Null Results in Brief

Vitamin D Receptor Polymorphism and Breast Cancer Risk[1]

Polly A. Newcomb,[2] Han Kim, Amy Trentham-Dietz, Fredrico Farin, David Hunter, and Kathleen M. Egan

Cancer Prevention Research Program, Fred Hutchinson Cancer Research Center, Seattle, Washington 98109 [P. A. N., H. K.]; University of Wisconsin Comprehensive Cancer Center, Madison, Wisconsin 53706 [P. A. N., A. T-D.]; Department of Epidemiology, Harvard School of Public Health, Boston, Massachusetts 02015 [D. H., K. M. E.]; and Center for Ecogenetics, Department of Environmental Health, University of Washington School of Public Health and Community Medicine, Seattle, Washington 98195 [F. F.]

Introduction

Epidemiological evidence suggests that vitamin D from sunlight and diet may be inversely associated with breast cancer incidence. $1,25(OH)_2D_3$, the physiologically active metabolite of vitamin D, exerts growth regulatory functions by binding to the VDR[3] (1). As with many tissues, the breast, both normal and malignant, expresses VDR. The *VDR* gene is polymorphic at several sites; the *Bsm*I, A*pa*I, and *Taq*I polymorphisms are in strong linkage disequilibrium in Caucasians. These common polymorphisms in the gene may alter transcriptional activity and mRNA stability, and may be associated with circulating levels of $1,25(OH)_2D_3$ (2). Several VDR polymorphisms have been associated with breast cancer risk (3–6). In our population-based study we investigated the association between the VDR polymorphism *Taq*I and breast cancer risk.

Materials and Methods

Incident cases of invasive breast cancer in women ages 20–69 years were identified by the Wisconsin statewide cancer registry from January to December 1998 as part of a multicenter population-based case-control study. Five hundred thirty-two cases completed the interview (overall response rate 82%). For comparison, controls were randomly selected from lists of drivers (ages <65 years) and Medicare beneficiary files (ages 65–69 years); 570 control women participated (overall response rate 80%).

All of the women completed a structured 45-min telephone interview covering breast cancer risk factors. Tumor stage information was available from registry files. DNA was collected from mouthwash samples obtained through a mailer (7). Kits were returned by 79% ($n = 420$) of the interviewed cases and 71% ($n = 405$) of the interviewed controls. Determination of *Taq*I genotype was conducted by the Molecular Biomarkers Laboratory in the Center of Ecogenetics and Environmental Health at the University of Washington, Seattle, WA, using a TaqMan assay.

The association between the *Taq*I VDR genotype and incidence of breast cancer was evaluated in multivariate logistic regression models. Effect modification between VDR genotype and breast cancer risk was evaluated by testing whether the inclusion of an interaction term in the logistic model significantly changed the log-likelihood.

Results

The control population was in Hardy-Weinberg equilibrium ($\chi^2 = 0.003$; $P > 0.99$). There was no overall association between VDR genotype and breast cancer risk (Table 1). Relative to the *TT* genotype, the OR for breast cancer was 1.06 (95% CI, 0.77–1.48) for the *Tt* genotype, and for the *tt* genotype the OR was 1.15 (95% CI, 0.72–1.82). The OR for the *tt* genotype was 0.75 (95% CI, 0.35–1.59) for regional/distant disease, whereas the OR for local disease was 1.31 (95% CI, 0.78–2.18; *P* interaction = 0.07). There was a suggestion that postmenopausal hormone users with the *tt* genotype were at decreased risk of breast cancer (OR = 0.35; 95% CI, 0.13–0.93; *P* interaction = 0.10). The association between VDR genotype and breast cancer risk did not vary by age (*P* interaction = 0.98; data not shown), menopausal status, family history, multivitamin use (a marker of calcium intake), or body mass index (Table 1).

Discussion

We found little evidence that variation in the 3′ region of the *VDR* gene was related to breast cancer incidence. Previous studies of the association between VDR polymorphisms have been inconsistent, and the results difficult to interpret because of small sample size, selected populations, and various genotypes examined (3–6). Two studies reported no overall association with *Taq*I polymorphisms (4, 6). A small case-control study showed elevated breast cancer risks for the *Apa*I aa genotype (OR = 1.56; 95% CI, 1.09–2.24) and the *Taq*I *TT* genotype (OR = 1.45; 95% CI, 1.00–2.00), although no case-control differences were observed for the 5′ *Fok*I site (5). The cohort study of Ingles *et al.* (3) was limited to Latinas (where the prevalence of the *Bsm*I *b* allele was 75%) and reported similar elevated results for the two polymorphisms at the 3′ end of the *VDR* gene, *Bsm*I (OR = 2.2; 95% CI, 1.0–4.7 for BB genotype) and polyadenylic acid (OR = 3.2; 95% CI, 1.5–6.9 for SS genotype).

