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Gene-environment interactions between *JAZF1* and occupational and household lead exposure in prostate cancer among African American men

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Abstract

Purpose—A single nucleotide polymorphism, rs10486567, in *JAZF1* has consistently been associated with increased risk of prostate cancer. The physical interaction of zinc finger proteins, such as *JAZF1*, with heavy metals may play a role in carcinogenesis. This study assessed potential gene-environment statistical interactions (GxE) between rs10486567 and heavy metals in prostate cancer.

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Conflicts of Interest: None

Methods—In a case-only study of 228 African American prostate cancer cases, GxE between rs10486567 and sources of cadmium (Cd) and lead (Pb) were assessed. Unconditional logistic regression was used to estimate interaction odds ratios and GEE was used for models containing nested data. Case-control validation of IORs was performed, using 82 controls frequency matched to cases on age-race.

Results—Among cases, a potential GxE interaction was observed between rs10486567 CC genotype and living in a Census tract with a high proportion of housing built before 1950, a proxy for household Pb exposure, when compared to CT or TT carriers (OR 1.81; 95% CI 1.04-3.16; p=0.036). A stronger GxE interaction was observed when both housing and occupational Pb exposure were taken into account (OR 2.62; 95% CI 1.03-6.68; p=0.04). Case-control stratified analyses showed the odds of being a CC carrier was higher in cases compared to controls among men living in areas with older housing (OR 2.03; CI 0.99-4.19; p=0.05) or having high occupational Pb exposure (OR 2.50; CI 1.01-6.18; p=0.05).

Conclusions—In African American men, the association between *JAZF1* rs10486567 and prostate cancer may be modified by exposure to heavy metals such as Pb.

Keywords

prostate cancer; *JAZF1*; lead; cadmium; housing; smoking; African American

Introduction

Prostate cancer accounts for nearly forty-percent of all new cancers diagnosed in African American men [1]. Although both genetic and environmental factors are considered to play a role in prostate cancer, specific gene-environment (GxE) interactions have remained elusive. Genome-wide association studies (GWAS) are identifying potentially important risk variants [2-4], and the functional genes associated with these variants, may ultimately provide insight into environmental risk factors for the disease.

A single nucleotide polymorphism (SNP), in intron 2 of the gene juxtaposed with another zinc finger protein 1 (*JAZF1*), rs10486567, has emerged as a locus of interest for prostate cancer [5]; and after additional sequencing within the gene, rs10486567 remains the strongest association with risk of prostate cancer [6]. Although the functional relevance of rs10486567 has yet to be identified, *JAZF1* is known to encode a cysteine₂ histidine₂ (Cys₂-His₂) zinc-finger protein, a structural type of zinc finger that has been shown to interact with heavy metals such as cadmium (Cd) and lead (Pb) in vitro [7,8]. In fact, interaction of zinc finger proteins with heavy metals is one of the proposed mechanisms for metal carcinogenesis [9-11]. Zinc finger motifs are involved in protein-protein and protein-DNA interactions and zinc finger proteins are involved in DNA repair, transcription, and tumor suppression. Heavy metals have already been shown to affect the structure and function of key zinc finger proteins involved in carcinogenesis such as the tumor suppressor p53 [12] and inhibition of the DNA strand break repair protein Poly (ADP-Ribose) Polymerase (PARP) [13]. In fact, each zinc finger appears to be affected by a specific metal or subset of metals [10].

Cd and Pb are known to adversely affect the male reproductive system [14] and are recognized as carcinogens in animals. The International Agency on Cancer Research (IARC) recognizes Cd as a carcinogen in humans as well. Although Cd has been implicated in prostate cancer, studies have been mixed [15]. Cd has been linked to other cancers including lung [16] cancer. The epidemiological evidence for Pb as a human carcinogen has been lacking. At present, inorganic Pb and Pb compounds are classified as probable human carcinogens (Group 2A), and organic Pb remains unclassifiable as to its carcinogenicity in humans (Group 3) [17,18]. Perhaps the most compelling evidence for considering Pb as a risk factor for prostate cancer is the observation by Telisman et al. [19] that Pb exposed workers have lower seminal fluid zinc levels compared to unexposed controls. The same observation has been made in prostate cancer cases compared to healthy controls [20], an interesting observation since the prostate produces thirty percent of seminal fluid and prostate tumor tissue contains significantly lower zinc than adjacent normal tissue [21]. Low seminal fluid zinc levels have been proposed as a biomarker for prostate cancer [22].

