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Review Article

Calcium intake and vitamin D metabolism and action, in healthy conditions and in prostate cancer

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An association between Ca intake and the risk of prostate cancer has been reported in some but not all epidemiological studies. Assuming that a pathophysiological relationship would underlie this association, a favoured hypothesis proposes that relatively high Ca consumption could promote prostate cancer by reducing the production of 1,25-dihydroxyvitamin D ($1,25(OH)_2D$; calcitriol), the hormonal form of vitamin D. The present review analyses the plausibility of this hypothesis by considering the quantitative relationships linking Ca intake to $1,25(OH)_2D$ production and action in healthy conditions and in prostate cancer. Changes in the plasma level of $1,25(OH)_2D$ in response to Ca intake are of very small magnitude as compared with the variations required to influence the proliferation and differentiation of prostate cancer cells. In most studies, $1,25(OH)_2D$ plasma level was not found to be reduced in patients with prostate cancer. The possibility that the level of $1,25(OH)_2D$ in prostate cells is decreased with a high-Ca diet has not been documented. Furthermore, a recent randomised placebo-controlled trial did not indicate that Ca supplementation increases the relative risk of prostate cancer in men. In conclusion, the existence of a pathophysiological link between relatively high Ca intake and consequent low production and circulation level of $1,25(OH)_2D$ that might promote the development of prostate cancer in men remains so far an hypothesis, the plausibility of which is not supported by the analysis of available clinical data.

Calcium intake: Vitamin D metabolism: Prostate cancer

An association between Ca intake and prostate cancer has been reported in several but not all epidemiological studies (Giovannucci *et al.* 1998; Schuurman *et al.* 1999; Chan *et al.* 2000; Chan & Giovannucci, 2001; Tavani *et al.* 2001; Berndt *et al.* 2002; Kristal *et al.* 2002; Rodriguez *et al.* 2003; Qin *et al.* 2004*b*; Giovannucci, 2005; Gross, 2005; Sonn *et al.* 2005; Tavani *et al.* 2005; Tseng *et al.* 2005; Kesse *et al.* 2006). The aim of the present report is not to review these various studies. The reader can obtain detailed information from a recent thorough meta-analysis conducted on prospective studies that examined the association between dairy product consumption and/or Ca intake and prostate cancer risk (Gao *et al.* 2005). To summarise the main results of this meta-analysis, the overall pooled relative risk of total prostate cancer was 1·11 (95 % CI 1·00, 1·22; $P=0·047$) for the highest *v.* the lowest intake categories of dairy products. It was 1·39 (95 % CI 1·09, 1·77; $P=0·018$) for the highest *v.* lowest intake categories of Ca (Gao *et al.* 2005). The pooled relative risk of advanced prostate cancer was not significantly associated with either dairy product consumption or Ca intake (Gao *et al.* 2005). The authors concluded that a high intake of dairy products and Ca may be associated with an increased risk of prostate cancer, although the increase is small (Gao *et al.* 2005). Inclusion of a still more recent prospective study (Severi *et al.* 2006*a*) slightly reduced the pooled relative risk from 1·11 to 1·09 ($P=0·059$) for the highest relative to the lowest dairy intake category, and from 1·39 to 1·32 ($P=0·026$) for high *v.* low Ca intake (Gao *et al.* 2006).

The main objective of the present report is indeed to examine whether the association, whenever found to be statistically significant, between Ca intake and prostate cancer could mechanistically be related to an effect on vitamin D metabolism. The favoured hypothesis for pathophysiologically linking dietary Ca to prostate cancer assumes that the production of the active metabolite of the endocrine vitamin D system, namely 1,25-dihydroxyvitamin D ($1,25(OH)_2D$ or calcitriol), would be reduced by relatively high Ca consumption. Such a Ca-mediated reduction in the production of $1,25(OH)_2D$ would alter the proliferation and/or differentiation of prostate cells. By this very specific physiological mechanism on

Abbreviations: IGF, insulin-like growth factor; 25(OH)D, 25-hydroxyvitamin D; $1,25(OH)_2D$, 1,25-dihydroxyvitamin D; PTH, parathyroid hormone.

