

PROCEEDINGS OF THE 4TH INTERNATIONAL
SYMPOSIUM ON VITAMIN D AND ANALOGS
IN CANCER PREVENTION AND THERAPY

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Preface

Vitamin D and its Analogs in Cancer Prevention and Therapy

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Scientists interested in the pleiotrophic biological effects of vitamin D are working on a fascinating topic that is of great relevance for prevention and therapy of many diseases, including cancer. In recent years, our knowledge about the great impact of vitamin D on the prevention of various types of malignancies has been greatly increased and new promising strategies for the therapeutic use of vitamin D and analogs in oncology are being developed. Focused on this topic, the Fourth International Symposium entitled “Vitamin D and Analogs in Cancer Prevention and Therapy”, that was organized by the Klinik für Dermatologie, Venerologie und Allergologie, Universitätsklinikum des Saarlandes, Homburg/Saar, Germany, and the Klinik für Frauenheilkunde und Geburtshilfe, Helios Klinikum Krefeld, Krefeld, Germany, was held from May 20-21, 2011 at the Schlossberg Hotel in Homburg, Germany. Selected articles related to presentations at this symposium are published in this Special Issue of Anticancer Research. The symposium was held under the auspices of the Deutsche Forschungsgemeinschaft (DFG), the Deutsche Krebshilfe (DKH), the Deutsche Gesellschaft für Ernährung (DGE), and the Ministerium für Gesundheit und Verbraucherschutz des Saarlandes. It was the aim of this scientific meeting to present and to discuss the latest developments in epidemiology, molecular oncology, metabolism, biologic effects, epigenetics and clinical applications of vitamin D and its analogs that have lead to fascinating new strategies for the application of these compounds in cancer prevention and therapy. After the welcome address of Minister G. Weisweiler (Saarland Ministry of Health and Consumer Protection) and the opening remarks of J. Reichrath and M. Friedrich, thirty-eight keynote lectures by leading scientists were presented and the resulting conclusions were summarized and discussed at the end of this

symposium in a round table discussion. The most important findings and conclusions of this meeting can be summarized as follows:

Cancer Prevention: Convincing evidence from epidemiological and laboratory investigations and from animal studies now clearly demonstrates that vitamin D deficiency/insufficiency is largely underestimated worldwide and is related to a broad variety of severe health problems, including increased cancer risk and unfavourable prognosis of cancer. However, there is still urgent need for additional well-designed studies (randomized, placebo controlled, double-blind clinical trials) to define the optimal vitamin D status (25-hydroxyvitamin D serum level), especially to answer the question whether there is a so-called U-shaped curve, with risks at both low and high vitamin D serum levels. Moreover, there is an urgent need for campaigns to better inform both the public and the medical profession about health risks related to vitamin D deficiency and insufficiency. In this context, a recently published report (1) of the Institute of Medicine (IOM), analyzing the population needs for calcium and vitamin D in North America was discussed and criticised. On the one hand, the IOM Committee had concluded in its comprehensive review that available scientific evidence supports a key role of calcium and vitamin D in skeletal health, consistent with a cause-and-effect relationship and providing a sound basis for determination of intake requirements. On the other hand however, for extraskeletal outcomes, including cancer, they concluded that the evidence was inconsistent, inconclusive as to causality, and insufficient to define nutritional requirements. Moreover they stated that randomized clinical trial evidence for extraskeletal outcomes was limited and in general uninformative. Based on bone health, the IOM committee concluded that recommended dietary allowances (RDAs; covering requirements of $\geq 97.5\%$ of the population) for vitamin D of 600 IU/d for ages 1-70 years and 800 IU/d for ages 71 years and older, corresponding to a serum 25-hydroxyvitamin D level of at least 20 ng/ml (50 nmol/l), meet the requirements of at least 97.5% of the population. Higher values were, according to their analysis, not consistently associated with greater benefit, and for some outcomes, U-

