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Commentary: Vitamin D and pancreatic cancer: a pooled analysis from the pancreatic cancer case-control consortium

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A commentary on

Vitamin D and pancreatic cancer: a pooled analysis from the pancreatic cancer case-control consortium

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Waterhouse et al. criticized the association between vitamin D intake and the prevention of pancreatic cancer (1), an association that has been thoroughly reviewed in recent years (2, 3). Yet, randomized controlled clinical trials (RCTs) very rarely produced encouraging and reliable results on the field (4–7). Negative evidence in animal models and experimental studies (8, 9) should suggest that the chemopreventive role of $1,25(OH)_2D_3$ deserve particular attention when dietary vitamin D_3 is considered (10). Best correlations were reported on vitamin D_3 deficiency and cancer malignancy (11–14) or on frequent dietary intake of vitamin D_3 and tumor prevention (15). The chemopreventive role might closely depend on plasma bioavailability of $25(OH)D_3$ and genetic polymorphism of vitamin D receptor (VDR) (16, 17). Physicians are asking whether vitamin D_3 supplementation may really contribute in preventing cancer (18, 19) and, at the same time, they suggested recommendations to fortify foods with supplemented vitamin D_3, to achieve optimal levels of plasma $25(OH)D_3$ (20, 21).

Waterhouse et al. showed that cancer risk increased with higher levels of vitamin D intake, although they did not exclude the possibility that vitamin D obtained through ultraviolet exposure has a beneficial effect (1). In the future, $25(OH)D_3$ may become of major importance in assessing the role of the plasmatic content of vitamin D_3 to prevent chronic diseases and cancer. Dietary vitamin D_3 exhibited the same anti-cancer activity than $1,25(OH)_2D_3$ in mice (9), a chemically modified form of $25(OH)vitD_3$ exerts a chemotherapeutic effect on neuroblastoma xenograft mouse model (22), an imbalance in plasma availability of $25(OH)D_3$ is considered a risk factor for carcinoma (23) and $25(OH)D_3$, likewise $1,25(OH)_2D_3$, exerts an anti-inflammatory effect (24–26). Most of the recent evidence should suggest that plasma level of $25(OH)D_3$ has a fundamental role in warranting protection against chronic immune disorders and cancer (27). However, any approach to enhance $25(OH)D_3$ bioavailability with diet does not appear sufficient to improve vitamin D_3-related outcome, due to genetic variability within the population (28). This evidence may appear therefore quite discouraging. Physicians are wondering how to focus onto vitamin D_3 dietary intake to prevent chronic immune disorders and cancer. Yet, a proper determination of plasmatic $25(OH)D_3$ metabolites is highly recommended (29, 30). Clinical chemists have some difficulty in evaluating plasmatic $1,25(OH)_2D_3$, particularly because it is rapidly degraded by 24-hydroxylases. Conversely, $25(OH)D_3$ biochemical activity should be attributed fundamentally to the 1-α-hydroxylated form,

TABLE 1 | Flow chart of vitamin D dietary evaluation.

Pre-analytical stage
a) *The population undergoing vitamin D3 supplementation*: this point should be addressed by considering the main geographical area and whether population is coming from developing or industrialized countries (this fact should focus on the dietary habit), their sex, their age
b) *Genetic polymorphism and mutational analysis*: particular genetic polymorphism for VDR should be highlighted (48–50). Moreover, genetic mutations for P450 cytochromes (particularly for CYP24A1) should be investigated (51, 52)
c) *Metabolic homeostatic balance*: particular importance should be given to the metabolic homeostatic machinery held by the subject prior to his intake of vitamin D_3 (calcidiol level, presence of insulin resistance or metabolic syndrome, metabolic markers, etc.)
d) *Diet survey*: depending on the diet habit and life style, vitamin D_3 supplementation might be accordingly adjusted, for a better performance
Analytical stage
e) *Data on vitamin D_3 availability*: pharmacokinetics of vitamin D_3, particularly when in association with chemopreventive drugs (53) should be known. A proper dosage of plasmatic calcidiol should be performed. A reappraisal on calcitriol determination should be conducted
Post-analytical stage
f) *Prospective studies and epidemiology*: further detailed studies on the association between vitamin D_3 dietary intake and cancer development should give a sound contribution for the comprehension of the chemopreventive role of vitamin D_3

