Transdisciplinary Science

Context-Dependent Effects of Genome-Wide Association Study Genotypes and Macroenvironment on Time to Biochemical (Prostate Specific Antigen) Failure after Prostatectomy

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Abstract

Background: Disparities in cancer defined by race, age, or gender are well established. However, demographic metrics are surrogates for the complex contributions of genotypes, exposures, health care, socioeconomic and sociocultural environment, and many other factors. Macroenvironmental factors represent novel surrogates for exposures, lifestyle, and other factors that are difficult to measure but might influence cancer outcomes.

Methods: We applied a “multilevel molecular epidemiology” approach using a prospective cohort of 444 White prostate cancer cases who underwent prostatectomy and were followed until biochemical failure (BF) or censoring without BF. We applied Cox regression models to test for joint effects of 86 genome-wide association study–identified genotypes and macroenvironment contextual effects after geocoding all cases to their residential census tracts. All analyses were adjusted for age at diagnosis and tumor aggressiveness.

Results: Residents living in census tracts with a high proportion of older single heads of household, high rates of vacant housing, or high unemployment had shorter time until BF postsurgery after adjustment for patient age and tumor aggressiveness. After correction for multiple testing, genotypes alone did not predict time to BF, but interactions predicting time to BF were observed for MSMB (rs10993994) and percentage of older single heads of households ($P = 0.0004$), and for HNF1B/TCF2 (rs4430796) and census tract per capita income ($P = 0.0002$).

Conclusions: The context-specific macroenvironmental effects of genotype might improve the ability to identify groups that might experience poor prostate cancer outcomes.

Impact: Risk estimation and clinical translation of genotype information might require an understanding of both individual- and macroenvironment-level context. Cancer Epidemiol Biomarkers Prev; 19(9); 2115–23. ©2010 AACR.

Introduction

Interindividual variability in common disease etiology and outcomes likely represents the complex interactions of multiple factors including genetic susceptibility; individual behavior, lifestyle, and exposures; macroenvironmental-level (e.g., neighborhood, area, community) contextual factors; and health care access including screening and treatment (1). The elucidation of interactions among these multiple factors might require novel, transdisciplinary approaches. We hypothesize that methods which account for the joint effects of both individual-level and macroenvironmental effects using a multilevel strategy (2-4) might capture etiologic agents that are not seen in studies which consider one or a few factors at a time. We propose a “multilevel molecular epidemiology” (MME) approach that is grounded in multilevel analytic frameworks that have used both individual-level risk factors as well as macroenvironmental contextual factors (5). Macroenvironmental factors may serve as surrogates for a wide range of exposures, lifestyle, and other factors that are difficult to measure. We extend this concept to hypothesize that prediction of risk and outcome by inherited genotype information (and other biomarker data) might depend on both individual-level and macroenvironmental context. Disease risk and outcomes are influenced by both “differences” (i.e., naturally occurring or achieved factors) as well as “inequities” (i.e., factors ascribed to groups as a function of their social position; ref. 6). Using the MME framework, we can hypothesize that differences (e.g., genetics, race, and possibly other innate biological factors) might be acting in the context of inequities (e.g., discrimination, segregation,
or access) and lead to observed disease risks and outcomes. Related models that define “gaps” occurring between discrete groups in the population (e.g., defined by genotype, ethnicity, gender, or other discrete characteristics), as well as effects that are defined by “gradients” across continuously distributed variables might influence risk and outcomes (7). Thus, we consider models that consider the effect of genotypes as well as macroenvironmental factors.

To illustrate this approach, we have undertaken a multilevel, transdisciplinary analysis of susceptibility genotypes, individual-level factors, macroenvironmental factors, and prostate cancer outcomes. Prostate cancer is the second leading cause of cancer deaths in Americans (8) and is associated with extreme variability in outcomes, including extreme incidence and mortality differences by race, age, geography, and other factors (9, 10). In particular, prostate cancer outcomes represent a complex and multifactorial phenomenon likely to be caused by complex interactions of genetic susceptibility, individual risk factors, and macroenvironmental factors (11). Genome-wide association studies (GWAS) have identified a number of loci that are likely to affect prostate cancer outcomes by race, age, geography, and other factors (9, 10). In particular, prostate cancer outcomes represent a complex and multifactorial phenomenon likely to be caused by complex interactions of genetic susceptibility, individual risk factors, and macroenvironmental factors (11). Genome-wide association studies (GWAS) have identified a number of loci that are likely to affect prostate cancer outcomes by race, age, geography, and other factors (9, 10).

