The vitamin D question: what's the best advice?

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The beta-carotene fiasco warned oncologists off suggesting supplements on the basis of observational studies. But with vitamin D now in the spotlight, how should doctors respond when their patients ask if it could help?

A diagnosis of cancer can prompt a patient to make all kinds of changes. Many adopt a holistic attitude to their health, altering their lifestyle, and especially their diet, in the hope it will help. Some start taking supplements. And one supplement in particular is at the centre of a simmering controversy about whether it might help or harm. That's vitamin D.

In one camp are researchers and clinicians who argue there's no convincing data that vitamin D supplementation can improve cancer prognosis, and who fear it might even be dangerous. In the other, researchers and oncologists who argue that vitamin D deficiency is so widespread, and the preliminary clinical and lab data on cancer is so persuasive, it's high time to ensure that patients at least meet the current recommended levels.

"Although epidemiological and early clinical trials are inconsistent, and randomised clinical trials in humans do not yet exist to conclusively support a beneficial role for vitamin D, accumulating results from preclinical and some clinical studies strongly suggest that vitamin D deficiency increases the risk of developing cancer and that avoiding deficiency and adding vitamin D supplements might be an economical and safe way to reduce cancer incidence and improve cancer prognosis and outcome," wrote David Feldman, emeritus professor of medicine at Stanford University School of Medicine, and colleagues, in *Nature Reviews Cancer* last year (vol 14, pp 342–357).

In the same year, Bernd Richter,

of Heinrich-Heine University Düsseldorf, coordinating editor of the Cochrane Metabolic and Endocrine Disorders Review Group, was prompted to write a cautious editorial in the wake of an equivocal Cochrane Review on the impacts of vitamin D on cancer risk.

"As with other interventions, supplements are a deep interference with people's lives and they have to prove that the benefits as measured by patient-important outcome parameters outweigh the harms," he said, adding that: "Not many interventions in medicine are as much evaluated as vitamin supplementation – and have provided so little good evidence at the same time."

While the debate goes on, one thing is clear: patient interest in vitamin D is growing. While in the UK it's far from routine to check cancer patients' vitamin D status, in the US it's becoming much more common, says Kimmie Ng, assistant professor of medicine at the Dana-Farber Cancer Institute at Harvard Medical School. Ng is studying vitamin D status and colorectal cancer prognosis, for which there is some of the strongest observational data indicating a link. "I believe most US oncologists are aware of the data on vitamin D and colorectal cancer," she says. "Importantly, many patients are also very aware of this data. More and more oncologists whom I have spoken to are routinely checking levels in patients."

So how might vitamin D help cancer patients? And what advice should oncologists give to patients who say they want to start taking supplements?

Vitamin D can be obtained through diet or in supplements as vitamin D3 or vitamin D2. But synthesis in skin exposed to UVB light is an important source for most people. Vitamin D3 (cholecalciferol) made in the skin is converted by the liver into 25-hydroxy vitamin D [25(OH)D3], which is usually measured in blood to determine vitamin D status. Circulating 25(OH)D3 is then converted in the kidneys into calcitriol, a potent steroid hormone, and the biologically active form of vitamin D.

US and UK government guidelines recommend 25(OH)D3 levels of around 20 ng/mL of blood, while the US Endocrine Society recommends 30 ng/mL Yet one study of white Britons found that, in winter and spring, about half have vitamin D levels below the lower recommended figure, and 15% are deficient year-round. People with darker skin living at high latitudes are at an even higher risk of deficiency.

While it has long been known that vitamin D is essential for bone mineralisation, over the past twenty years it has become clear that it plays a role in the health of the immune system. Low levels have been linked to an increased risk of some autoimmune disorders – in particular, multiple sclerosis – and to more frequent upper respiratory tract infections.

The cancer link

The earliest suggestions of a link between vitamin D and cancer risk came from epidemiological studies finding variations in the incidence of certain types of cancer at different latitudes.

In 2008, for example, researchers at the Moores Cancer Center at the University of California, San Diego, looked at data on worldwide cancer

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incidence and concluded there was a "clear association" between deficiency in exposure to UVB and breast cancer. Earlier work by the team, again using global cancer incidence data, found a "strong" association between latitude (and so perhaps UVB exposure) and kidney, ovarian and endometrial cancer.