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shaped associations were observed, with risks at both low and high levels. Moreover, the IOM committee concluded that the prevalence of vitamin D inadequacy in North America has been overestimated. These key findings of the IOM report were discussed and criticised by the majority of participants of this meeting. The majority of participants were convinced of results of an increasing number of epidemiological and laboratory investigations that demonstrate an association of various types of cancer, including colon, prostate and breast cancer, with low estimated exposure to solar UV-radiation, low vitamin D intake, or vitamin D deficiency or insufficiency. Although many participants agreed that several of these studies are limited due to methodological problems including a relatively low number of observation years or difficulties in assessing correct estimates of vitamin D status (exposure to solar UV radiation, vitamin D intake or 25(OH)D measurements), the majority of participants agreed that a large number of epidemiologic and laboratory investigations now clearly support an association between vitamin D deficiency/insufficiency and multiple independent diseases, including various types of cancer. More recently, an Endocrine Society clinical practice guideline for the evaluation, treatment, and prevention of vitamin D deficiency has been published (2), whose conclusions are more in line with the lectures presented at this symposium as compared with those of the IOM report (1). Considering that vitamin D deficiency is very common in all age groups and that few foods contain vitamin D, the Endocrine Society Task Force recommended supplementation at suggested daily intake and tolerable upper limit levels, depending on age and clinical circumstances. In general, these recommended supplementations were higher than those recommended by the IOM report. It has now been widely recognized by the scientific community that the discovery of extrarenal 25(OH)D-1 α -hydroxylase (CYP27B1) activity in a broad variety of different tissues is of particular importance for the role of vitamin D in cancer prevention. Nevertheless, there was general consensus at this meeting that further evidence has to be obtained from well-designed clinical studies that are currently being carried out (randomized double-blind clinical trials, prospective case-control and cohort studies), using multivariate analysis of a large population and many observation years to clarify the role of vitamin D and analogs in cancer prevention and to impute a causal relationship between lack of adequate vitamin D and cancer. In this context, it is of particular importance for future investigations to measure plasma 25(OH)D levels from individuals at several time points and not to generally speculate what their vitamin D levels might be using geographical latitude as a parameter of possible exposure to solar UV radiation. Moreover, plasma 25(OH)D levels should be analyzed in combination with other factors that are of importance for vitamin D signaling, such as distinct polymorphisms of the vitamin D receptor (VDR) gene, which have recently been identified to be associated with an increased risk for and an unfavourable outcome of various types of cancer.

In vitro investigations: Many presentations were related to antitumor effects of 1,25-dihydroxyvitamin D (1,25(OH)₂D, calcitriol) and its analogs. New and important laboratory investigations analyzing the molecular mechanisms that underly nuclear/genomic and nongenomic vitamin D signaling pathways, including a genome-wide perspective on vitamin D signaling and new paradigms for gene regulation by calcitriol, and their importance for antitumor effects of vitamin D analogs were discussed. It was shown that a multitude of independent molecular events are involved in antitumor effects of vitamin D, including effects on the immune system, cell proliferation, differentiation, apoptosis and DNA repair, and that these effects can be modulated by other compounds, including epigenetic drugs. However, the molecular mechanisms for these actions are complex and importantly, an understanding of the very early events is still lacking. Several papers presented at this meeting were focused on vitamin D receptor (VDR) mediated nuclear/genomic effects, in particular on the impact of chromatin organization of vitamin D-regulated target genes and the effect of epigenetic modulating drugs, on the recruitment of cofactor proteins to the VDR, the interaction of VDR with components of the basal transcription apparatus, and on the regulation of VDR expression by microRNAs and other molecules.

Cancer therapy: Our knowledge about the antitumor effects of vitamin D and analogs has markedly increased in recent years; however, results from the first clinical trials have not been convincing, at least in part due to poor study design of these clinical trials. Nevertheless, new findings, such as on the epigenetic modulation of vitamin D signaling, further support the concept that vitamin D analogs may represent promising compounds for cancer therapy, most likely in combination with other agents. However, the era of vitamin D analogs in cancer therapy has just begun and efforts to perform well designed clinical studies and to develop new vitamin D analogs that reveal less systemic side-effects have to be enforced.

Another highlight of this symposium was the award of the Arnold-Rikli-Price 2010 to Jürgen Schaubert (München, Germany) for his outstanding work analyzing the regulation of the immune system by the vitamin D pathway.

References

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