**Materials and Methods**

**Study participants and individual-level data: the Study of Clinical Outcomes, Risk, and Ethnicity (SCORE)**

Our primary goal in this analysis was to evaluate the role of genotype and macroenvironmental context in predicting adverse clinical outcomes after a prostate cancer diagnosis. To focus these analyses and control for unmeasured confounding, we limited our sample to 444 White incident prostate cancer cases (i.e., diagnosed within 12 months of study ascertainment) that were identified through Urologic Oncology Clinics at the Hospital of the University of Pennsylvania between 1995 and 2008, and who participated in SCORE. Case status was confirmed by medical records review using a standardized abstraction form. Patients who were nonincident cases (i.e., those diagnosed more than 12 months prior to the date of study ascertainment), or had a prior diagnosis of cancer except nonmelanoma skin cancer, were excluded. To further limit heterogeneity due to access and treatment, we limited the study sample to men who underwent prostatectomy as the primary treatment of their disease. No men in this sample underwent any other treatments besides prostatectomy before the occurrence of a failure event or censoring.

Individual risk factors, medical history, and prostate cancer diagnostic and treatment information were obtained by using a standardized questionnaire and review of medical records. Information collected included previous cancer diagnoses, demographic information, and primary tumor characteristics as well as Gleason score (grade) and stage. We also created a summary tumor aggressiveness scale that reflects the highly correlated variable (i.e., tumor stage, and grade) to use as a single adjustment in the multivariate survival models. This composite variable was defined as nonaggressive if cases had both noninvasive cancer (stage I-II) and low Gleason score (<7) tumors, and was defined as aggressive otherwise. All study participants provided written informed consent for participation in this research under a protocol approved by the Committee for Studies Involving Human Subjects at the University of Pennsylvania.

**Biosample collection and genotype analysis**

Genomic DNA for the present study was self-collected by each study participant using sterile cheek swabs (Cyto-Pak Cytosoft Brush, Medical Packaging Corporation), and processed using either a protocol modified from Richards et al. (12) as described previously (13), or using a modified protocol on the Qiagen 9604B robot with the QIAamp 96 DNA Buccal Swab Biorobot Kit. One hundred and nine variants at 30 loci, identified from linkage studies and GWAS that have been independently validated as prostate cancer susceptibility genes (14), were selected for analysis. These include one of the confirmed single nucleotide polymorphisms (SNP) at each of the following GWAS loci without known genes: 3p12 (15), multiple regions at 8q24 (16-18), 11q13 (15, 19), 17q24 (18); as well as those with putative candidate genes including CTBP2 (10q26; ref. 19), HNF1B/TCF2 (17q12; refs. 20, 21), JAZF1 (7p15.2; ref. 19), LMTK2 (7q21; ref. 15), MSMB (10q11; refs. 15, 19), and NUDT (Xp11; refs. 15, 22). We also considered two loci (MS1 and RNASEL) that were identified in linkage studies (10, 23). To ensure adequate power for our analyses, we only considered SNPs with a minor allele frequency of ≥10% in the failure/censoring groups. We also excluded SNPs with genotyping failure rates of >5% or with an SNP sample size of <100 cases. No SNPs deviated significantly from Hardy-Weinberg proportions. After applying these criteria, 23 SNPs were removed from consideration, leaving 86 SNPs that were included in the analysis (Supplementary Table S1).

Prior to genotyping, the whole genome of the samples was amplified using the GenomePlex Complete Whole Genome Amplification kit (Sigma). Genotyping was done either by TaqMan assay using the 7900HT Fast Real-time PCR Machine or using an Illumina GoldenGate Platform. For TaqMan, all mixes of primers and probes were predesigned by and purchased from Applied Biosystems. We included one negative control and three positive controls for each assay and each 384-well plate, and duplicated at least 8% of the samples for each assay. We designed an Illumina GoldenGate assay considering only SNPs with scores of ≥0.59 and including at least 10% of duplicated samples. Quality control for both assays is as follows: excluding

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all individuals that failed for at least 15% of the SNPs attempted, then by excluding any SNP with a call rate of <95%, and any SNPs that had >2% discordance between genotypes in duplicate samples.

