Null Results in Brief

Germ Line Variation at 8q24 and Endometrial Cancer Risk

Veronica Wendy Setiawan,1 Giske Ursin,1 Pamela L. Horn-Ross,2 David Van Den Berg,1 Loic Le Marchand,3 Brian E. Henderson,1 Leslie Bernstein,1 and Christopher A. Haiman1

1Department of Preventive Medicine, Keck School of Medicine, University of Southern California, Los Angeles, California; 2Northern California Cancer Center, Fremont, California; and 3Epidemiology Program, Cancer Research Center of Hawaii, University of Hawaii, Honolulu, Hawaii

Introduction

Germ line variants at chromosome 8q24 have been associated with prostate, colorectal, and breast cancer risk (1-7). This region is also frequently amplified in many tumor types (8, 9) including endometrial cancer (10-13). The involvement of germ line and somatic variations at 8q24 suggests a common biological mechanism in the pathogenesis of epithelial cancers. In the present analysis, we used data from two nested case-control studies, conducted within the Multiethnic Cohort (MEC) and the California Teachers Study (CTS), to investigate the hypothesis that the known risk variants in the region might also affect the risk of endometrial cancer.

Materials and Methods

The MEC includes more than 215,000 individuals from Hawaii and Los Angeles and was assembled between 1993 and 1996. The cohort is composed predominantly of African Americans, Native Hawaiians, Japanese Americans, Latinos, and Whites (ages 45-75 years at baseline) and has been described in detail elsewhere (14). Incident cancer cases in the MEC are identified through annual linkage to the Surveillance, Epidemiology, and End Results cancer registries. The nested endometrial cancer case-control study in the MEC consists of 531 invasive cancer cases (328 incident cases diagnosed up to December 31, 2003, and 203 prevalent cases) and 1,878 controls who were free of breast and uterine cancer up to December 31, 2003. Controls were selected from the breast cancer case-control study in the MEC (15) and were women without a previous report of hysterectomy at baseline. The majority of women (>90%) in the MEC were postmenopausal. Participation rates for providing blood samples were ≥65% for cases and controls. The CTS consists of 133,479 current and former female professional school employees who were recruited in 1995 from the rolls of the Defined Benefit Program of the California State Teachers Retirement System (16). Participants entered the cohort by returning a self-administered questionnaire that asked detailed information about medical history and lifestyle factors. Incident cancer cases in the CTS are identified through annual linkage to the California Cancer Registry, which is part of the Surveillance, Epidemiology, and End Results program. Collection of blood/buccal samples from endometrial cancer cases, diagnosed through December 31, 2004, and controls within the CTS was initiated in 2002 and limited to women 50 years or older at diagnosis or reference date. The present study consists of 386 incident invasive endometrial cancer cases and 651 controls with intact uteri who were frequency matched to cases based on age (in 5-year age groups), race/ethnicity, and geographic region of residence within California. The majority of cases and controls were White (>91%). Women were of ages 51 to 92 years at specimen collection and >90% were postmenopausal.