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vitamin D metabolism, Ca intake would be implicated in the development and progression of prostate cancer.

The present review analyses the plausibility of this hypothesis by considering the quantitative relationships linking Ca to vitamin D metabolism and the action of its hormonal form, $1,25(OH)_2D$. Under the first three sections, essential notions on the renal and extra-renal production of $1,25(OH)_2D$ and its action on normal and cancer prostate cells are reviewed. Then, in the fourth part of the present review we consider these quantitative experimental notions in order to analyse the level of evidence supporting the purported pathophysiological Ca–vitamin D mechanism link evoked as a risk of prostate cancer.

Renal production of 1,25-dihydroxyvitamin D

Under physiological circumstances $1,25(OH)_2D$, the most active metabolite of vitamin D, is synthesised in the kidney (Feldman *et al.* 2001). It is produced within the cells of the proximal tubules by the enzyme 25(OH)D-1α-hydroxylase from its specific precursor 25-hydroxyvitamin D (25(OH)D). In the renal tubule the synthesis of $1,25(OH)_2D$ is stimulated by parathyroid hormone (PTH) (Bell, 1998) and insulin-like growth factor (IGF)-1 (Caverzasio *et al.* 1990; Bell, 1998). A low intake of inorganic phosphate is a strong enhancer of renal $1,25(OH)_2D$ production (Maierhofer *et al.* 1984). A low intake of Ca also enhances the synthesis of $1,25(OH)_2D$ by the kidney, but this effect is largely mediated by the increased secretion and plasma level of PTH (Adams *et al.* 1979; Bell, 1998). In healthy human adults the renal production of $1,25(OH)_2D$ is tightly regulated. Thus, administration of physiological doses of vitamin D that results in an elevation in the circulating concentration of 25(OH)D does not alter the plasma level of $1,25(OH)_2D$ (Bell, 1998; Feldman *et al.* 2001). Likewise, seasonal variation in 25(OH)D is associated with opposite change in the plasma level of PTH, while $1,25(OH)_2D$ remains constant (Holick, 1994). Note that $1,25(OH)_2D$ exerts a negative feedback on its own renal production by inhibiting 25(OH)D-1α-hydroxylase. This inhibition is mediated by the binding of $1,25(OH)_2D$ to its vitamin D receptor (Feldman *et al.* 2001). In physiological situations with increased bone mineral demand, such as growth, pregnancy and lactation, there is an increment in the production of $1,25(OH)_2D$ (Bell, 1998; Feldman *et al.* 2001; Kalkwarf & Specker, 2002). Such a response explains the enhancement in the intestinal absorption of Ca and inorganic phosphate that is observed in these physiological conditions. The intestinal epithelium, which is equipped with vitamin D receptor, particularly at the level of the duodenum, is the main target organ of $1,25(OH)_2D$ (Feldman *et al.* 2001).

Extra-renal production of 1,25-dihydroxyvitamin D

Besides the renal tubular epithelium, several types of cells can produce $1,25(OH)_2D$ from its physiological precursor 25(OH)D (Bell, 1998; Feldman *et al.* 2001; Holick, 2003). These cells are endowed with the required enzymic machinery to synthesise $1,25(OH)_2D$. This capacity has been observed in macrophages, as well as in prostate, colon, skin and osteoblast-like cells (Bell, 1998; Feldman *et al.* 2001; Holick, 2003). In contrast to the tight renal regulation of $1,25(OH)_2D$ synthesis, extra-renal production is dependent upon the concentration of 25(OH)D. Such a substrate-dependent extra-renal production of $1,25(OH)_2D$ was well documented in the macrophages present in sarcoidosis (Bell, 1998). In patients with sarcoidosis, an increase in plasma $1,25(OH)_2D$ and abnormal Ca metabolism, particularly hypercalcaemia with hypercalciuria, often occurs by the end of summer after longer exposure to sunshine leading to a rise in the circulating level of 25(OH)D (Bell *et al.* 1979; Papapoulos *et al.* 1979). The same alterations in $1,25(OH)_2D$ and Ca metabolism can be observed after administration of vitamin D to sarcoidosis patients, but not in healthy subjects (Bell, 1998).