**Macroenvironmental data**

In the United States, census tracts are commonly used to define neighborhoods, despite limitations in accurately delineating neighborhood boundaries (24), to allow replication across studies (25). Therefore, we used the 2000 census tract boundaries to group individuals by residence (26). The 2000 census was used because it approximates the median of our SCORE accrual period (1995-2009). Census tracts are U.S. Census Bureau-defined, standardized, and relatively permanent geographical units. Census tracts are constructed specifically to include, on average, 4,000 people which is intended to reflect fairly homogeneous population characteristics, economic position, and living conditions. Federal, state, and local governments routinely use census tracts as administrative units (27).

We geocoded the residential addresses of our patients using ArcGIS or American FactFinder (http://factfinder.census.gov/home/saff/main.html?_lang=en), and methods outlined by The Public Health Disparities Geocoding Project (http://www.hsph.harvard.edu/thegecoding-project/webpage/monograph/geocoding.htm).

To obtain census tract level data about demographic, education, socioeconomic, and relationship/social isolation measures, we linked the geocoded addresses from our data set with variables from the Geographical Comparison Tables of the U.S. Census Bureau’s American FactFinder (http://factfinder.census.gov/servlet/GCTSelectedDatasetPageServlet?_lang=en&_ts=247057910048). The Geographical Comparison Tables were accessed for 24 counties in and around Philadelphia: Kent, New Castle, and Sussex Counties in Delaware; Atlantic, Burlington, Camden, Cape May, Gloucester, Hunterdon, Mercer, Monmouth, Ocean, Salem, and Warren Counties in New Jersey; and Berks, Bucks, Chester, Delaware, Lehigh, Luzerne, Monroe, Montgomery, Northampton, and Philadelphia Counties in Pennsylvania. The 444 study participants resided in 342 census tracts. A subset of variables in the Geographical Comparison Tables was selected for analysis to represent various classes of neighborhood factors including aging and social isolation (percentage of residents ages 65 years or older, percentage of households with a single resident age 65 years or older), education (percentage of college graduates among those 25-34 years old), neighborhood housing quality (percentage of houses vacant and not for sale, rent, or vacation), and socioeconomic status (percentage of unemployed individuals ages 16 years or older and per capita income in $1,000).

**Statistical methods**

To test the joint effects of genotype and neighborhood context, we modeled time to biochemical failure (BF) after treatment of prostate cancer by prostatectomy with a Cox proportional hazards model. Time to BF was chosen as the primary outcome of interest because it afforded sufficient power to consider these interactions, and was defined as having experienced a postprostatectomy prostate-specific antigen (PSA) value of >0.2 mg/dL. We also allowed outcomes of interest to be the diagnoses of metastases. However, no men in our sample were found to have metastasis after initial diagnosis and before BF. Censored observations had an end of follow-up without BF. Analysis time was defined as time from surgery until BF or censoring.

Covariates included in all models as potential confounder variables were age at diagnosis and tumor aggressiveness. The main effects of interest were susceptibility genotypes and macroenvironmental context variables, as described above.

For tests of genotype effects in the context of macroenvironmental factors, we evaluated the first-order interaction of these factors by using a Cox proportional hazards model with an interaction between census tract characteristics as a continuous variable and SNP per allele effects. We also considered the effect of clustered sampling of individuals within census tracts on the standard error and 95% confidence interval (CI) estimates associated with model variables by using the robust variance estimation approach of Lin and Wei (28). Two-sided P values were corrected for multiple hypothesis tests using the false discovery rate method of Benjamini and Hochberg (29). All analyses were done in STATA (version 10.1, STATA Corporation).

**Results**

Of the 444 White prostatectomy cases followed prospectively from the time of surgery, 397 (89%) did not experience BF during a mean (median) follow-up period of 26.8 (21) months, whereas 47 (11%) men experienced BF during a mean (median) follow-up period of 22.5 (19.1) months. Six men in the cohort died; death was not used as a censoring event because their PSA status was unknown at the time of death. As expected, tumor stage [I + II versus II + IV; hazard ratio (HR) = 3.12; 95% CI, 1.75-5.56], Gleason grade (<7 versus 7+; HR = 6.22; 95% CI, 2.79-13.89), and a combined metric of tumor aggressiveness (odds ratio = 8.11; 95% CI, 2.91-22.60) were significant predictors of time to BF in univariate analyses. Other individual-level factors including age at diagnosis, marital status, and education were not significant predictors of time to BF (results not shown). All subsequent analyses were adjusted for age at diagnosis and tumor aggressiveness to evaluate the potential additional effect of genotype and/or neighborhood factors on time to BF after these traditional outcome predictors were considered.

