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Short Communication

Serum 25-hydroxyvitamin D at pregnancy and risk of breast cancer in a prospective study

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ABSTRACT

Background: Several laboratory and epidemiological studies have inversely linked endogenous vitamin D and the risk of breast cancer. The acquisition of vitamin D over time on the relative risk (RR) of the disease development is not known. In a longitudinal study, we evaluated the association between vitamin D levels at pregnancy over time with the risk of breast cancer, and pregnancy-associated breast cancer.

Method: The risk for subsequent development of breast cancer associated with serum 25-hydroxyvitamin (25-OHD) levels was assessed for consecutive (1st and 2nd pregnancy) samples of 100 cases, with mean lag times (μ_t) of 7.4 and 4.6 years between sampling and the diagnosis, and matched (parity, age, year, season) controls. Pregnancy-associated breast cancer (PABC, 111 case–control pairs, μ_t = 1year) risk was also studied. Odds ratios (ORs) with 95% confidence intervals (CI) were calculated using the lowest quintile as the reference.

Results: Serum 25-OHD level was not associated with an increased risk neither at the 1st nor at the 2nd pregnancy samples (OR = 1.4, 95%CI 0.6–3.4; OR 1.4, 95%CI 0.7–2.8, respectively), but was associated with an increased risk of PABC (OR = 2.7, 95%CI 1.04–6.7).

Conclusion: Generally, vitamin D may not be related to breast cancer risk but the increased PABC risk fits the association of vitamin D with the most aggressive cancers, and warrants caution with vitamin D supplementation during pregnancy.

1. Introduction

Vitamin D can inhibit breast cancer cell proliferation as well as promote apoptosis and cell differentiation in normal and malignant breast tissues.[1–4] In post-menopausal women, low levels of 25-OHD are associated with an increased risk of breast cancer.[5,6] Although a similar observation has been made in premenopausal women,[7] the opposite may be true.[5,8]

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Levels of vitamin D, a pro-hormone primarily synthesised via exposure to ultraviolet B (UVB) radiation from sunlight, are subject to great variation over time. However, no study with prediagnostic serial samples has evaluated the acquisition of vitamin D and relative risk for the subsequent development of breast cancer.

We conducted a prospective nested case–control study within the Finnish Maternity Cohort (FMC), the world's largest serum bank for female donors,[9] to evaluate the risk of breast cancer associated with vitamin D (as measured by 25-OHD) levels at the 1st and the 2nd pregnancy. We also determined the relationship between 25-OHD levels and risk of pregnancy-associated breast cancer (PABC, diagnosed within one year of delivery). Since 1983, virtually all (>98%) Finnish women (altogether 750,000 women) have donated 1st trimester serum samples to the FMC at each pregnancy.[9] Cases and controls were ascertained by the Finnish Cancer Registry (FCR).[10] The study was approved by the local ethical committee.

2. Materials and methods

We identified 100 cases with at least two singleton pregnancies (follow-up time $\leqslant$ 10 years) before the diagnosis of breast cancer, and matched them to cancer-free controls for season of blood withdrawal [summer (May–August) or winter (December–March)], sampling age (±1 year), sampling year and parity (±1). Stratification by age at diagnosis as previously defined[8] did not identify post-menopausal breast cancer cases.

In addition, all PABC cases (111 in total) were identified and matched with controls for age (±1 year), parity (±1) and date of index blood sampling (±15 d). The cases were matched with the controls on a one-to-one basis.

25-OHD was measured by 25-OHD IDS-radioimmunoassay (RIA) from IDS Ltd., Boldon, UK. Mean coefficients of variations were 2.0% at 28.0 nmol/l (intra-assay) and 2.8% at 26.7 nmol/l (inter-assay). Lab analyses were done blinded using a single batch of the assay kits. Mean differences in 25-OHD levels were compared by the Mann–Whitney non-parametric test. Quintile cut-off points for the analysis were determined using 25-OHD quintiles levels of the controls. These quintiles were then used to estimate the relative risk (expressed as odds ratio (OR)) of breast cancer at 95% confidence intervals (CI) using multivariate conditional logistic regression. The multivariate model was adjusted for gestational day at sampling. Trend analyses were performed using a linear-by-linear association chi-square statistics on ORs directly. Separate analyses were performed for the first and second pregnancy levels. The risk of breast cancer was also evaluated by comparing the lowest quintile to the other quintiles combined. A two-sided p value <0.05 was considered statistically significant. All statistical analyses were performed using SPSS 15 for windows (SPSS Inc., Chicago, IL).

3. Results

With the exception of time-lag between sampling and cancer diagnoses, the study groups were comparable (Table 1). We also found no major differences in the 25-OHD levels between cases and controls for the 1st or the 2nd pregnancy samples (mean difference, $\mu_t = 0.09$, $p = 0.7$; $\mu_t = 8.0$, $p = 0.1$, respectively). Using the lowest quintile as the reference, we found no significant association of serum 25-OHD levels with the relative risk of breast cancer quintile by quintile (Table 2), or other (2nd to 5th) quintiles combined, neither for the 1st (OR = 1.4, 95%CI 0.6–3.4) nor for the 2nd pregnancy samples (OR = 1.4, 95%CI 0.7–2.9), Table 2). On the contrary, higher levels of vitamin D (2nd to 5th quintiles combined against the lowest quintile) were associated with an increased risk of PABC (OR = 2.7, 95%CI 1.04–6.8). The PABC-associated risk was two- to four-fold higher in the different quintiles of vitamin D levels compared to the reference (Table 2). Adjustment for gestational day had no material effect on the results.