Since then, various teams have taken a closer look at actual vitamin D status and cancer risk. Here, the evidence is inconsistent. A systematic review in Medline of prospective studies published up to February 2012 did find, though, that the majority of studies in cancer patients showed those with higher serum 25 (OH) D3 levels had a decreased risk of mortality. This was particularly clear in patients with colorectal cancer. Another systematic review and meta-analysis of prospective cohort studies of serum 25 (OH) D3 levels and survival in colorectal and breast cancer, specifically, found that higher levels (>30 ng/mL) were associated with "significantly reduced" mortality.

Yet another review of studies, which collectively examined vitamin levels in 17,332 cancer patients, found that overall a 4 ng/mL increase in vitamin D levels was associated with a 4% increase in survival. The strongest associations were between vitamin D levels and breast cancer, lymphoma and colorectal cancer. The association was less strong for lung, gastric, and prostate cancers, leukaemia, melanoma and Merkel cell carcinoma, but it still held. "Considering that vitamin D deficiency is a widespread issue all over the world, it is important to ensure that everyone has sufficient levels," says Hui Wang, professor of the Institute for Nutritional Sciences at the Shanghai Institutes for Biological Sciences, who led the research. "Physicians need to pay close attention to vitamin D levels in people who have been diagnosed with cancer."

Cedric Garland at the University of California, San Diego, who was part of the team that published the analysis of global cancer incidence and latitude, has also been involved in work investigating the vitamin D status of breast cancer patients. This work (*Breast Journal* 2008, 14:255–260) found that those with "high" levels of vitamin D in their blood (with an average of at least 30 ng/mL of 25 (OH) D3) were twice as likely to survive the disease (at a nine-year follow up) than patients with low levels (with an average of 17 ng/mL).

In the wake of these particular results, Garland said: "There is no compelling reason to wait for further studies to incorporate vitamin D supplements into standard care regimens, since a safe dose of vitamin D to achieve high serum levels above 30 nanograms per milliliter has already been established."

There are others who, like Garland, would certainly like to see more randomised clinical trials involving giving supplements to patients, but think the current observational data is compelling. But there are also critics of some of the conclusions drawn from the observational studies.

Correlation or causation?

Kimmie Ng's own work has found improved survival in colorectal cancer patients with higher vitamin D levels. But, as she says, hers and other prospective observational studies "do not prove causality". She adds: "There is still quite a debate, with many scientists on both sides. Most people agree that the epidemiological data has been strongest and most consistent in colorectal and breast cancer. Sceptics point out that higher vitamin D levels may simply be a surrogate for a healthier lifestyle, and thus better outcome. Yet other sceptics argue that higher levels of inflammation in cancer patients – or other poor prognosis factors associated with more aggressive disease – lead to lower vitamin D levels and thus poorer survival."

Like David Feldman at Stanford,

Sceptics point out that higher vitamin D levels may simply be a surrogate for a healthier lifestyle

SOURCES OF VITAMIN D

Most people meet at least some of their vitamin D needs through exposure to sunlight. Season, time of day, length of day, cloud cover, smog, skin melanin content, and sunscreen are among the factors that affect UV radiation exposure and vitamin D synthesis. Some studies suggest that approximately 5–30 minutes of sun exposure between 10 am and 3 pm at least twice a week to the face, arms, legs, or back without sunscreen usually lead to sufficient vitamin D synthesis. Very few foods in nature contain vitamin D. The flesh of fatty fish (such as salmon, tuna, and mackerel) and fish liver oils are among the best sources, while small amounts of vitamin D are found in beef, liver, cheese, and egg yolk. Vitamin D is often added as a supplement to breakfast cereals, orange juice and, in some countries, milk.

Source: US National Institutes of Health http://ods.od.nih.gov/factsheets/VitaminD-HealthProfessional/

* Value for 1 cup of orange juice fortified with vitamin D (check product labels, as amount of added vitamin D varies)

Cedric Garland points to lab research demonstrating that vitamin D has anticancer properties. This work is "abundant", Ng agrees. Vitamin D receptors have been found on a wide range of tumour cells, and Ng says: "We know that vitamin D can decrease cell proliferation, induce cell division and apoptosis, inhibit angiogenesis and metastasis, and has anti-inflammatory properties. Vitamin D can also stimulate host immunity against tumours."

And in January 2015, a team involving researchers at the Dana-Farber Cancer Institute published a paper in *Gut* (doi:10.1136/gutjnl-2014-308852), showing an effect of vitamin D on anti-cancer immune function in actual patients.