Exposure to Cd and Pb can occur through several sources including occupation and smoking. A less frequently considered exposure source for adults is older housing which contains Pb-based paint. Although household Pb exposure is generally associated with children, adult blood Pb levels have been correlated with household dust Pb levels [23], peeling paint [24] and the year housing was built [25,26]. Krieger with others [27,28] used the proportion of housing built before 1940 and Sargent et al. [29] used housing built before 1950 to demarcate housing with high likelihood for Pb exposure. In 1997, the Centers for Disease Control recommended blood Pb testing for children living in zip codes with 27 % of homes built before 1950 [30]. African American men who predominantly reside in urban areas with older housing stock and lower household incomes may be at particular risk for metal exposure associated with Pb-based paint.

Epidemiological studies of the association between Cd [31-34] and Pb [35,36] and prostate cancer have shown mixed results but no study to date has accounted for genetic variation that may predispose some men to greater pathological or physiological effects of these metals. Therefore, using a statistically efficient case-only design, we evaluated the potential for an interaction between the *JAZF1* rs10486567 polymorphism and sources of Cd and Pb exposure in African American prostate cancer cases, and case-control analyses were carried out to validate the case-only findings.

Methods

Prostate cancer cases and controls

Cases and controls included in this study enrolled in the *Gene-Environment Interaction in Prostate Cancer* (GECAP) study between 2001 and 2004. Further details on these subjects can be found in previous reports [37,38]. In brief, GECAP was designed as a case-only [39] study, an efficient method for identifying gene-environment interactions, and includes 273 African-American cases. A small number of age and race frequency matched controls were enrolled (1 control: 3 cases) so that the case-only assumption of gene-environment independence at the population level could be verified. GECAP cases and controls were patients of a large urban health system that serves workers from the automotive industry and

associated manufacturing companies. All incident pathologically confirmed prostate cancer cases who met study enrollment criteria (<75 years of age) were contacted for participation in GECAP. Cases and controls were required to have at least one primary care visit within the health system in the five years prior to diagnosis or study enrollment, so that basic medical history information was available for all subjects. Controls provided a blood sample for PSA testing at the time of enrollment and had no prior history of prostate cancer. African American GECAP subjects who gave consent for use of their DNA were genotyped for *JAZF1* rs10486567 as part of the Men of African Descent and Prostate Cancer Consortium (MADCaP) [40]. GECAP is the only study within the MADCaP Consortium to have captured detailed occupational histories and to have had those histories semi-quantitatively coded by trained industrial hygienists. All study protocols were approved by the Institution's Human Subjects Committee.

JAZF1 Genotyping

JAZF1 rs10486567 genotyping was completed at the University of Pennsylvania in 230 cases and 90 controls by TaqMan™ assay using the 7900HT Fast Real-Time PCR Machine. Mixes of primers and probes were pre-designed by and purchased from Applied Biosystems [40]. Two cases were removed who had low levels (< 2%) of West African ancestry, as determined in previous study [41].

Occupational metal exposure, smoking, and clinical history

Lifetime cumulative occupational exposure to Cd and Pb was captured during extensive face-to-face interviews. As previously reported [37], job histories from the age of 18 to diagnosis (cases) or enrollment (controls) were collected by a trained study interviewer and included job-specific modules to enhance collection of relevant information for the exposures of interest, metals and polycyclic aromatic hydrocarbons. Job histories were then reviewed by one of two industrial hygienists, using semi-quantitative exposure assessment. Ten percent of job histories were reviewed by both IH across the course of the study to insure similar coding practices. For each job, the industrial hygienist assessed the probability of exposure, the years exposure likely started and ended, the percent of work time per year the exposure likely occurred, and the route of exposure (contact, respiratory or both). Respiratory exposures were coded by intensity. Smoking was self-reported and included information on start and stop dates, as well as the quantity of cigarettes smoked per day. Medical record review was conducted by certified medical record abstractors and included history of benign prostatic hypertrophy (BPH) for all subjects. PSA at diagnosis and pathological findings were abstracted from medical records for cases. A PSA test for the GECAP study was completed on all controls at enrollment.