The effects of macroenvironmental factors on time to BF are presented in Table 1. Three macroenvironmental factors were significantly associated with BF: a demographic measure (percentage of residents ages 65 or older; HR = 1.02; 95% CI, 1.00-1.04; P = 0.049), a measure of
neighborhood degradation (percentage of vacant housing; HR = 1.28; 95% CI, 1.09-1.51; \( P = 0.002 \)), and a measure of socioeconomic status (percentage of unemployed individuals ages 16 years or older; HR = 1.08; 95% CI, 1.00-1.17; \( P = 0.044 \)). Because all variables selected from the Geographical Comparison Tables were percentiles, except per capita income, the HR estimates represent a change in relative risk for each unit of 1% increase in the neighborhood variable. For per capita income, the HR reflects change per $1,000 increase in income.

Although the genotypes studied here have previously been identified as being strongly associated with prostate cancer etiology in case-control studies (14), these loci have largely not been studied for a role in prostate cancer outcomes. Therefore, we evaluated the per-allele effect of the 86 variants on time to BF after adjustment for age at diagnosis and tumor aggressiveness (Fig. 1). Four loci were associated with time to BF at the \( P < 0.05 \) level of significance: Chr8q24 (rs4871799, \( P = 0.018 \)), KLK3 (rs1506684, \( P = 0.033 \)), OATP1B1 (M233I; rs7311358, \( P = 0.044 \)), and KLK3 (rs2569739, \( P = 0.049 \)). However, none of these remained significant after correcting the significance level for multiple testing by false discovery rate.

Finally, we evaluated whether genotype interacted significantly with macroenvironmental effects to influence time to BF. Figure 2 presents the results of per allele by census tract variable interactions. Numerous interactions reached a significance level of \( P < 0.05 \), but after correction for multiple hypothesis testing, only two highly significant interactions remained. First, we identified an interaction between MSMB rs10993994 and a measure of neighborhood social isolation (percentage of census tract for older single heads of household). For each percentage of increase in the neighborhood percentage of heads of households ages 65 or older living alone, there was a 10% decrease in time to BF among men who carried the TT genotype at this locus, whereas there was no increase in time to BF among men who carried any other genotype (HR = 1.10; 95% CI, 1.06-1.14, interaction \( P = 0.0004 \); Fig. 3).

Second, we identified a statistically significant interaction between HNF1B/TCF2 rs4430796 and a measure of neighborhood socioeconomic status (census tract per capita income). For each $1,000 increase in neighborhood per capita income, there was a 3% decrease in time to BF among men who carried the TT genotype at this locus (HR = 1.03; 95% CI, 1.02-1.04), while there was a 7% increase in time to BF for every $1,000 increase in per capita income among men who carried the CC genotype (HR = 0.93; 95% CI, 0.89-0.98; interaction \( P = 0.0002 \); Fig. 3).

**Table 1.** Macroenvironmental variables and HR associations with biochemical failure (PSA failure) after prostatectomy adjusted for age at diagnosis and tumor aggressiveness among incident White prostate cancer cases treated with prostatectomy

<table>
<thead>
<tr>
<th>Variable</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Residents ages 65 or older (%)</td>
<td>1.02 (1.00-1.04)</td>
</tr>
<tr>
<td>Older single head of household (%)</td>
<td>1.02 (0.98-1.07)</td>
</tr>
<tr>
<td>Vacant housing (%)</td>
<td>1.28 (1.09-1.51)</td>
</tr>
<tr>
<td>College graduates, ages 25-34 (%)</td>
<td>0.99 (0.98-1.01)</td>
</tr>
<tr>
<td>Unemployed, age 16 or older (%)</td>
<td>1.08 (1.00-1.17)</td>
</tr>
<tr>
<td>Per capita income (per $1,000)</td>
<td>1.01 (0.98-1.03)</td>
</tr>
</tbody>
</table>

**Figure 1.** Hazard ratios associated with biochemical failure and their associated \( P \) values.
**Discussion**

We have identified statistically significant joint effects between genotypes known to be involved in prostate cancer etiology and macroenvironmental effects on BF in White men. These results cannot be interpreted as having direct biological implications of neighborhood or area-level effects. Just as race or gender is used as surrogates for differences in socioeconomic status, health care access, exposures, and other factors, we interpret our statistically significant interactions as reflecting the surrogate effects causal factors in the environment that are measured by census tract-level variables. Thus, the inferences made here are not necessarily biological in nature but might provide an improved understanding of the contextual relationship of genotype effects in contextual (e.g., neighborhood) setting. The goal of these analyses is to identify whether information about the neighborhood in which an individual lives provides knowledge that is predictive of prostate cancer outcomes. Because we were able to identify significant census tract effects as well as genotype by neighborhood interactions after we considered individual factors, our data support the hypothesis that census tract variables contain information that is not captured at the individual level. By providing additional surrogate metrics of factors that might be correlated with disease risk, outcomes, and disparities, the present results might provide information that moves research in these areas away from more misclassified variables (e.g., race) and toward variables that might be less misclassified and point toward specific areas in which targeted interventions might be developed to reduce disparities.

