Effect of follow-up time on the relation between prediagnostic serum 25-hydroxyvitamin D and all-cause mortality rate

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Evidence continues to mount that vitamin D reduces the risk and mortality rates of many types of disease. However, evidence from prospective cohort studies is sometimes weaker than that from case–control and ecological studies. A suggested reason for this discrepancy is that, because serum levels of 25-hydroxyvitamin D [25(OH)D] change over time, a single 25(OH)D concentration measurement taken at study enrollment does not reliably indicate 25(OH)D concentration related to the health outcome. To evaluate this suggestion further, this paper plots results from 12 prospective cohort studies of all-cause mortality rate vs. follow-up time. The regression fit to the hazard ratio per 20-nmol/l increase in serum 25(OH)D concentration vs. time increased from 0.82 (95% CI, 0.67–1.02) for 6 y to 0.96 (95% CI, 0.90–1.01) for 14 y. The value extrapolated for zero follow-up time was 0.72 (95% CI, 0.50–1.03), giving a hazard ratio reduction 3.5 times higher than the standard result from the meta-analysis [0.92 (95% CI, 0.89–0.95)]. Using the example of the Vitamin D Pooling Project of Rarer Cancers, this paper also discusses follow-up time's effect in interpreting prospective cohort studies of cancer outcome. This paper recommends that meta-analyses of prospective cohort studies account for follow-up time and, if possible, that studies measure serum 25(OH)D concentration every 2–4 y.

Introduction

Evidence for beneficial effects of solar ultraviolet-B (UVB) irradiance and vitamin D in reducing the risk of adverse health outcomes comes from a variety of study types: ecological, cross-sectional, case-control, cohort, and intervention. Vitamin D researchers consider the evidence of beneficial effects to be strong.[1-3] However, others have conducted systematic reviews that find the evidence lacking[4,5]—partly because at the time of the reviews, few well-conducted randomized controlled trials (RCTs) with vitamin D existed to analyze its nonskeletal effects.[6] Also, findings from cohort studies[7,8] sometimes disagree with results from ecological studies.[9]

A recent paper argued that prospective studies with long follow-up times lead to errors because the single serum 25-hydroxyvitamin D [25(OH)D] concentration measurement taken at study enrollment loses prognostic value over time.[10] For breast cancer, the linear regression line fit to the relative risk increased from 0.61 for case–control studies with no follow-up period to 0.95 for a 7-y follow-up, whereas for colorectal cancer, the regression line fit increased from 0.48 for case-control studies

with no follow-up to 0.72 for a 14-y follow-up. For prostate cancer, no statistically significant correlation emerged with respect to 25(OH)D concentration for any follow-up time between 4 and 28 y. Further support for this assertion is that a prospective study of breast cancer incidence found a strong inverse correlation with high vitamin D intake in the first 5 y after baseline dietary assessment (relative risk = 0.66; 95% CI, 0.46–0.94 compared with lowest-intake group), with the association diminishing over time.[11] Also, for a nested case-control study of lymphoma in Finland, the odds ratio for chronic lymphocytic leukemia or small lymphocytic lymphoma was 0.41 (95% CI, 0.15–1.09) for follow-up time shorter than 7 y but was 1.15 (95% CI, 0.44–3.01) for follow-up longer than 7 y.[12]

A recent meta-analysis of all-cause mortality rate with respect to prediagnostic serum 25(OH)D concentration mentioned that the cohort studies with shorter follow-up times had a stronger association than those with longer follow-up.[13] This paper uses the data in that study to extend that analysis of follow-up time's role in cohort studies of health outcomes with respect to prediagnostic serum 25(OH)D concentration.
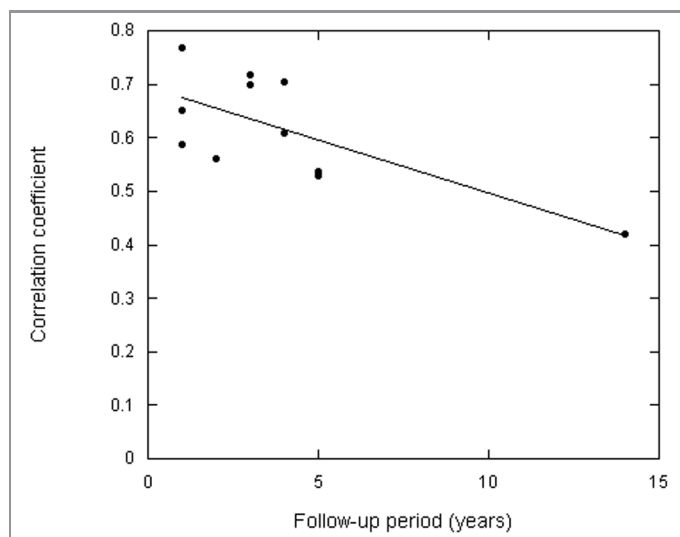
Figure 1. Correlation coefficient of serum 25(OH)D concentration measured in two periods vs. follow-up period.