Census Tract Data

Residential address at the time of diagnosis was geocoded using MapInfo Professional®v7.0 and MapMarker®v.8.1 software programs (MapInfo Corporation, Troy, NY), in conjunction with Spatial Re-Engineering Consultant's (SRC) Portfolio Desktop® (Orange, CA). Age of Census tract housing and median household income were captured using the U.S. Census 2000 Summary File 3. The percent of homes in the Census tract that were built before 1950

was used as the proxy for potential household Pb exposure and was calculated as $((H034009 + H034010)/H034001)*100$, where H034009 is equal to the total housing units built between 1940 and 1949, H034010 is equal to the total housing units built before 1939, and H034001 is the total housing units in the Census tract.

Statistical Methods

Evaluation of genotype frequencies for Hardy-Weinberg equilibrium was accomplished with the chi-square test among controls. In all of the analyses, *JAZF1* rs10486567 genotype is coded as CC versus the referent of TC/TT (i.e. a recessive genetic model). This coding was selected because so few subjects carried the TT genotype.

To estimate both respiratory and cutaneous cumulative lifetime occupational Cd and Pb exposure, a semi-quantitative exposure index was calculated for each study subject based on his job-specific IH exposure assessment [37]. We used lifetime cumulative respiratory exposure to Cd (no, yes) or Pb (no, low, high) in this analysis as cutaneous exposures were not graded by intensity and because of the difficulty in ascertaining relative intensities and doses between cutaneous and respiratory Cd and Pb. In addition, cutaneous absorption of Pb is affected by inorganic versus organic status of the metal, cleaning methods, perspiration level, and skin integrity [42-46], making exposure very difficult to estimate. Further, occupational cutaneous and respiratory metal exposures were highly correlated. Low and high respiratory Pb exposure was determined according to the median Pb exposure for all subjects exposed (157 cases and 56 controls) since the primary study design was case-only and only a small number of controls were enrolled to confirm GxE independence. Smoking status was categorized as never, the median (20.5 pack years) pack years, or > than the median pack years, with “never” used as the referent. Census tract housing built before 1950 was categorized as low or high based on the median percentage in Census tracts among all study subjects (low 48.4 %, high > 48.4 %).

Gene-environment interactions between *JAZF1* and occupational lead exposure were tested in the case sample using logistic regression models that had genotype as the dependent variable and the exposure as the independent variable. Models also controlled for confounders such as age and BPH. The case-only design relies on an assumption of gene and environment independence at the population level [47]. Therefore, we additionally conducted standard case-control models to validate this assumption, with each GxE interaction coded as a multiplicative term in the model. Generalized estimating equations (GEE) were used to address the nesting within Census tracts. Case-only gene-environment interaction odds ratios (OR) and case-control odds ratios (OR) and interaction odds ratios (IOR) were computed from the respective logistic models and are reported with corresponding 95% confidence intervals (95% CI). Hypothesis testing was carried out using a likelihood ratio test. P-values of .05 were considered statistically significant. All analyses were carried out using IBM® SPSS® statistical software (version 19).

