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Re: Visvanathan et al. Circulating vitamin D and breast cancer risk: an international pooling project of 17 cohorts

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The recent article by Visvanathan et al. conducted a pooled analysis of 17 prospective cohort studies of breast cancer incidence with respect to baseline serum 25-hydroxyvitamin D [25(OH)D] concentration in an effort to determine whether vitamin D reduces risk of breast cancer [1]. Even though the range of 25(OH)D concentration extended from <20 nmol/L to >125 nmol/L, no significant correlations between 25(OH)D concentration and incidence of breast cancer were found. As the authors noted in the introduction, there is compelling evidence that vitamin D can inhibit cancer initiation and progression in experimental models. Thus, two questions arise: 1 – has vitamin D status been found to reduce risk of breast cancer incidence using other epidemiological approaches?; and, 2 – what might be the problem with prospective observational studies for breast and other types of cancer?

Regarding the first question, both case-control (CC) studies with serum 25(OH)D concentrations measured near time of breast cancer diagnosis and geographical ecological studies have found strong support for vitamin D and solar UVB dose, an index of vitamin D production, in reducing breast cancer incidence and/or mortality rates [2]. CC studies are usually overlooked regarding the role of vitamin D in health outcomes for two reasons: 1 – that the disease state might affect serum 25(OH)D concentrations (reverse causality); and 2 – that the choice of controls might introduce bias. As for the disease state affecting 25(OH)D concentrations, as was discussed in [2], it is mainly found with acute inflammatory illnesses that reduce serum 25(OH)D concentrations near the time of disease onset. A good example is COVID-19, for which the body's immune response often includes rapidly raising pro-inflammatory cytokine concentrations, thereby raising inflammatory biomarkers such as C-reactive protein, and reducing 25(OH)D concentrations. The physiological indication is a fever. However, the increase in C-reactive protein associated with cancer incidence is very small, and cancer patients do not have fevers. As for matching controls, approaches such as propensity score matching are now being applied, which helps ensure that cases and controls are well matched. Also, since the findings for breast cancer risk reduction with respect to 25(OH)D concentrations from CC studies are very similar, it does not appear that bias is an important concern.

What are the problems with prospective observational studies of cancer with respect to serum 25(OH)D concentrations? As shown in 2011, the longer the follow-up time, the smaller the observed difference in cancer incidence rates between high and low baseline 25(OH)D concentrations [3]. In Figure 1 of [3], for four studies with >4 years of follow up, no significant reductions of breast cancer with respect to 25(OH)D concentration were found. (This is essentially the same as for the 17 studies included in [1] as in that article's Figure 3.) However, for CC studies and one prospective study with a 3-year follow up, the mean relative risk (RR) for breast cancer incidence with respect to 25(OH)D concentrations was near 0.6 and was significant for all studies. For colorectal cancer (CRC), RR was significantly below one out to 14 years of follow up. As mentioned in [3], there is evidence that breast cancer tumors can develop very rapidly to a size that is easily detected. That is consistent with the fact that breast cancer screening is recommended every one-to-two years, while CRC screening is recommended every ten years.

It is noted that a meta-analysis of 17 cohort studies regarding CRC incidence from this consortium found a significantly reduced odds ratio (OR) for CRC incidence with respect to serum 25(OH)D concentration for women, but not for men [4]. As shown in Figure 1 in [2] for a similar analysis of OR vs. follow-up time for CRC showed that when the OR are plotted vs. median follow-up time to diagnosis, the OR for zero years of follow up is 0.77 for males and 0.74 for females, in stark contrast to their finding that results were not significant for men. The reason why no significant reduction in CRC risk was found for men is that the slope of the OR for men was 0.031/year while that for women was 0.0081/year. Why the slopes differ is not known.

Additional support for the fact that breast cancer tumors can grow rapidly to detectable size is given in an analysis of breast cancer seasonality [5]. They included observational studies from 64 global regions over time spans from 2 to 53 years. The primary finding was that in the northern hemisphere, breast cancer incidence is more frequently detected from September through November and again from February or March through May or June, with the minimum of detection in July and August and a weaker minimum from December to February until April. They hypothesized that solar UVB production of vitamin D explained the summer minimum, and that increased melatonin due to weak solar radiation levels in winter explained the winter minimum. They cited a number of articles regarding the role of melatonin in reducing risk of breast cancer. Figure 5 in [5] shows a model pattern for relative breast tumor volume vs. time oscillating from lower in summer and winter, higher in spring and fall, superimposed on a continuously rising trend.

Conclusion: The role of vitamin D in reducing risk of breast and other cancers should be evaluated using findings from mechanism studies, geographical ecological studies, observational studies using either short follow-up times after blood draw for serum 25(OH)D concentration measurements or correction for long follow-up times, and properly designed randomized controlled trials, i.e., based on serum 25(OH)D concentrations, enrolling participants with low 25(OH)D concentrations, and giving large vitamin D doses [2]. In addition, the assumptions regarding the reliability of various approaches should be carefully studied.

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