Results

Figure 1 is a scatterplot of the correlation coefficient for serum 25(OH)D concentration measurements vs. interval. The value changes from a zero intercept of 0.7 to 0.42 for 14 y. The square of the correlation coefficient gives the fraction of the variance explained by the model. The shortest interval is 1 y.

Figure 2 plots the hazard ratios vs. follow-up period. The regression fit to the hazard ratio per 20-nmol/l increase in serum 25(OH)D concentration vs. time increased from 0.82 (95% CI, 0.67–1.02) for 6 y to 0.96 (95% CI, 0.90–1.01) for 14 y. The
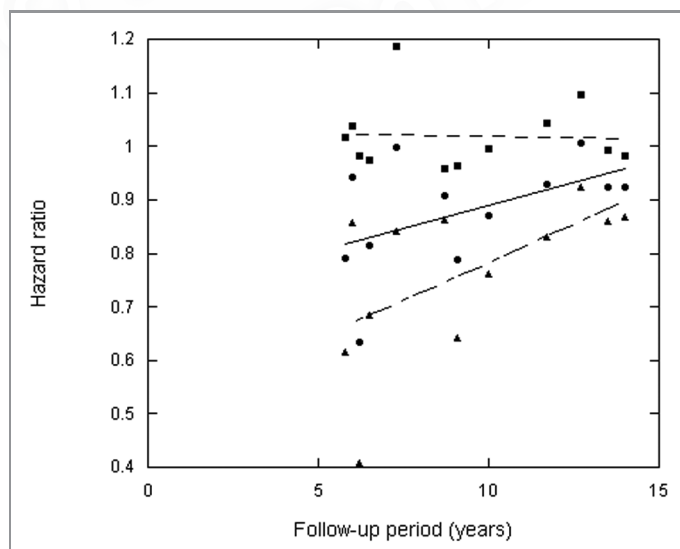

Figure 2. Hazard ratios (HRs) for all-cause mortality rate per 20-nmol/l increase in serum 25(OH)D concentration, using data from Figure 3 in Schöttker et al.13 vs. follow-up period. The equations for the regression fits are: HR = 0.72 + 0.017 t; HR [lower confidence interval (CI) = 0.50 + 0.029 t]; HR (upper CI) = 1.03 – 0.0009 t, where t = time (years).

zero follow-up time value is 0.72 (95% CI, 0.50–1.03). These values differ considerably from the values in the meta-analysis by Schöttker and colleagues[13] of 0.92 (95% CI, 0.89–0.95), which corresponds to a value for 12 y for the regression fit in Figure 2. However, the mean follow-up time of all 12 studies weighted by the relative weights in Schöttker's Figure 3 is 9.6 y. Thus, the results based on extrapolation to zero follow-up time find 3.5 times as great a risk reduction, whereas the ratio for 6 y is 2.3 times as great. Although the extrapolated 95% CI values for zero follow-up time are large, the values would be much smaller if the values were averaged, say, for each three values.

Discussion

The results in Figure 2 suggest that a 20-nmol/l increase in vitamin D serum level reduces the risk of all-cause mortality rate by 18–28%. The 18% is similar to the 7–17% reduction achieved by increasing serum 25(OH)D concentration from 54 to 110 nmol/l, as estimated in a recent study based on the serum 25(OH)D concentration–disease outcome relation for diseases contributing the most to all-cause mortality rate: cancer, cardiovascular disease, diabetes mellitus, respiratory diseases, respiratory infections, and tuberculosis.[14] This reduction in mortality rate would increase life expectancy by an estimated 2 y.

However, because the 25(OH)D concentration–mortality rate relation is nonlinear, changing rapidly for low serum 25(OH)D concentrations and very little above 80 nmol/l, determining a more precise estimate would require a more careful analysis. On the basis of Figure 4 in Zittermann and colleagues,[15] the 8% reduction in Schöttker et al.[13] is consistent with an increase of serum 25(OH)D from 50 to 70 nmol/l.

These results further support the assertion that the apparent risk of adverse health outcomes decreases with longer follow-up time. However, in nested case-control studies, shorter follow-up times have fewer cases and thus wider 95% CIs. The rationale for conducting nested case-control studies instead of case-control studies with no follow-up interval includes concerns about bias in selecting controls and that the disease may affect the health outcome. For mortality rates, death often comes after long-term illness, which can affect serum 25(OH)D concentrations. For cancer incidence rates, this concern is not as well founded: people who have cancer often do not find out until diagnosis through screening (for breast and colorectal cancer) or until they notice persistent pain for a short time. For breast cancer, case-control studies found much greater inverse correlations between serum 25(OH)D concentration and incidence than did nested case-control studies.[10]

This study recommends that meta-analyses of cohort study findings incorporate follow-up time, as demonstrated here. It also suggests comparing case-control study results with those of cohort studies by plotting the results vs. follow-up interval; if the data from both types of studies can be modeled with a linear or second-order regression fit without large deviations, the case-control results should be afforded more credibility. This study also recommends that prospective cohort studies regularly measure serum 25(OH)D concentration, perhaps every 2–4 y. Doing so

would add additional costs to the studies but would yield more accurate results.