In each study, DNA was extracted from blood or buccal cells using the Qiagen 96 DNA Blood Kit. We genotyped six of the seven variants spanning a 430-kb region of 8q24 (128.17-128.60 Mb in build 35 of the reference sequence), which each independently predicts prostate cancer risk in our previous study (ref. 4; Table 1; all except the microsatellite DG8S737-8); one of these variants is also a marker of colorectal cancer risk (rs6983267; ref. 7). We also examined rs13281615, a variant located within the same region (128,424,800 Mb in build 35 of the reference sequence), which each independently predicts prostate cancer risk in our previous study (ref. 4; Table 1; all except the microsatellite DG8S737-8); one of these variants is also a marker of colorectal cancer risk (rs6983267; ref. 7). We also examined rs13281615, a variant located within the same region (128,424,800 Mb in build 35 of the reference sequence), which each independently predicts prostate cancer risk in our previous study (ref. 4; Table 1; all except the microsatellite DG8S737-8); one of these variants is also a marker of colorectal cancer risk (rs6983267; ref. 7). We also examined rs13281615, a variant located within the same region (128,424,800 Mb in build 35 of the reference sequence), which each independently predicts prostate cancer risk in our previous study (ref. 4; Table 1; all except the microsatellite DG8S737-8); one of these variants is also a marker of colorectal cancer risk (rs6983267; ref. 7). We also examined rs13281615, a variant located within the same region (128,424,800 Mb in build 35 of the reference sequence), which each independently predicts prostate cancer risk in our previous study (ref. 4; Table 1; all except the microsatellite DG8S737-8); one of these variants is also a marker of colorectal cancer risk (rs6983267; ref. 7). We also examined rs13281615, a variant located within the same region (128,424,800 Mb in build 35 of the reference sequence), which each independently predicts prostate cancer risk in our previous study (ref. 4; Table 1; all except the microsatellite DG8S737-8); one of these variants is also a marker of colorectal cancer risk (rs6983267; ref. 7). We also examined rs13281615, a variant located within the same region (128,424,800 Mb in build 35 of the reference sequence), which each independently predicts prostate cancer risk in our previous study (ref. 4; Table 1; all except the microsatellite DG8S737-8); one of these variants is also a marker of colorectal cancer risk (rs6983267; ref. 7). We also examined rs13281615, a variant located within the same region (128,424,800 Mb in build 35 of the reference sequence), which each independently predicts prostate cancer risk in our previous study (ref. 4; Table 1; all except the microsatellite DG8S737-8); one of these variants is also a marker of colorectal cancer risk (rs6983267; ref. 7). We also examined rs13281615, a variant located within the same region (128,424,800 Mb in build 35 of the reference sequence), which each independently predicts prostate cancer risk in our previous study (ref. 4; Table 1; all except the microsatellite DG8S737-8); one of these variants is also a marker of colorectal cancer risk (rs6983267; ref. 7). We also examined rs13281615, a variant located within the same region (128,424,800 Mb in build 35 of the reference sequence), which each independently predicts prostate cancer risk in our previous study (ref. 4; Table 1; all except the microsatellite DG8S737-8); one of these variants is also a marker of colorectal cancer risk (rs6983267; ref. 7). We also examined rs13281615, a variant located within the same region (128,424,800 Mb in build 35 of the reference sequence), which each independently predicts prostate cancer risk in our previous study (ref. 4; Table 1; all except the microsatellite DG8S737-8); one of these variants is also a marker of colorectal cancer risk (rs6983267; ref. 7). We also examined rs13281615, a variant located within the same region (128,424,800 Mb in build 35 of the reference sequence), which each independently predicts prostate cancer risk in our previous study (ref. 4; Table 1; all except the microsatellite DG8S737-8); one of these variants is also a marker of colorectal cancer risk (rs6983267; ref. 7). We also examined rs13281615, a variant located within the same region (128,424,800 Mb in build 35 of the reference sequence), which each independently predicts prostate cancer risk in our previous study (ref. 4; Table 1; all except the microsatellite DG8S737-8); one of these variants is also a marker of colorectal cancer risk (rs6983267; ref. 7).
study-stratified analyses. Before pooling the genetic data, tests for homogeneity of the ORs across ethnicity (in the MEC) and study were conducted. These tests were done using a likelihood ratio test following the inclusion of an interaction term between each genotype and ethnicity or study in the logistic regression model. All analyses were conducted in SAS 9.0 (SAS Institute).

The study protocol was approved by the Institutional Review Boards at the University of Southern California, the University of Hawaii, and the Northern California Cancer Center.

Results and Discussion

The allele frequencies of the seven variants were similar to those published previously in the same populations, with Broad11934905 only observed at an appreciable frequency in African Americans (Table 1; ref. 4). We found no significant association between these variants and endometrial cancer risk in any of the racial/ethnic populations. Except for rs13281615 ($P_{het} = 0.03$), we observed little evidence for heterogeneity of effects across populations ($P_{het} \geq 0.32$) or between studies (Whites only, $P_{het} \geq 0.14$). In the pooled analyses, none of these variants were statistically significantly associated with endometrial cancer risk. Removal of the prevalent cases ($n = 203$) or adjustment for established endometrial cancer risk factors (MEC only) did not alter the results. Associations between each genotype and endometrial cancer risk by racial/ethnic group and study are provided in Supplementary Tables S1 to S3.

Our results suggest that the seven variants at 8q24 are not major contributors to endometrial cancer risk. Pooling the genetic data from these two studies (917 cases and 2,529 controls) provided 80% power (assuming a log additive model, a two-sided test, and using $z = 0.05$) to detect ORs ranging from 1.17 to 1.27 per allele for a variant with 10% to 40% allele frequency. The common variants in this region have been associated with ORs ranging from 1.2 to 1.5 for prostate (4), 1.2 for colorectal cancer (7), and 1 for breast cancer (6); thus, we could not rule out very modest effects, which may be expected based on the observed associations of these alleles with other cancers. The identification of multiple risk variants at 8q24 for several cancers (i.e., seven variants for prostate, four for colorectal, and one for breast) suggests that the region at 8q24 is involved in the development of several cancers.
prostate cancer, one for colorectal cancer, and one for breast cancer) supports comprehensive testing of all common and rare variations in this region, to define risk variants specific for endometrial cancer, if they exist.

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References
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