Results

Subject Characteristics

Characteristics of prostate cancer cases and controls are summarized in Table 1. More than half (55.8 %) of all subjects were carriers of the *JAZF1* CC genotype. Seventy percent of subjects had a history of smoking, and the median proportion of housing built before 1950 in Census tracts was 48.4%. Industrial hygienist review of in-depth interviews identified occupational Cd and Pb exposure in 17 % and 69 % of subjects, respectively. Initial exposure took place prior to diagnosis/enrollment an average of 28.9 years for Cd (range 4-51 years) and 37.2 years for Pb (range 3-54 years). Cases were exposed to Cd at a younger age on average than controls (Table 1). It should be noted, however, that only ten controls were determined to have occupational exposure to Cd. The predominant route of exposure was through respiration for both metals. Cd and Pb exposure were highly correlated, with Pb exposure occurring in 49 of the 51 subjects determined to have an occupational Cd exposure. Smoking status and the proportion of housing built before 1950 in the Census tract were not associated with occupational Pb (smoking status $\times$ job Pb, $p=0.72$; older housing $\times$ job Pb, $p=0.87$) or Cd (smoking status $\times$ job Cd, $p=0.48$; older housing $\times$ job Cd, $p=0.35$) exposure among all subjects, confirming that a variety of separate pathways exist for Cd and Pb exposure.

GxE interaction analyses between *JAZF1* rs10486567 and sources of metal exposure

Case-only GxE statistical interactions between *JAZF1* rs10486567 and sources of Cd and Pb exposure are reported in Table 2, along with the corresponding case-control interaction odds ratios. Of the four separate proxy measures of metal exposure, Census tract housing was the only exposure that showed a statistically significant interaction with *JAZF1* rs10486567. Cases living in Census tracts with a high proportion of older housing were more likely to carry the CC genotype than cases in tracts with a low proportion of older housing (OR= 1.81; 95% CI 1.04-3.16; $p=0.036$), and the magnitude of this interaction was consistent with the IOR from the standard case-control analyses (OR 2.33; 95% CI 0.77-7.03; $p=0.13$), although this analysis is less powerful than the case-only. Additionally, stratum specific case-control analyses (Table 3) suggested that residence in a Census tract with a higher proportion of older housing, was associated with increased odds of being a CC genotype carrier (OR, 2.03; 95% CI, 0.99-4.19; $p=0.05$) among cases in comparison to controls. For subjects living in Census tracts with a lower proportion of older housing, no association was evident (OR, 0.84; 95% CI, 0.36-1.95; $p=0.68$). Further, in the case-only analysis, carriage of the CC genotype was modestly elevated in those exposed to high occupational Pb compared to those with no occupational Pb exposure (Table 2). Although this result was not statistically significant, the case-control results were again consistent with this finding. In case-control stratum specific analyses (Table 3), cases exposed to high levels of Pb at work had an increased odds of the CC genotype (OR, 2.50; 95% CI, 1.01-6.18; $p=0.05$) compared to controls, while there was no evidence of association in the “None” (OR, 1.13; 95% CI, 0.46-2.79; $p=0.79$) or “Low” (OR, 0.79; 95% CI, 0.32-1.95; $p=0.62$) occupational Pb stratum. No significant interaction was observed for *JAZF1* $\times$ occupational Cd exposure or smoking after adjustment for age, BPH and/or the other three exposures. Results remained

the same after removing subjects (one with Cd and three with Pb exposure) with a first exposure less than 10 years prior to diagnosis.

As Census tract housing built before 1950 was our proxy for household Pb exposure and high occupational Pb exposure showed modest association with *JAZF1* genotype, we combined the two categories for housing (low and high proportion built before 1950) with the three categories of occupational exposure (none, low, high) to form an indicator of “overall” Pb exposure. Table 4 includes case-only interactions between *JAZF1* and overall Pb exposure and indicates the strongest GxE interaction effect at the highest overall Pb exposure level (OR=2.62; 95%CI=1.03-6.68, p=0.04). In case-control analysis of the 54 men exposed to a high proportion of older housing and high levels of occupational Pb, there was substantial increase in the odds of carrying the CC genotype among prostate cancer cases in comparison to controls (OR, 3.48; 95%CI, 1.00-12.16; p=0.05). Among 53 men who had low proportions of older housing in their Census tract and no occupational Pb exposure, the odds of being a CC carrier were lower among cases in comparison to controls (OR, 0.49; 95% CI, 0.13-1.78; p=0.28).