Julia Newton Bishop is a professor of dermatology and a clinician, who leads the Melanoma Research Group at the Leeds Institute of Cancer & Pathology, in the UK. She and her colleagues have found that vitamin D can inhibit melanoma cell growth in the lab. Her team has also published work finding that patients with higher levels of vitamin D had thinner tumours at diagnosis. Still, she's cautious about extrapolating lab findings to people. "I don't think there's any doubt that if you put a variety of different cell lines in culture and you add vitamin D you can stop them proliferating. We've reproduced that in our lab, and are just writing the paper up. That is agreed. But of course when you're growing cells in the lab, it's quite artificial. How that translates into man is what we're working on at the moment."

Data from various animal cancer models show that dietary vitamin D3, calcitriol and its analogues cause "a significant reduction in tumour growth and eventual tumour burden," write Feldman and his team in their 2014 review. They write: "The preclinical findings suggest how calcitriol regulation of crucial molecular pathways might inhibit the development and progression of multiple cancers." But, so far, the results of vitamin D intervention trials in people have been, as Newton Bishop puts it, "disappointing".

The 2014 Cochrane Review of randomised trials testing the effect of supplementation (whether with D3, D2 or calcitriol) concluded the results were "contradictory". While there was no increase or decrease in cancer occurrence, there was some evidence for lower cancer mortality following vitamin D3 supplementation, although the overall quality of the evidence was rated as low.

The wrong dose?

With colorectal cancer, the few randomised clinical trials that have been done have either not shown a benefit for vitamin D supplementation on colorectal cancer risk, or have looked at it as a secondary, rather than a primary endpoint, says Ng. One debate centres over the serum levels that may be most beneficial, and so the doses that should be used in trials. One large US Women's Health Initiative

trial, involving calcium and vitamin D supplementation, found no improvement in colorectal cancer risk. But Ng argues there were many limitations to the study. It used what she calls a "very low" dose of vitamin D (400 IUs) and had, she argues, too short a duration of supplementation (the women, aged 50 to 79, were followed for an average of seven years). In addition, she notes, there was poor compliance with the supplementation protocol.

Many cancer patients in the US, after being checked for vitamin D, are being repleted to at least 20 or 30 ng/mL or higher, Ng says. And some patients may be reaching significantly higher levels.

Nithya Ramnath, associate professor of medical oncology at the University of Michigan Health System, has found anti-proliferative effects of calcitriol in lung adenocarcinoma (in *in vitro* studies). "Many of the [lung cancer] patients in the US are already on 1000–2000 IUs per day, prescribed by their primary care doctors," she says.

It's unclear what level of vitamin D might be needed for anti-cancer effects, but the animal work suggests that it's higher than the level recommended for bone health, Feldman and his team point out. The research on multiple sclerosis suggests that blood levels above 40 ng/mL are most beneficial. One large multicentre clinical trial that has been underway at Johns Hopkins University, in Baltimore, Maryland, and elsewhere, for over a year, on patients with multiple sclerosis, uses doses of up to 10,000 IUs of vitamin D per day. So far, there have been no reports of any cases of hypercalcaemia, which is the most likely risk from high doses of vitamin D.

Since the body self-regulates levels of vitamin D synthesised in the skin, some researchers argue that sun exposure may be a safer way for some people to get as much vitamin D as possible. The advice may not be very practical for people who live in a part of the world that provides inadequate UVB year-round. There's also the problem that sun exposure is the biggest major environmental exposure increasing susceptibility to melanoma of the skin.

However, the epidemiological evidence suggests that it's intermittent sun exposure – the sort experienced on sunny holidays, and which is often associated with sunburn – that explains most melanoma in genetically susceptible people (those with pale skin, freckles, a tendency to red hair, lots of moles and a family history), says Newton Bishop. There's evidence that these people are often deficient in vitamin D, and they will probably need supplements to obtain adequate amounts, she says. Other groups of people should be able to spend some time in the sun (without burning) without raising their melanoma risk, she says. NICE, the UK's National Institute for Health and Care Excellence, is currently developing a public health guideline on the health benefits versus risks of sun exposure, she adds.

But some researchers think the debate about the desirable dosage for intervention trials is, at least in the case of some cancers, questionable – because researchers have been using not the wrong dose, per se, but the wrong *type* of vitamin D.

The wrong type?

Ronald Evans, director of the Gene Expression Laboratory at the Salk Institute in La Jolla, California, is involved in human trials of a vitamin D derivative, paricalcitol, in combination with regular chemotherapy in patients with pancreatic cancer. This follows work by his team finding that paricalcitol can collapse the 'living shield' of protective cells that a pancreatic tumour generates around itself, and which can stop therapeutic drugs from getting through.