Although some studies have reported associations of SNPs with disease aggressiveness (19, 30), most of the loci or combinations of loci studied to date have not been associated with disease aggressiveness or outcomes (30-33). Therefore, we attempted to take a novel approach that identified contextual factors that might be associated with prostate cancer outcomes and considered information beyond genotype alone. We identified two statistically significant HNF1B/TCF2 or MSMB by census tract interactions. HNF1B is the hepatocyte nuclear factor

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**Figure 2.** Interaction of per-allele by macroenvironmental variables on biochemical failure, with ordered P values for interaction.
1 homeobox B, also known as transcription factor 2 (TCF2). HNF1B/TCF2 is a member of the transcription factor superfamily that interacts with HNF1A (TCF1), HNF4A, CDH16, ONECUT1, and NR2F2. The HNF1B/TCF2 protein is involved in the metabolism of glucose, cholesterol, and uric acid and is expressed not just in hepatocytes but also in prostate and other tissues. Genotypes at HNF1B/TCF2 have been identified in prostate cancer risk (20, 22), diabetes risk (20, 34), male infertility (35), and other traits. Therefore, there is evidence that this protein is involved in a wide variety of metabolic processes that reflect potential hormonal, cardiovascular, and diabetes risk.
In our data, we found that time to BF decreased with census tract per capita income in prostate cancer cases with TT genotype at rs4430796, whereas time to BF increased with census tract per capita income in prostate cancer cases with CC genotype at rs4430796. Because these factors have been associated with adverse cardiovascular, diabetes, and obesity phenotypes, we also evaluated whether additional adjustment for body mass index might in part explain our observed associations. After adjusting these analyses for obesity (i.e., body mass index, <30 versus ≥30), there was no substantial difference in the HR effects or interaction inferences (results not shown). Therefore, if there is a relationship between HNF1B, obesity, and time to BF, it is not explained by confounding in our data.

MSMB (microseminoprotein-β) encodes PSP94 (prostate secretory protein of 94 amino acids), which is found in semen and has been proposed as a prostate cancer screening and prognosis biomarker (36, 37). A SNP in MSMB, rs10993994, has been reported in multiple GWAS to be associated with prostate cancer etiology (15, 19, 38, 39). Rs10993994 is located 57 bp upstream of the MSMB transcription start site and has been suggested to regulate PSP94 expression. We reported that men with TT genotype at rs10993994 were at increased time to BF risk if they lived in census tracts with a higher percentage of older single heads of households. This suggests that the effect of MSMB might be correlated with factors related to age or social isolation. This effect was present even after adjusting for age at diagnosis and tumor aggressiveness.

The MME approach is novel, yet the application presented here is limited. First, our data included only White men who were seen at a tertiary referral hospital and underwent prostatectomy as their primary treatment. The advantage of this sample selection is that it involves a narrowly defined patient and treatment population within a single hospital which avoids some extraneous variability that might cloud the results. However, these patients are not representative of either the general population or patients who were not treated with prostatectomy. Therefore, these results might not reflect the same effects as could be seen in men of other ethnicities, those who received treatment other than prostatectomy, or those who were diagnosed and treated in community hospital or clinic settings. We would expect that the individual risk factor and macroenvironmental variable distributions would be different from the distributions observed in the present study population. Similarly, genotype frequencies in this study population of White men are also likely to differ from those in non-White populations. Therefore, although we found provocative associations of time to BF with individual-level and macroenvironmental factors and with genotype interacting with macroenvironmental factors, these may be quite different in other populations. In particular, future studies should include African American populations that suffer from the greatest prostate cancer disparities.