Discussion

In this case-only study of African American men with prostate cancer, we found indications of a gene-environment interaction between *JAZF1* rs10486567 and a high proportion of Census tract housing built before 1950, our proxy for household Pb exposure. Further there was suggestive evidence of a similar interaction with occupational Pb exposure. Upon combining these two Pb exposure measures, we found an even stronger association between the *JAZF1* high risk genotype (CC) and overall Pb exposure in prostate cancer cases. These results are interesting given that the *JAZF1* rs10486567 risk allele (“C”) frequency does not differ greatly between African (0.68) and European men (0.73) [48], but African American men have historically been residentially segregated to neighborhoods with older housing and have been shown to have higher body burden of Pb than European American men [49,50].

While our most suggestive finding occurred with the exposure of older housing, it should be noted that this exposure could be a marker of many exposures other than Pb. For example, a study of breast cancer on Long Island found higher exposure to electromagnetic fields (EMF) in neighborhoods with a higher proportion of housing built before 1950, although EMF was not associated with breast cancer risk [51]. The higher EMF was due to differences in the configuration of electrical lines in older neighborhoods compared to more recently constructed subdivisions. In a study of electrical workers [52], workers in the top 10 percent of EMF exposure had double the prostate cancer mortality of those with the lowest EMF exposure. Older housing has also been associated with higher rates of infection in children [53], potentially leading to higher rates of inflammation. However, a study of middle-aged African Americans showed no difference in markers of inflammation by housing conditions [54], although they did not specifically consider age of housing. A higher proportion of older housing is also correlated with lower income and education levels and could be associated with other social variables that may explain our findings as well. However, it is well established that living in housing built before 1950 can result in exposure to Pb and given what is currently known about *JAZF1*, a GxE interaction between

JAZF1 and Pb is biologically plausible. In addition, the results for occupational Pb exposure and older housing were consistent.

The *JAZF1* gene encodes a triple-Cys₂His₂ zinc finger protein [55] and previous reports indicate that Pb and Cd can inhibit the DNA-binding capacity of this type of zinc finger protein. Triple- Cys₂His₂ proteins are part of a large family of zinc finger proteins that also include multiple-adjacent- and separated-paired- Cys₂His₂ zinc finger proteins. Hanas et al. [7] reported that Cd and Pb both inhibited the DNA-binding capacity of TFIIIA, a triple-Cys₂His₂ zinc finger, in *Xenopus* and using Cd and zinc fingers with other structures, showed specific effects of the metal with triple-Cys₂His₂ zinc finger proteins. Inhibition of DNA binding was reported at concentrations as low as 0.1 µM for Cd which is a physiologically relevant level. Later work by this same group, showed that low levels of Pb (5 to 10 µM) inhibited DNA-binding of TFIIIA and another zinc finger with similar structure, Sp1, but not AP2 a transcription factor with no cysteine-rich finger motifs [8].

Changes in JAZF1 DNA-binding by Pb may affect JAZF1 and its direct repression of nuclear receptor subfamily 2, group C, member 2 (NR2C2) [55]. NR2C2 is over expressed in prostate tumor tissue [56,57]. Pb may be able to inhibit the *JAZF1* protein, allowing NR2C2 to go unchecked. NR2C2 interacts with the androgen receptor [58,59] and its expression is also positively associated with glucose production in a human hepatoma cells [60]. NR2C2 controls the expression of the oncoprotein Bcl-2 as well. Bcl-2 is over expressed in many tumors and has anti-apoptotic effects. Therefore, changes that may result from the inhibition of JAZF1 DNA binding may lead to deleterious downstream effects. No published reports, however, have confirmed an effect of Pb or other heavy metals on JAZF1 function. In addition, there is no clear understanding of the functional role rs10486567, an intronic SNP, might play. If rs10486567 affects transcription of the *JAZF1* gene, and thereby the amount of protein produced, it may be harmless when the Pb to Zn ratio is low but harmful when this ratio is high.