Thus, in studies such as the Vitamin D Pooling Project of Rarer Cancers,[7] the disagreement with ecological studies may be due partly to the long mean follow-up time of 6.63 y. Some of the disagreement can also be due to the few cases for each type of cancer. Also, the role of solar UVB and vitamin D appears to be stronger for mortality rates than for incidence rates in ecological studies.[17,18] Ecological studies of the seven types of cancers in the Vitamin D Pooling Project of Rarer Cancers [endometrial, esophageal, gastric, kidney, ovarian, pancreatic cancer and non-Hodgkin lymphoma (NHL)] strongly support beneficial effects of solar UVB in reducing mortality rates.[9] The evidence of beneficial effects for incidence rates for these types of cancer in ecological studies is weaker.[17,18] Results from prospective cohort studies also support a protective role of UVB irradiance for NHL[19-21] and 25(OH)D concentration for gastric[22] and pancreatic[23] cancer, with moderate support for a role of serum 25(OH)D concentration in ovarian cancer[24,25] but no support for endometrial cancer[26] or NHL.[17,27] However, long follow-up times could adversely affect some observational studies for endometrial and ovarian cancer and NHL.

There are some limitations of ecological studies. For one, there are risk-modifying factors that are not included in the analyses, such as physical activity, obesity rates, and immigration. For example, in the United States, there was considerable migration from the Northeast to the South and West in the second half of the twentieth century. The strength of the ecological approach is demonstrated in the fact that the results for many types of cancer are often repeated for different populations.[9]

This study offers additional support for the thesis that long follow-up times adversely affect nested case-control studies from prospective cohort studies regarding the role of prediagnostic serum 25(OH)D concentration in health outcomes such as all-cause mortality rate and many types of cancer. It is hoped that the research communities and health policy makers will take this thesis into account when analyzing epidemiological studies and making recommendations regarding vitamin D.

This study also indicates that observational studies can strongly support the UVB-vitamin D-disease reduction hypothesis if the existing studies in the journal literature are carefully assessed and systemic biases in the interpretation of the data are removed. Unfortunately, the Institute of Medicine Committee on Dietary Reference Intakes for Vitamin D and Calcium[5] did not undertake that task. They opted instead to wait another 5–6 y for a "definitive" RCT of vitamin D supplementation.[28] As Kristal[29] and another paper in this issue[30] pointed out, RCTs have several problems that, if not carefully addressed, can result in poor-quality studies. Ideally, results from all types of studies—clinical, cross-sectional, ecological, laboratory and observational—would be considered together and reasons for differences resolved.

Materials and Methods

Findings in the literature for the correlation coefficient for serum 25(OH)D concentrations for a single cohort for different measurement intervals (**Table 1**) are plotted vs. time. The correlation coefficients were of two types: Pearson coefficient and Spearman rank coefficient. Good agreement exists between the two types of coefficients. However, because the Pearson coefficient is more appropriate for continuous variables, it is used in the graph when both coefficients are given.

The data for this study are from a recent meta-analysis of prospective cohort studies of all-cause mortality rate.[13] This study uses the statistics for the 12 studies included in that meta-analysis for hazard ratios per 20-nmol/l-increase in serum 25(OH)D concentration (Fig. 3 in Schöttker et al.[13]). The values are given in **Table 2**. These values are plotted vs. follow-up period. A complication exists in that the 25(OH)D-mortality rate relationship is nonlinear,[15] but both Schöttker et al.[13] and this study ignore that fact.

The data were plotted using KaleidaGraph 4.0 (Synergy Software).

Table 1. Correlations between serum 25(OH)D concentrations measured at different intervals

Location	Mean age at first measurement (years)	Interval (years)	Pearson coefficient	Spearman rank coefficient	Ref.
U.S.	61	1		0.65	31
Denmark	64	1	0.59, 0.77	0.56, 0.74	32*
Denmark	64	2	0.56	0.55	32*
Denmark	64	3	0.72	0.67	32*
U.S.	59	3	0.70		33
Denmark	64	4	0.70	0.64	32*
U.S.	61	4		0.61	31
Denmark	64	5	0.54	0.49	32*
U.S.	61	5		0.53	31
Norway	52.5	14	0.42		34

*Personal communication from L. Rejnmark in addition to published data.

Table 2. Statistics for the all-cause mortality rate data used in this study[13]

Hazard ratio	Lower limit	Upper limit	Follow-up period (years)	Ref.
0.943	0.856	1.039	6.0	35
0.634	0.409	0.983	6.2	36
0.816	0.684	0.975	6.5	37
0.999	0.842	1.186	7.3	38
0.791	0.615	1.018	8.0	39
0.909	0.862	0.959	8.7	40
0.787	0.643	0.963	9.1	41
0.870	0.761	0.995	10.0	42
0.930	0.830	1.042	11.7	43
1.007	0.925	1.096	12.7	44
0.923	0.859	0.992	13.5	45
0.924	0.869	0.983	14.0	46
0.919	0.887	0.952	9.6	Total

Disclosure of Potential Conflicts of Interest

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