Vitamin D system in cancer, with special emphasis on prostate carcinoma

Independent observations suggest that variations in vitamin D metabolism could play a role in the geographical prevalence of several neoplasias. These epidemiological data have been interpreted in relation to the production and action of vitamin D metabolites. More precisely, the frequently put-forward hypothesis causally relates the following independent observations:

(1) The risk of developing and dying of colon, breast, ovarian, oesophageal, prostate and other cancers, is related to living in higher latitudes (Schwartz & Hulka, 1990).
(2) The geographic pattern of prostate cancer mortality in the USA was found to be inversely related to the availability of UV radiation at the level of the county (Grant, 2002).
(3) The risk of developing vitamin D insufficiency is greater in higher latitudes, presumably because of the reduced production of vitamin D in the skin (Holick, 2003).
(4) Prostate cancer cells can express the vitamin D receptor. Exposure of most prostate cancer cells to $1,25(OH)_2D$ results in an inhibition of proliferation, invasiveness and metastasis, both *in vitro* and in animal models of the human disease. Note that some lines and primary cultures of prostate cancer cells are resistant to the growth inhibition by $1,25(OH)_2D$ (Miller, 1998; Peehl & Feldman, 2003). This suggests that resistance to the hormonal form of vitamin D may develop with the progression of prostate cancer (Miller, 1998; Peehl & Feldman, 2003).
(5) In normal prostatic cells 25(OH)D-1α-hydroxylase is expressed and 25(OH)D can be converted into $1,25(OH)_2D$ (Schwartz *et al.* 1998). Indeed, intracellular accumulation of $1,25(OH)_2D$ can occur when normal prostatic cells are exposed to 25(OH)D (Schwartz *et al.* 1998).
(6) In normal prostate tissue, 25(OH)D, like $1,25(OH)_2D$, inhibits cellular proliferation while it promotes their differentiation (Schwartz *et al.* 1998; Barreto *et al.* 2000).

Approach to the use of vitamin D metabolites for the treatment of prostate cancer

The series of observations described in the previous section led to investigation of the possiblity of using vitamin D metabolites as therapeutic tools in the management of prostate cancer.

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A first approach was to explore whether $1,25(OH)_2D$ might be a therapeutic agent for prostate cancer. However, it was rapidly realised that this was not suitable because of the occurrence of hypercalcaemia and hypercalciuria, since the concentration required to inhibit prostate cancer cell proliferation was much higher than that found physiologically in the systemic circulation (Peehl & Feldman, 2003).

A second strategy was to synthesise $1,25(OH)_2D$ analogues with similar antiproliferative activity, but devoid of hypercalcaemic activity (Feldman *et al.* 2001; Holick, 2003; Peehl & Feldman, 2003). Until now this logical strategy, widely explored, did not lead to the development of $1,25(OH)_2D$ analogues usable in the treatment of human prostate cancer. Only a few clinical trials of phase I or II including a small number of subjects have been so far reported, as for instance the study published by Woo *et al.* (2005).

A further approach was to examine the possibility of using the precursor of $1,25(OH)_2D$, namely 25(OH)D, at a non-hypercalcaemic dose, exploiting the presence of the 25(OH)D-1α-hydroxylase enzymic machinery in prostatic tissue in order to increase locally the concentration of the active metabolite of the vitamin D system. An obvious prerequisite for this strategy to be successful is the expression of the 25(OH)D-1α-hydroxylase with substantial converting activity in prostate cancer cells. This issue is discussed below.