Second, the present study does not fully explore the relationship of susceptibility genotypes, individual-level risk factors, and macroenvironmental factors. Additional research might be needed to understand the relationship of these factors and the optimal approach toward their modeling. Other variables not studied here should be considered that might influence prostate cancer outcomes, including individual insurance or other metrics of health care access as well as prostate cancer screening history. Furthermore, we have used a data set that includes a very narrowly defined sample set (i.e., White men undergoing prostatectomy within a single hospital) to limit the heterogeneity that might mask the effects seen here. However, these sample restrictions also limit the inferences because of the relatively narrow spectrum of the population being studied. Thus, broader sample definitions should be considered in the future to more fully address questions of prostate cancer disparities by race or other factors. Conceptually, the MME approach discussed here is tied to that of Mendelian randomization (40), which uses observational study designs to evaluate genetic effects indirectly via exposures of interest. As such, some of the analytic approaches and pitfalls of the Mendelian randomization framework might be applied in the future to the type of studies proposed here. In addition, we have not fully explored whether macroenvironmental factors are a better measure of disadvantage than individual-level variables. Because various macroenvironmental variables are correlated with one another, and presumably with individual-level factors (many of which remain unmeasured here), it is likely that the effects of these variables do not represent independent associations. Therefore, the associations reported here might reflect similar or even identical phenomena measured through different analytic variables. Additional exploration of how correlated neighborhood variables measure related phenomena that influence prostate cancer outcomes is required.

Third, our study uses a relatively small sample size of 444 White men followed prospectively from the time of prostate cancer diagnosis. The sample size studied here included 444 men residing in 342 census tracts. Although the factors studied here reflect macroenvironmental effects, the small number of men in a single census tract limits the “multilevel” nature of the analysis. Despite the limited sample size, our study was adequately powered to detect the effects reported here. The MME approach used here involved continuously distributed macroenvironmental effects, which provides generally greater power than discrete variables. We also limit our genotype analyses to those variants with ≥10% allele frequency to ensure reasonable statistical power, as specified a priori in our study design, and to those SNPs with a sample size of 100 or more cases. Also, we have limited our sample set to include only a narrow range of men (i.e., White men from a single hospital who have undergone prostatectomy) to minimize the potential for unmeasured confounding that might influence our results. We have taken this approach as a demonstration of MME. However, it is also likely that the effects of GWAS...
genotypes, individual-level effects, and macroenvironmental effects on time to BF are small in magnitude. For example, it is possible that the sample size used here was too small to detect the effects of genotypes on time to BF if they are of a similar magnitude as seen in etiology studies. In addition, although we have identified statistically significant interactions between genotypes and macroenvironmental context, larger studies will be required to confirm these results and to extend them to other populations. Furthermore, studies with greater statistical power and longer follow-up will be required to assess neighborhood and/or genotype effects on other outcomes, including disease recurrence or death.

Finally, macroenvironmental variables are generally derived from administrative databases found through the U.S. Census or other community surveys and linked back to the individual by geocoding the person to their place of residence (41). However, because macroenvironmental effects are broad and clearly represent surrogates for both differences and inequities, the approach presented here is valid for the prediction of risk or outcomes, but not necessarily as a means of identifying underlying etiology. We also considered a limited range of metrics and only continuously distributed neighborhood variables. Future studies should consider the optimal coding of these variables.

Using a MME approach, we have identified associations of candidate prostate cancer loci that are dependent on the context in which these genotype effects might be acting to predict prostate cancer outcomes. This approach could provide useful information in studies of cancer outcomes and disparities. Use of macroenvironmental variables rather than (or in addition to) other surrogates such as age, gender, or race might provide better indices of disadvantage. Research related to cancer disparities which uses this approach might benefit from having measures other than race to compare groups that may differ in ways relevant to health disparities. These groups might represent target populations in which interventions could be designed and implemented around potentially modifiable factors. These macroenvironmental factors may also identify novel genotype-environment interactions. However, because macroenvironmental effects are broad and clearly represent surrogates for both differences and inequities, the approach presented here might be valid for the prediction of risk or outcomes, but not necessarily as a means of identifying the underlying etiology. Thus, the MME approach defined here might provide new avenues for research in cancer health disparities.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Acknowledgments

The authors acknowledge the support of Drs. S. Bruce Malkowicz and Alan J. Wein in the collection of data used in this study.

Grant Support

Public Health Service grants R29-ES08031, R01-CA85074, and P50-CA105641 (T.R. Rebbeck), and K07-CA106730 (C. Zeigler-Johnson).

Received 02/15/2010; revised 06/23/2010; accepted 07/01/2010; published online 09/08/2010.

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