Commentary: Progress of a paradigm

Cedric F Garland1,2 and Frank C Garland1,2

‘It is proposed that vitamin D is a protective factor against colon cancer.’ These 13 words started the abstract of our paper1 and said it all. The concept that vitamin D can prevent cancer was born. Vitamin D was raised from being a nearly forgotten compound into the dustbin of medical history. Mention of rickets or vitamin D metabolism in adult man in health and in disease. The idea that UVB irradiance and vitamin D might save the then-USSR.3 These two studies were quickly followed by a study in the US that found higher levels of solar radiation and thinner stratospheric ozone were associated with lower breast cancer mortality rates.4 With the publication of a study reporting that sunlight exposure was associated with lower mortality rates of ovarian cancer,5 it was becoming apparent that vitamin D resulting from UVB exposure had a beneficial role across a broad range of cancers.

Vitamin D comes from two sources, diet and solar radiation. This is unique, and is one reason why the association was not immediately obvious. Either could mask the other, making it hard to recognize vitamin D’s importance. Another reason that
the role of vitamin D deficiency had gone unrecognized was that it was broadly accepted that there was no vitamin D deficiency in the US.

The next step in the progression of developing evidence was a historical prospective study based on detailed dietary records from a cohort of 1954 men in Chicago that had been followed-up for 19 years. The cohort’s organizers and Dr Elizabeth Barrett-Connor provided an opportunity for us to look in this cohort for an association of vitamin D with incidence of colon cancer. The study found that people in the upper half of intake of vitamin D had half the incidence rate of colon cancer than those in the lower half.

Dietary studies could tell only half the story, though. While dietary Vitamin D was inversely associated with risk in a Northerly population, it remained to be shown that vitamin D in the serum had a similarly powerful association.

The main circulating vitamin D metabolite, 25-hydroxyvitamin D [25(OH)D], is stable over time, and can be readily measured in serum that has been frozen for years. A good way to account for both the solar and dietary contributions to vitamin D status could be a study of this vitamin D metabolite in the serum, since it varies considerably according to solar UVB exposure and oral intake. We had an opportunity to perform a nested case-control study in a cohort of 25,620 volunteers that we helped assemble 8 years earlier at the Johns Hopkins Community Laboratory in Hagerstown MD. The study revealed that risk of colon cancer in those whose serum 25(OH)D was >20 ng/ml was only a third that of those with <20 ng/ml.

We received an unexpected invitation in 1990 from Dr Sam Broder, Director of the National Cancer Institute, to present a Director’s Seminar. Dr Broder understood the potential of vitamin D in reducing incidence of colon and breast cancer, and invited us to present the concept and our data in a unique forum that brought together heads of all departments of the Institute. The result was a lively discussion, followed by a telephone call by Dr Broder to Dr Bernadine Healy, Secretary of Health and Human Services, who had proposed, and was designing, the Women’s Health Initiative, the largest clinical trial designing, the Women’s Health Initiative, the largest clinical trial ever conducted. Dr. Broder asked that a vitamin D arm be included the study. Before long, ~30,000 women were randomized to this arm of the trial and are being followed-up for events.

We were struggling in the meantime to create a public health recommendation based on the data that we had. We did not want to suggest even modest exposure to solar radiation if it would increase risk of melanoma. Startlingly, melanoma incidence rates rose 12-fold during 1935–90 in the US, a rise that was unique to industrialized countries. The prevailing explanation was that it was due to excessive intermittent UVB exposure.

One of the primary preventive measures was use of UVB-absorbing sunscreens. Unfortunately, the sunscreens were transparent to UVA, and far greater exposure to UVA than ever was a result of the false sense of security and longer duration of exposure that they allowed. We published a study marshalling the evidence that the melanoma epidemic was due to increased exposure to UVA (315–400 nm), to the surprise of the dermatological community.

The evidence revealed that sunscreens were subverting the normal photoprotective response—thickening of the epidermis, release of melanin, and upregulation of DNA repair enzymes due solely to UVB exposure. Within a year, almost all sunscreen formulas were changed to include UVA absorbers or physical barriers such as titanium dioxide, and the scientific community began to reconsider the benefits and risks of exposure to each part of the solar spectrum. This evidence led to the recognition that overexposure to UVA is harmful, while moderate exposure to UVB may be beneficial for photosynthesis of vitamin D.