To date, most of the focus on metals and prostate cancer risk has been on Cd [31,61,15], and few epidemiological studies have assessed associations between Pb and prostate cancer risk [35,36]. Surprisingly, most of the evidence against an association between Pb and prostate cancer has come from retrospective studies that failed to find higher prostate cancer mortality rates in Pb exposed workers [62-66]. But mortality may not be a good outcome for identifying environmental risk factors for prostate cancer, as most men die with prostate cancer, not from prostate cancer. Pb exposure has been associated with deaths due to cancers of the lung, brain, stomach, and kidney, which all have much shorter survival times and higher mortality rates.

Studies which have investigated the association between Pb exposure and risk of prostate cancer have been mixed. Using the Adult Blood Lead Epidemiology Surveillance System (ABLES) matched to the New Jersey State Cancer Registry, Lam et al. [35] found an overall deficit in cancer diagnoses among Pb exposed workers and lower than expected incidence of prostate cancer (Standardized Incidence Ratio 0.35 (0.20-0.57)). Rousseau et al. [36] in a case-control study in Montreal, Canada (1979 to 1985), conducted occupational interviews with 449 prostate cancer and 533 population controls and found a non-significant elevated

risk for prostate cancer among those exposed to organic Pb (number of cases exposed =15; OR, 1.9; 95% CI 0.8-4.6) and those exposed to inorganic Pb (cases exposed =78; OR, 1.1; 95% CI 0.7-1.6). Pb in gasoline emissions (cases exposed =169) was not associated with increased risk of prostate cancer (OR, 0.9; 95% CI 0.7-1.2). It is widely known that the male reproductive system is adversely affected by Pb [67,68], and Pb has been associated with poorer sperm quality[69] and erectile dysfunction [70]. Higher PSA levels have also been reported to be associated with Cd [71] and with Pb [72] exposure. However, while some have argued that significant main effects should be present in order to evaluate gene-environment interactions [73], others [74] have noted that this requirement may miss true gene-environment interactions when associations are in opposite directions across different exposure categories or genotypes. Teasing apart prostate cancer risk associated with Pb and Cd exposure, which has been equivocal to date [35,32,36,15], likely requires consideration of genetic variation, such as *JAZF1* rs10486567, that potentially modifies prostate cancer risk via GxE.

There were several limitations to this study. First, while the primary hypotheses tested (i.e. the four case-only GxEs) were narrowly defined and had an a priori biological basis, it is possible that these results were due to chance alone, and additional evidence is necessary to validate the suggestive and thought provoking GxE interaction effect between *JAZF1* rs10486567 and Pb exposure on prostate cancer risk. Although initial exposure to Cd or Pb took place many years prior to the prostate cancer diagnosis or study enrollment, lending plausibility to our findings, we had no direct measurement of Cd or Pb in prostate tissue was not available, a common problem among environmental exposure studies. However, in a study of adult brain tumors, Bhatti et al. [75] reported, that using a method similar to our lifetime occupational exposure assessment with expert review of detailed work histories was superior in detecting effect modification between lead exposure and genotype than a less intensive method using a job exposure matrix. Still our categorizations of lead and cadmium level, which is common practice in occupational exposure assessment, may be problematic as there could be random misclassification which would typically attenuate estimates towards the null. However, with our small sample size these estimates could be further affected. We also did not attempt to collect information on metal exposure prior to the age of 18, although many of these older African American men likely worked in heavily contaminated environments in their youth. We anticipate this omission would, again, have biased our results to the null. In addition, we were only able to assess the Census tract housing associated with the address at time of diagnosis. During the time this study was conducted, Michigan had the third highest home ownership rate in the nation (73.8%) and a relatively high homeownership rate among African Americans (50.7%). Among the African American men in GECAP, 70.3% were homeowners. Home owners have longer tenure than renters, this may account for our findings using only one place of residence. We could not adequately evaluate Cd interactions or disentangle combined Cd-Pb interactions with *JAZF1* because of the small number of occupationally exposed individuals. However, smoking, considered one of the greatest sources of cadmium in the U.S. population, showed no interaction with *JAZF1* in our subjects. It should be noted that although old housing is best known for Pb exposure, small quantities of Cd are contained in house paint [76]. Finally, Pb exposure has been associated with erectile dysfunction [70] and male fertility [14], two

variables we did not have in our data set. We did control for benign prostatic hyperplasia which did not change results appreciably.

