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Invited Commentary

Exploration of possible mechanisms linking vitamin D status and dietary calcium to prostate cancer

Epidemiology is a powerful tool in the medical sciences. It can provide clues about how disease develops in a population. It can identify the pattern whereby infectious diseases spread. It can raise a myriad of questions that stimulate further fruitful research. However, what epidemiology cannot do is to define the patho-physiological mechanisms by which environmental factors lead to disease.

In recent years there have been many epidemiological reports that relate patterns of disease such as diabetes, cancer and autoimmune disorders to the geographical latitude where people live. The latitude of residence is also the main determinant of vitamin D status in populations and this varies seasonally, following closely the winter/summer season al variation in the intensity of solar UV light at the earth's surface. In general, populations living further from the equator have lower average vitamin D status than those at lower latitudes. Hence, from these two observations, epidemiology has found statistical associations between low vitamin D status and the prevalence of some diseases (Grant, 2006).

One of the physiological functions of the hormone, 1,25-dihydroxyvitamin D ($1,25(OH)_2D$) is to help maintain a constant extracellular ionised Ca concentration as part of the process of Ca homeostasis. In particular, it acts to enhance the absorption capacity for dietary Ca from the small intestine. When the concentration of extracellular Ca^{2+} tends to fall, (e.g. during bone growth or in lactation), the capacity for intestinal Ca absorption is increased. This increase in capacity is associated with an elevated secretion into the circulation of $1,25(OH)_2D$ from the kidney, promoted particularly by increased secretion of parathyroid hormone. If dietary Ca is low and vitamin D status is poor, then it may be difficult to maintain Ca homeostasis, because the supply of $1,25(OH)_2D$ is insufficient to enhance Ca absorption. Such deficiencies of Ca and/or vitamin D result in hypocalcaemia and the classical bone disease of rickets in children or osteomalacia in adults. Although there may be further knowledge to glean about the patho-physiological mechanisms leading to these abnormalities, the general principles can be defined from existing information.

On the other hand, the mechanisms that link variations in dietary Ca or in vitamin D status to other pathologies are far from clear (Peterlik & Cross, 2005). Cancer of the prostate is one disease where there is an epidemiological association with low vitamin D status (Hanchette & Schwartz, 1992). A recent review by Tuohimaa *et al.* (2005) explored ideas about how low concentrations of 25-hydroxyvitamin D (25(OH)D), the precursor of $1,25(OH)_2D$, might influence the development of prostate cancer. This is a logical path to follow because vitamin D status is defined by the concentration of 25(OH)D in blood so that when exposure to solar UV light is limited, the level of 25(OH)D is low. Another thoughtful analysis is presented in this issue of the *British Journal of Nutrition* by Bonjour *et al.* (2007), who consider ideas from a number of epidemiological studies that report an increased risk of prostate cancer in men with relatively high intakes of dietary Ca. Such a statistical link could be helpful in devising mechanistic hypotheses, although caution is needed because not all epidemiological studies have found an association between Ca intake and prostate cancer. The hypothesis reviewed by Bonjour *et al.* is that a high Ca intake would depress production of $1,25(OH)_2D$ and that this would alter the proliferation or differentiation of prostate cells. Their conclusion was that this hypothesis was unlikely to explain the epidemiological association because large variations in Ca intake lead to only minor changes in the level of $1,25(OH)_2D$ in blood. Despite the many studies showing that $1,25(OH)_2D$ production occurs in normal prostate cells and that the addition of $1,25(OH)_2D$ to malignant prostate cells *in vitro* modifies their rate of proliferation and their differentiated function (reviewed by Tuohimaa *et al.* 2005), a simple mechanistic explanation linking dietary Ca, vitamin D metabolism and prostate cancer is not apparent from current knowledge.

Nevertheless, it is a worthy goal to seek mechanisms to explain these epidemiological relationships. Not only would a verifiable mechanism improve our understanding of the pathogenesis of prostate cancer, it would also provide a firm basis for public health policy to reduce the risk of the disease. Already there is good reason to consider that the average vitamin D status in many populations is too low. While most people can maintain a vitamin D status of 30–40 nmol 25(OH)D per litre blood plasma, which is sufficient to avoid vitamin D deficiency osteomalacia, it now appears that maximum intestinal Ca absorption capacity is only acquired with a higher vitamin D status of about 80 nmol/l (Heaney, 2005). Is this higher vitamin D status needed also to diminish the risk of cancer and other diseases of complex aetiology? The true benefit of discovering epidemiological associations is the stimulus they provide to seek mechanistic answers to questions such as this.

There are indeed quite a number of challenging questions arising from the analysis of Bonjour *et al.* (2007). Because high Ca diets usually depend on dairy products as the major source of Ca, could the association reviewed by Bonjour *et al.* be not directly with dietary Ca but rather with the intake of dairy foods? Can any plausible mechanism be proposed as to why dairy product consumption might have an association with disease? Again, if the association between dietary Ca with risk of prostate cancer is not explained by changes in circulating $1,25(OH)_2D$, could the link between dietary Ca, vitamin D status and prostate cancer be through the supply of 25(OH)D? Does the blood level of 25(OH)D influence vitamin D function in various cells, independently of the classical vitamin D role in Ca homeostasis?

Perhaps the greatest challenge from all these epidemiological associations is to learn about the real physiological mechanism by which adequate vitamin D status is maintained from exposure of skin to solar UV light. Why does man in many affluent societies appear to have difficulty in achieving a desirable vitamin D status throughout the year? This is a problem that most wild mammals seem to avoid. What is man doing wrong?

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