Null Results in Brief

Vitamin D Receptor Polymorphism and Breast Cancer Risk

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Introduction

Epidemiological evidence suggests that vitamin D from sunlight and diet may be inversely associated with breast cancer incidence, 1,25(OH)2D3, the physiologically active metabolite of vitamin D, exerts growth regulatory functions by binding to the VDR1 (1). As with many tissues, the breast, both normal and malignant, expresses VDR. The VDR gene is polymorphic at several sites; the BsmI, Apal, and TaqI 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)2D3 (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 TaqI 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 TaqI 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 TaqI 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, 0.78–2.18; 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 TaqI polymorphisms (4, 6). A small case-control study showed elevated breast cancer risks for the Apal aa genotype (OR = 1.56; 95% CI, 1.09–2.24) and the TaqI TT genotype (OR = 1.45; 95% CI, 1.00–2.00), although no case-control differences were observed for the S′ FokI site (5). The cohort study of Ingles et al. (3) was limited to Latinas (where the prevalence of the BsmI b allele was 75%) and reported similar elevated results for the two polymorphisms at the 3′ end of the VDR gene, BsmI (OR = 2.2; 95% CI, 1.0–4.7 for BB genotype) and polyadenyllic 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, TaqI, 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...
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