies and randomized controlled trials on the association of vitamin D insufficiency and risk of cancer mortality are largely but not consistently in favour of the hypothesis that a sufficient vitamin D status protects against the initiation and progression of cancer. To provide an overview of the published study results in this field we listed the risk reduction of cancer per increase of 25 nmol/l (10 ng/ml) in 25(OH)D levels by using and/or extrapolating the results from the aforementioned studies (see Table I). It turned out that the vitamin D effects on cancer were relatively well comparable among the studies with available data ranging from a cancer risk reduction of 17% to 60% per increase of 25 nmol/l (10 ng/ml) in 25(OH)D levels (Table I). We are aware that the data from Table I are based on some assumptions (*e.g.* linearity of the association of 25(OH)D and cancer risk) which should not be made lightly. However, the results which we present are simply an estimate to give an idea of the effects and the differences in the vitamin D cancer associations of the currently available study results (Table I).

There is compelling molecular and epidemiological evidence that vitamin D protects against cancer. The central question is whether the current evidence is sufficient for public health recommendations for vitamin D

supplementation and/or increased UV-B exposure? In our opinion, we still need further evidence to strengthen the notion that vitamin D protects against cancer. However, when considering general recommendations for maintaining a sufficient vitamin D status it should also be emphasized that vitamin D insufficiency has been associated with several diseases such as autoimmune, cardiovascular, neurological, metabolic or infectious diseases as well as fractures and falls (2, 4, 29). Hence, in view of the multiple health benefits of vitamin D, the high prevalence of vitamin D insufficiency, and the easy, safe and inexpensive way in which vitamin D can be supplemented, in our opinion, it is time to implement public health strategies for maintaining a sufficient vitamin D status of the general population (28, 32, 33).

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