Calcium intake and vitamin D metabolism in healthy conditions and in prostate cancer

As indicated in the introduction, a relative risk or odds ratio above unity for Ca and/or dairy products has been found in some observational studies on prostate cancer (Giovannucci *et al.* 1998; Chan & Giovannucci, 2001; Rodriguez *et al.* 2003; Tseng *et al.* 2005; Kesse *et al.* 2006); hence the hypothesis that high Ca consumption would decrease the production of $1,25(OH)_2D$ by its inhibitory effect on the secretion and circulating level of PTH, and maybe through an additional direct negative influence of the increased extracellular Ca concentration on 25(OH)D-1α-hydroxylase activity. In order to be plausible, this hypothesis should be based on several experimentally testable criteria. The relatively high *v.* low Ca intakes should be associated with a biologically significant difference in the circulating level of $1,25(OH)_2D$.

Healthy adults

A large increase in Ca intake, from 300 to 1400 mg/d, was associated with a relatively small decrease in the circulating concentration of $1,25(OH)_2D$, from 40 to 30 pg/ml (Gallagher *et al.* 1979). This small variation was within the reference values, which range from 16 to 56 pg/ml (Favus, 2003). Still, an inverse relationship between Ca intake and $1,25(OH)_2D$ serum level was observed in subjects aged 30–65 years but not in normal subjects older than 65 years, or in patients with osteoporosis (Gallagher *et al.* 1979). In a more recent prospective controlled study in healthy men, variations in dairy product intakes that increased the daily Ca consumption from 590 (SEM 100) to 1660 (SEM 150) mg reduced $1,25(OH)_2D$ plasma levels by only 3·9 pg/ml (Ferrari *et al.* 2005). Again, this minor reduction from 39·5 to 35·6 pg/ml remained well within the normal range (17–55 pg/ml) of serum $1,25(OH)_2D$ for the studied population (Ferrari *et al.* 2005). In a randomised clinical trial in men (mean age 62 years), serum $1,25(OH)_2D$ decreased from 42·9 to 41·2 pg/ml after the 4 years of intervention in the group assigned to receive a daily Ca supplementation of 1200 mg (Baron *et al.* 2005). The results of these three human studies (Gallagher *et al.* 1979; Baron *et al.* 2005; Ferrari *et al.* 2005) concur at demonstrating that large variations in Ca intakes induce quite minor fluctuations in serum $1,25(OH)_2D$. These data contrast with the necessity of using pharmacological and thereby hypercalcaemic doses of $1,25(OH)_2D$ in order to reduce the invasiveness and metastasisation of prostate cancer in appropriate animal models (Peehl & Feldman, 2003).

Prostate cancer patients

Several studies have examined whether patients with prostate cancer would have a relatively low circulating level of $1,25(OH)_2D$, in order to provide support to the Ca–vitamin D hypothesis. Out of six case–control studies (Corder *et al.* 1993; Braun *et al.* 1995; Gann *et al.* 1996; Nomura *et al.* 1998; Jacobs *et al.* 2004; Platz *et al.* 2004), only one (Corder *et al.* 1993) reported an inverse association between $1,25(OH)_2D$ serum level and the subsequent risk of prostate cancer. However, in this 'positive' study, the mean plasma level of $1,25(OH)_2D$ was only 1·81 pg/ml lower in prostate cancer cases than in controls (Corder *et al.* 1993). This difference has to be considered in relation to reference values ranging from 16 to 56 pg/ml with a mean of 36 pg/ml (Favus, 2003). It is difficult to conceive that this very small decline in circulating $1,25(OH)_2D$ could have played a mechanistic role in the progression of the prostatic tumours recorded in this case–control study (Corder *et al.* 1993). It might be argued that such a very mild plasma level reduction, within the $1,25(OH)_2D$ reference range, could still prevent the initial development of prostate cancer but not control the further proliferation of pre-existing cancerous cells. However, there are no data supporting this hypothesis.

The reports on the circulating level of 25(OH)D and prostate cancer risk remain inconsistent. One study described an increased risk with low levels (Ahonen *et al.* 2000). Another one reported an increment in risk with either a low or high level (Tuohimaa *et al.* 2004), whereas four studies did not find any association (Braun *et al.* 1995; Nomura *et al.* 1998; Jacobs *et al.* 2004; Platz *et al.* 2004). Note that Ca does not influence the circulating level of 25(OH)D, the hepatic production of which essentially depends upon the supply of vitamin D to the liver (Feldman *et al.* 2001; Heaney *et al.* 2003).