4. Discussion

This is the first study to look at vitamin D during pregnancy in relation to the risk of subsequent development of breast cancer. The breast cancer cases diagnosed among the donors of the Finnish Maternity Cohort were premenopausal, and the null association found in our paired (pregnancy) sample material is in line with a recent study on premenopausal breast cancer showing no association between serum vitamin D levels and risk of breast cancer.[5] A null association was also observed in older women in the large case–control study nested within the Prostate, Lung, Colorectal and Ovarian (PLCO) cancer trial.[8] Our study adds to these findings since even the over time assessment of vitamin D acquisition did not disclose any significant risk associated with premenopausal breast cancer.

It is intriguing that higher levels of serum 25-OHD were associated with a two- to fourfold increased risk of PABC, the more aggressive sub-entity of breast cancer.[11] This is also the first longitudinal study to evaluate the relationship between vitamin D levels and PABC. Although the results contradict experimental evidence,[1–4] they are in line with studies on the association of increased 25-OHD levels and elevated risk of aggressive prostate cancer.[12,13]

Levels of vitamin D binding protein (VDBP) are significantly increased during pregnancy.[14] It is the carrier protein of vitamin D in circulation, with higher affinity for 25-OHD than for 1, 25-$(OH)_2$D,[15] which probably favours increased relative availability of the biologically more active, anti-carcinogenic form, 1, 25-$(OH)_2$D. Our observation might reflect an inverse association between the free levels of the two forms of vitamin D. On the other hand, higher 25-OHD levels within the body may affect its metabolism, e.g. increased 24-hydroxylation,[16] and lead to reduced tissue concentrations of 1, 25-$(OH)_2$D, with consequent low anti-proliferative activity again.

In conclusion, the findings from our study do not support the hypothesis that prediagnostic circulating vitamin D levels are associated with risk of premenopausal breast cancer. We, however, observed the possibility that higher levels of vitamin D may be associated with increased risk of breast cancer arising soon after pregnancy. Further, independent studies on vitamin D and risk of pregnancy-associated breast cancer are warranted. We propose that recommendations for dietary

Table 1 – Baseline characteristics of breast cancer cases and controls with consecutive samples and pregnancy-associated breast cancer cases and controls of the Finnish Maternity Cohort.

	1st pregnancy samples		2nd pregnancy samples		PABC[a]	
	Cases	Controls	Cases	Controls	Cases	Controls
Number (N)	100	100	100	100	111	111
Mean age[b]	30.5	30.5	33.3	33.3	34.4	34.4
Gestational day (d)	73.4	73.5	78.7	77.1	77.9	
Parity	2.0	2.1	3.1	3.4	2.0	2.3
Follow-up time[b]	7.4		4.6		1	
Age at diagnosis (range)	38.0 (25.1–50.0)				35.6 (24.9–43.9)	

a Pregnancy-associated breast cancer (diagnosed within 1 year of sampling).
b Calculated in years.

Table 2 – Relative risks (odds ratio (OR) with 95% confidence interval, CI) of breast cancer and pregnancy-associated breast cancer by quintiles of serum vitamin D concentrations.

25-(OH)D	Cases	Controls	OR (95%CI)	*p* Value	p_{trend}
First pregnancy					
Quintiles[c]					
Q_1[a]	16	19	1.0		
Q_2	23	20	1.5 (0.5–2.0)	0.5	
Q_3	19	20	1.2 (0.4–3.6)	0.8	
Q_4	19	20	1.2 (0.4–3.7)	0.7	
Q_5	23	21	1.4 (0.5–4.2)	0.6	0.4
$Q_{2–5}$	84	81	1.4 (0.6–3.4)	0.5	
Second pregnancy					
Quintiles[d]					
Q_1[a]	16	21	1.0		
Q_2	18	21	1.0 (0.4–2.6)	1.0	
Q_3	26	20	1.7 (0.7–4.2)	0.2	
Q_4	11	20	0.7 (0.2–1.9)	0.7	
Q_5	29	18	2.1 (0.8–5.1)	0.1	0.5
$Q_{2–5}$	84	79	1.4 (0.7–2.8)	0.4	
PABC[b] subjects					
Quintiles[e]					
Q_1[a]	12	22	1.0		
Q_2	29	23	2.9 (1.0–8.4)	0.05	
Q_3	21	23	2.0 (0.7–6.0)	0.2	
Q_4	31	21	3.7 (1.2–11.8)	0.03	
Q_5	18	22	1.9 (0.5–6.7)	0.3	0.4
$Q_{2–5}$	99	89	2.7 (1.04–6.7)	0.04	

a The lowest (reference) quintile of serum 25-hydroxy vitamin D.
b Pregnancy-associated breast cancer (follow-up time up to 1 year following pregnancy).
c Quintiles($\leqslant$27.5[a], 27.6–37.5, 37.6–48.5, 46.6–55.5, $\geqslant$61.6 nmol/l).
d Quintiles ($\leqslant$27.8, 27.9–36.9, 37.0–46.5, 46.6–55.5, $\geqslant$56.6 nmol/l).
e Quintiles ($\leqslant$25.8, 25.9–34.9, 35.0–44.7, 44.8–64.0, $\geqslant$64.1 nmol/l).

supplementation of vitamin D during pregnancy are reconsidered.

Conflict of interest statement

None declared.

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