These initial lab findings were a big surprise, because vitamin D had been tried multiple times as a therapy for pancreatic cancer, and never worked, Evans says. This is partly because it turns out that normal vitamin D is rapidly broken down by the pancreatic stellate cells, which prevents it from binding to the vitamin D receptor on these cells. Paricalcitol, in

VITAMIN D LEVELS AND DOSES

20 ng/mL: guideline serum level of 25(OH)D3 recommended by US and UK governments

30 ng/mL: guideline serum level of 25(OH)D3 recommended by the US Endocrine Society

400 IUs: daily vitamin D supplement for melanoma patients recommended by head of Melanoma Research Group at Leeds Institute of Cancer & Pathology (UK) in patients with 25(OH)D3 levels below 24-34ng/mL range

1000–2000 IUs: daily vitamin D supplement prescribed in US to many lung cancer patients

2000 IUs: daily vitamin D supplement being trialled as a cancer preventive in people with a prior history of cancer (VITAL trial)

Up to 10,000 IUs: daily vitamin D supplement being trialled for people with multiple sclerosis

"We all have to live with probabilities instead of certainties of the results of medical research"

contrast, he says, is very resistant to degradation. So it can successfully inactivate the cells, weakening the wall around a tumour. It's important to note that vitamin D isn't attacking the tumour, he adds – but rather making standard chemotherapy more effective. A study published by the team in September 2014 in *Cell* (vol 159, pp 80–93) found that mice given paricalcitol plus regular chemotherapy lived 50% longer than mice given chemotherapy alone.

Yes, he says, many vitamin D intervention trials have failed to provide positive results. "However, these trials may have been doomed to fail, as our work suggests that the standard vitamin is rapidly degraded by tumours. This is why the use of a modified form is important," he says. Evans hopes it may also be useful for other cancers. "We suspect colon cancer and liver cancer may also benefit from this type of therapy, and we are exploring this possibility," he says.

But while some researchers are clearly excited or at least encouraged about the potential for vitamin D in cancer treatment, others are very cautious.

A major reason for widespread wariness, at least among oncologists in the UK, is because of what happened with beta-carotene, Newton Bishop says. Epidemiologic studies had suggested that vitamin E and beta-carotene were associated with a reduced risk of lung cancer. But a big Finnish study found that men who were given beta-carotene were more likely to die of lung cancer. "That terrified a lot of people," says Newton Bishop. "It gave people the view that you really can't trust observational studies… But if it wasn't for observational studies we wouldn't know that lung cancer is caused by cigarette smoking. These studies are a way of identifying a potentially important thing, which you then have to prove. And then it's difficult to prove. But that's what we're looking at now."

A few randomised controlled trials investigating the impacts of vitamin D on cancer are ongoing. The VITamin D and OmegA-3 (VITAL) trial, for instance, is investigating whether daily dietary supplements of 2000 IUs of vitamin D or 1 gram of fish oil or both reduce the risk of developing cancer (as well as heart disease and stroke) in people without a prior history of these illnesses. But the results will not be available for many years – and the findings may still engender controversy, say David Feldman and his team.

When patients ask...

For now, in the absence of convincing data to the contrary, Newton Bishop says she feels most comfortable aiming for a 25(OH)D3 serum range of 25–35ng/mL – roughly the level recommended by the US Endocrine Society. A supplement of 400 IUs per day should bring most people into that range, she says. With her own melanoma patients, she says: "in practice, we've measured vitamin D and if it's low, then I've counselled very slow but steady supplementation to that range."

At the moment, patients being treated in Leeds don't tend to ask for vitamin D testing themselves. "It isn't common in Yorkshire to be asked about vitamin D. But I think there's regional variation in interest. Certainly, one gets a lot of email from the US, where they tend to be much more proactive with their health," says Newton Bishop.

Given the abundance of current research, particularly in the US, and the publicity it's attracting, it seems likely that more European cancer patients will start asking for tests. And while many oncologists may be cautious about any potential role for vitamin D, it is something they can expect to be increasingly asked by their patients to advise on.

"The vitamin D story is a… good example of how difficult it is to adequately analyse and critically appraise scientific data," argues Berndt Richter in his editorial. "We all have to live with probabilities instead of certainties of the results of medical research, and this has to be openly and sensitively communicated during any patient–doctor encounter to optimise shared decision making."

On the basis of the existing evidence, Feldman and his team conclude that, while they believe adequate anti-cancer 25(OH)D3 levels "probably exceed" 30 ng/mL: "The easy availability, economy and safety of this multipurpose pre-hormone indicate to us that the benefits of dietary vitamin D can be recommended, even while we await RCT data." ■