William Grant performed an ecological study of US states that identified several other cancers as inversely associated with solar UVB irradiance, including bladder, oesophageal, kidney, lung, pancreatic, stomach, and corpus uteri. In parallel with this work, the effects of vitamin D are now being explored widely for cancer prevention. The 1989 serum study led to three similar studies, the largest of which replicated the initial serum study, in a far larger cohort. Meanwhile, Dr Heide Cross and her co-workers made the important discovery that peripheral tissues convert 25(OH)D to 1,25(OH)2D, adding greatly to the understanding of the mechanism of vitamin D metabolites in cancer prevention and helping to account for the effect of UBV on risk. Their current work is disclosing the roles of certain micronutrients in vitamin D metabolism.

Studies of the role of vitamin D in cancer prevention are now under way in many cohorts. Promising new results supporting vitamin D’s role in reducing incidence and mortality rates of a broad range of cancers in the Harvard Nurses’ Health Study and Health Professionals’ Follow-Up Study were reported by Dr Edward Giovannucci. The results of the Women’s Health Initiative are now being analyzed.

Based on research to date, the current recommendation of 200–600 IU/day of vitamin D is too low. It is reasonable to suggest, based on current data, that 1000–1950 IU per day would be a more optimal level of intake for adults and children ≥6 years. Oral intake should, of course, be kept below the National Academy of Sciences’s No Adverse Health Effect Level of 2000 IU/day. UVB exposure should be limited to no more than 15 min per day in whites, 30 min in those of other races, and should be minimized in the very fair or those with specific disorders that would preclude any solar exposure.

There is excitement regarding a role of vitamin D as part of cancer therapy. Cancer patients who live in places with high solar UVB radiation have better survival rates than those in areas deprived of solar UVB radiation, and patients whose cancers are treated during the summer months also have better survival rates. This has led to the search for vitamin D derivatives that could play a role in less toxic approaches to chemotherapy.

As Professor Abe Lilienfeld, our mentor and friend at Johns Hopkins, said, the basic observational and inferential aspects of epidemiology—time, place, and person—are the key elements in the understanding of disease. There elements have almost faded into history as epidemiologists pursue clinical trials and study the genome. When observation and inference from time, place, and person are applied, though, they bring new perspectives and paradigm shifts that benefit the orderly progression of scientific knowledge.

References

In 1980, Garland and Garland hypothesized that vitamin D status accounted for the inverse association between UV-B radiation exposure and risk of colon cancer.1 The title of their article was posed as a question, ‘do sunlight and vitamin D reduce the likelihood of colon cancer?’ At the time, essentially nothing was known about the biology of vitamin D and colon cancer, and epidemiological data were sparse. Largely stimulated by this article, substantial research in this area has been conducted over the past 25 years. The biological underpinnings of this hypothesis have become quite strong; colorectal cells contain vitamin D receptors, and express 1-alpha-hydroxylase, and are thus able to convert 25(OH) vitamin D into 1,25(OH)2 vitamin D. Activation of these receptors by 1,25(OH)2D induces differentiation and inhibits proliferation, invasiveness, angiogenesis, and metastatic potential. The biological basis of the hypothesis can now be considered strong, if not compelling, and has been reviewed elsewhere.2 This commentary will focus on human studies.

From an epidemiological perspective, the hypothesis that vitamin D lowers cancer risk has been tested in at least six ways. First, given that solar UV-B radiation is the major source of vitamin D for most people, one would predict that greater average UV-B radiation in geographical region of residence would correlate with lower risk of colon cancer. Indeed, it was this approach that Garland and Garland used to formulate the vitamin D–cancer hypothesis. Although such ecological data are informative, one of the potential weaknesses is the inability of such ecological data to examine vitamin D intake in relation to risk of colorectal neoplasia. A caveat is that vitamin D intake at typical levels currently does not raise 25(OH)D levels substantially. For example, a recent analysis in the Nurses’ Health Study,4 the difference in plasma 25(OH)D levels between high and low quintiles was ~50 nmol/l, but an increment of 400 IU/day (e.g. four glasses of fortified milk) is expected to increase circulating 25(OH)D by <10 nmol/l. Studies that have examined total vitamin D intake (including supplements that broaden the contrast) have generally found an inverse association with colorectal cancer or adenoma.5,6 Many of

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Commentary: Vitamin D and colorectal cancer—twenty-five years later

Edward Giovannucci1,2,3

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