Nevertheless, it could be hypothesised that the plasma levels of $1,25(OH)_2D$ might not reflect its concentration within the prostate tissue. Thus, a high-Ca diet associated with a relatively low concentration of circulating PTH might reduce the synthesis of $1,25(OH)_2D$ in the prostatic cells and thereby could affect cellular growth and differentiation by autocrine and/or paracrine signalling pathways. The plausibility of this hypothesis is challenged by several experimental facts. In normal prostatic tissue, 25(OH)D-1α-hydroxylase is influenced neither by PTH nor by Ca (Young *et al.* 2004), in contrast to the renal enzyme that physiologically controls the production of $1,25(OH)_2D$ (Bell, 1998). Therefore, there is no evidence that variations, even of

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large magnitude, in the intake of Ca inducing substantial alterations in the circulating level of PTH could affect the local production of $1,25(OH)_2D$ in normal prostatic cells. Note that unlike kidney proximal tubular cells, prostate tissue does not appear to be equipped with PTH/PTHrP type 1 receptors (Young *et al.* 2004). A possibility remains that elevation in the circulating level of 25(OH)D, whether induced by an increase in the endogenous production of vitamin D or by a larger exogenous supply of either vitamin D or 25(OH)D, could cause an increased synthesis of $1,25(OH)_2D$ within the prostatic tissue. However, this potentiality appears to be confined to normal prostate cells. Indeed, prostate cancer tissue, both studied either in primary cultures or in cell lines, has greatly decreased activity of 25(OH)D-1α-hydroxylase, as compared with normal prostatic cells (Hsu *et al.* 2001; Ma *et al.* 2004). This deficiency probably explains why prostate cancer tissue is resistant to the tumour-suppressor activity of 25(OH)D (Hsu *et al.* 2001). In prostate cancer cell lines this decreased activity is due to reduced gene expression, whereas in primary cultures it appears to involve some post-translational mechanism (Ma *et al.* 2004). Furthermore, *in vivo* studies in nude mice bearing heterotopic LNCaP human prostate carcinoma, increasing the dietary supply of either Ca or vitamin D, given alone or together, did not affect the tumour growth rate, the final tumour weight and the serum level of prostate-specific antigen (Balaji *et al.* 2001). These results were obtained despite the fact that these dietary manipulations led to significant elevation in the serum concentration of both Ca and 25(OH)D (Balaji *et al.* 2001). Taking into account the capacity of normal prostate cells to convert 25(OH)D into $1,25(OH)_2D$ (Schwartz *et al.* 1998), it may be argued that increasing the vitamin D supply from cutaneous or intestinal sources, and thereby inducing an elevation in the plasma and intra-prostatic level of 25(OH)D, could still prevent the initial development of prostate cancer but not inhibit the further proliferation of pre-existing cancerous cells. Nevertheless, this possibility is not directly relevant to the main focus of the present review, since Ca intake does not influence the production and circulating level of 25(OH)D (Feldman *et al.* 2001; Heaney *et al.* 2003).