Unlike some previous studies, this study was population-based and had available extensive information on known risk factors for breast cancer. Our study had >95% power to detect a doubling of risk associated with the *TT* genotype. However, we evaluated a single polymorphism, *Taq*I, although at least three polymorphisms have been described (3). In addition, the functional significance of the TaqI polymorphism has not yet been ascertained. Finally, because multiple sources of vitamin

Received 6/19/02; revised 7/29/02; accepted 8/19/02.
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[1] This work was supported by CA47147 and CA71597 from the National Cancer Institute, NIH, Department of Health and Human Services, by Center Grant ES07033 from the National Institute of Environmental Health Sciences, and by institutional funds from the Fred Hutchinson Cancer Research Center.
[2] To whom requests for reprints should be addressed, at Cancer Prevention Research Program, Fred Hutchinson Cancer Research Center, 1100 Fairview, MP-900, Seattle, WA 98109.
[3] The abbreviations used are: VDR, vitamin D receptor; OR, odds ratio; CI, confidence interval.

Table 1 Association between *Taq*I genotype and breast cancer risk according to breast cancer risk factors (All tests for statistical significance were two-sided)

	Genotype (no. Cases/no. Controls)						*P* interaction
	TT (157/147)		*Tt (184/181)*		*tt (62/55)*		
	OR[a]	(95% CI)	OR[a]	(95% CI)	OR[a]	(95% CI)	
All subjects	1.00	(ref)	1.06	(0.77–1.48)	1.15	(0.72–1.82)	
Disease stage[b]							
Local	1.00	(ref)	1.10	(0.76–1.59)	1.31	(0.78–2.18)	
Regional/distant	1.00	(ref)	0.97	(0.61–1.56)	0.75	(0.35–1.59)	0.07
Menopausal status							
Premenopausal	1.00	(ref)	1.04	(0.59–1.86)	1.51	(0.67–3.41)	
Postmenopausal	1.00	(ref)	1.07	(0.47–1.62)	0.85	(0.47–1.54)	0.21
Family history							
No	1.00	(ref)	1.03	(0.98–1.79)	1.43	(0.74–2.06)	
Yes	1.43	(0.73–2.80)	1.23	(0.49–3.10)	0.68	(0.21–2.26)	0.68
Multivitamin use							
Never	1.00	(ref)	0.96	(0.46–2.01)	1.09	(0.40–2.98)	
Former	1.13	(0.58–2.22)	1.27	(0.51–3.17)	1.66	(0.46–5.98)	
Current	1.15	(0.60–2.24)	0.96	(0.39–2.35)	0.78	(0.23–2.66)	0.54
Postmenopausal hormone use[c]							
Never	1.00	(ref)	1.11	(0.72–1.71)	1.66	(0.93–2.99)	
Former/current	1.09	(0.65–1.82)	0.90	(0.46–1.75)	0.35	(0.13–0.93)	0.10
Body Mass Index (kg/m^2)[c]							
<24	1.00	(ref)	1.77	(0.84–3.67)	1.52	(0.56–4.11)	
24–27	3.23	(1.38–7.58)	0.29	(0.09–0.90)	0.23	(0.05–0.98)	
27+	1.76	(0.84–3.67)	0.67	(0.25–1.82)	0.70	(0.17–2.96)	0.34

[a] Adjusted for age, family history of breast cancer, body mass index, age at first birth, hormone replacement therapy, and menopausal status.
[b] Polytomous logistic regression model adjusted for age, family history of breast cancer, body mass index, age at first birth, hormone replacement therapy, and menopausal status.
[c] Postmenopausal women only.

D may impact on circulating levels of $1,25(OH)_2D_3$, our incomplete control of exposure may have limited our assessment.

In summary, we observed no overall association between the VDR *Taq*I polymorphism and breast cancer risk in our population-based sample; however, this polymorphism may modify the association between postmenopausal hormone use and breast cancer risk.

Acknowledgments

We thank Drs. Meir Stampfer, Walter Willett, Linda Titus Ernstoff, and Barry Storer for valuable advice at various stages of this project; Cassie Keener for laboratory analysis; Linda Haskins for project management; and Mari Nakayoshi and Mary Pankratz for editorial assistance.

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Cancer Epidemiol Biomarkers Prev 2002;11:1503-1504.