yet actually a more complex mechanism, involving multiple enzyme activity by P450 cytochromes and different metabolites, has been recently reviewed in Ref. (31). This should oblige nutritionists to be more cautious about the role of vitamin D_3 supplementation in cancer prevention. Active vitamin D_3 is a short-lived, potent hormonal molecule, whose efficacy seems to depend on the homeostatic level of circulating and available $25(OH)D_3$. The activity of the $25(OH)D_3$, is increased principally by the action of CYP27B1 but recent evidence has interestingly reported that a synthetic analog of $25(OH)D_3$, i.e., 5-hydroxy-16-ene-23-yne-D_3, is neither modulated by CYP27B1 nor by CYP24A1 and expressed a potent anti-proliferative effect likewise $1,25(OH)_2D_3$ (32). Furthermore, the use of synthetic analogs of $1,25(OH)_2D_3$ appears quite promising in this field (33). Further, RCTs are needed to shed a light on the availability of newly introduced synthetic active forms of vitamin D_3 for cancer prevention. The evidence should suggest that a possible way to enhance the anti-cancer activity of vitamin D_3 is to increase $1,25(OH)_2D_3$ effect by reducing the inhibitory action of CYP24A1, with molecules such as KD-35 or 4,5,6,7-tetrabromobenzimidazole (TBBz). This apparently simplistic point of view appeared quite encouraging (34, 35).

There are very few reports suggesting the possibility, through dietary intake, to improve the activity of $1,25(OH)_2D_3$ as an immune cytokine and/or an hormone. CYP24A1 inhibitors, such as the isoflavone genistein, could be theoretically assumed with diet and they might potentiate the effect of $1,25(OH)_2D_3$ in the immune response against cancer, although further randomized controlled trials are requested (36, 37).

Therefore, how to perform a correct dietary recommendation to promote vitamin D_3 as a possible chemopreventive molecule? Western diet might induce or promote tumors, particularly when deficient or lacking vitamin D_3 (38, 39). This should suggest why most of Western populations, living in industrialized countries, are often vitamin D_3 deficient. In this perspective, the initial concern is to establish the proper dietary supplementation of vitamin D_3, to achieve an optimal plasmatic level of $25(OH)D_3$. However, the correct supplementation of vitamin D_3 should depend on sex and age, dietary habits, level of $25(OH)D_3$, geographical areas, individual's gut microflora, and genetics of vitamin D_3 metabolism (P450 cytochromes and VDR) (40–42) and this, at least theoretically, would oblige nutritionists, physicians, and caregivers to ask for a reappraisal of a Consensus Panel suggesting the proper vitamin D_3 intake in relation to any of these factors (43). Due to the extreme difficulty in achieving this goal, any supplementation panel might be restricted to differential distributions in age clusters for both sexual groups and, anymore, to ensure an excess of circulating $25(OH)D_3$ in plasma. Notwithstanding, an excess of $25(OH)D_3$ may induce toxicity (44) and dampening the role of CYP24A1 in modulating $1,25(OH)_2D_3$ activity may cause serious damage to kidney and calcium homeostasis (45). Therefore, as a severe plasma $25(OH)D_3$ deficiency is considered a bad prognostic marker for tumors (46), $25(OH)D_3$ plasma bioavailability should be considered a major bullet point in the nutritional research of chemopreventive molecules. Yet, researchers trust the fact that vitamin D_3 should be particularly useful in cancer prevention (47). Plasma $25(OH)D_3$ might be considered of major important in the future, therefore, if associated with genomics and diet habits.

A suggested work flow to assess a possible correct intake of vitamin D_3, as a supplementation factor in diet to prevent cancer, should henceforth consider also a genomic and nutrition screening, most probably according to steps described in **Table 1**.

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