'Evidence-based medicine' consists of establishing a hierarchy in the level of evidence, taking into account the type of study design used for investigating putative causal relationships (Guyatt *et al.* 1995). Consistent results from an adequate meta-analysis based on well-conducted randomised controlled trials are set at the top of the evidence hierarchy. Results obtained in one single well-conducted randomised controlled trial are considered at the next highest level (Guyatt *et al.* 1995). Thus, a single trial achieves a higher degree of certainty than several observational studies. With respect to the influence of Ca on the development and progression of prostate cancer, a well-conducted randomised clinical trial was recently reported (Baron *et al.* 2005). In this trial enrolling 672 men, the effect of Ca supplementation (1200 mg/d), taken as carbonate salt for 4 years, was evaluated against a placebo (Baron *et al.* 2005). During the first 6 years, including 2 years of post-treatment follow-up, there was no increased risk of prostate cancer associated with Ca supplementation. There was even some suggestion of a protective effect (Baron *et al.* 2005). This randomised placebo-controlled interventional trial does not support the hypothesis made from observational studies that Ca would play a detrimental role in the development of prostate cancer. The interpretation of this important randomised controlled trial has nevertheless some limitations. The study was originally designed to evaluate the influence of Ca on the prevention of colorectal adenoma and not on prostate cancer (Baron *et al.* 1999). The number of cases was not very large, with only seventy prostate cancers diagnosed during the mean follow-up period of 10·3 years (Baron *et al.* 2005). Another limitation is the fact that the overwhelming majority of the prostate cancer cases had localised tumours (Baron *et al.* 2005). Therefore, this trial did not provide useful information pertaining to the possible influence of Ca supplementation on advanced prostate cancer.

A recent study indicates that higher Ca intake was not appreciably associated with total prostate cancer (Giovannucci *et al.* 2006). However, further analysis of the results in relation to the severity of the disease suggested that Ca intakes exceeding 1500 mg/d may be associated with a higher risk in advanced and fatal prostate cancer, but not with well-differentiated, organ-confined cancers (Giovannucci *et al.* 2006).

In the Ca intervention trial (Baron *et al.* 2005) discussed earlier, baseline dietary Ca, plasma levels of $1,25(OH)_2D$ and 25(OH)D were not associated with prostate cancer. Therefore, the hypothesis implying that variations in circulating $1,25(OH)_2D$ might mechanistically explain the association found in some observational reports between Ca intake and prostate cancer is not supported by most studies in which the active vitamin D metabolite has actually been measured in both cases and controls (Braun *et al.* 1995; Gann *et al.* 1996; Nomura *et al.* 1998; Jacobs *et al.* 2004; Platz *et al.* 2004; Baron *et al.* 2005). Furthermore, the serum level of $1,25(OH)_2D$ changed very little between the values at baseline and those determined at the end of the 4 intervention years; from 42·9 to 41·2 pg/ml and from 43·4 to 44·8 pg/ml in the Ca-supplemented and placebo group, respectively (Baron *et al.* 2005). This finding corroborates the notion that a large difference in Ca intake exerts only a very mild influence on the circulating level of $1,25(OH)_2D$.

In studies in which Ca intake was derived from dairy product consumption, it was suggested that other milk components might be causally related to prostate cancer risk. Two hypothetical hormonal candidates have been considered: IGF-1 with its IGF-binding protein-3 (Renehan *et al.* 2004; Severi *et al.* 2006*b*), and oestrogens (Qin *et al.* 2004*a*). It is not the purpose of the present review to analyse the plausibility of the hypothesis implying a role for these agents. This kind of analysis should first examine whether milk-borne IGF-1, IGF-binding protein-3 or oestrogens are both ingested and absorbed by the intestinal epithelium in sufficient amounts to contribute significantly to their plasma levels in adult men. Without this prerequisite information, it remains highly speculative to implicate these milk-borne hormonal factors in the development of prostate cancer, particularly as regards the very low relative risk associated with dairy product consumption as documented in the recent meta-analysis conducted on prospective studies (Gao *et al.* 2005, 2006).

Conclusion

Human studies in both healthy subjects and prostate cancer patients indicate that large variations in Ca intake lead to

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minimal fluctuations in $1,25(OH)_2D$ circulating level. This contrasts with the necessity to use hypercalcaemic and thereby toxic doses of $1,25(OH)_2D$ to inhibit prostate cancer development in experimental investigations. Thus, the hypothesis suggesting that a relatively high Ca intake could lead to a decrease in the $1,25(OH)_2D$ serum level that may quantitatively be substantial enough to influence the risk of developing prostate cancer is not sustained by a series of clinical and experimental results. Whether the statistical association reported in epidemiological studies between Ca intake and prostate cancer risk would reflect a biologically meaningful causal relationship remains to be demonstrated.

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