In conclusion, our findings suggest that the association between *JAZF1* rs10486567 and prostate cancer may be modified by Pb exposure (residential and possibly occupational) in African Americans. Basic science research on the effects of heavy metals on *JAZF1* would give further insight to our results. Further, replication of our findings, in larger studies and in other racial/ethnic groups, are needed to substantiate this initial GxE report. If upheld, our findings may have particular relevance for African American men who have been residentially segregated to urban environments and have historically been shown to have higher body burden of Pb [49,50].

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References

1. American Cancer S. Cancer Facts & Figures for African Americans 2011-2012. American Cancer Society; Atlanta: 2012.
2. Eeles RA, Kote-Jarai Z, Giles GG, Olama AA, Guy M, Jugurnauth SK, Mulholland S, Leongamornlert DA, Edwards SM, Morrison J, Field HI, Southey MC, Severi G, Donovan JL, Hamdy FC, Dearnaley DP, Muir KR, Smith C, Bagnato M, rdern-Jones AT, Hall AL, O'Brien LT, Gehr-Swain BN, Wilkinson RA, Cox A, Lewis S, Brown PM, Jhavar SG, Tymrakiewicz M, Lophatananon A, Bryant SL, Horwich A, Huddart RA, Khoo VS, Parker CC, Woodhouse CJ, Thompson A, Christmas T, Ogden C, Fisher C, Jamieson C, Cooper CS, English DR, Hopper JL, Neal DE, Easton DF. Multiple newly identified loci associated with prostate cancer susceptibility. *Nat Genet.* 2008; 40(3):316–321. [PubMed: 18264097]
3. Haiman CA, Chen GK, Blot WJ, Strom SS, Berndt SI, Kittles RA, Rybicki BA, Isaacs WB, Ingles SA, Stanford JL, Diver WR, Witte JS, Hsing AW, Nemesure B, Rebbeck TR, Cooney KA, Xu J, Kibel AS, Hu JJ, John EM, Gueye SM, Watya S, Signorello LB, Hayes RB, Wang Z, Yeboah E, Tettey Y, Cai Q, Kolb S, Ostrander EA, Zeigler-Johnson C, Yamamura Y, Neslund-Dudas C, Haslag-Minoff J, Wu W, Thomas V, Allen GO, Murphy A, Chang BL, Zheng SL, Leske MC, Wu SY, Ray AM, Hennis AJ, Thun MJ, Carpten J, Casey G, Carter EN, Duarte ER, Xia LY, Sheng X, Wan P, Pooler LC, Cheng I, Monroe KR, Schumacher F, Le ML, Kolonel LN, Chanock SJ, Berg DV, Stram DO, Henderson BE. Genome-wide association study of prostate cancer in men of African ancestry identifies a susceptibility locus at 17q21. *Nat Genet.* 2011; 43(6):570–573. [PubMed: 21602798]
4. Waters KM, Le ML, Kolonel LN, Monroe KR, Stram DO, Henderson BE, Haiman CA. Generalizability of associations from prostate cancer genome-wide association studies in multiple populations. *Cancer Epidemiol Biomarkers Prev.* 2009; 18(4):1285–1289. [PubMed: 19318432]
5. Liu H, Wang B, Han C. Meta-analysis of genome-wide and replication association studies on prostate cancer. *Prostate.* 2010
6. Prokunina-Olsson L, Fu YP, Tang W, Jacobs KB, Hayes RB, Kraft P, Berndt SI, Wacholder S, Yu K, Hutchinson A, Spencer FH, Thun MJ, Diver WR, Albanes D, Virtamo J, Weinstein S, Schumacher FR, Cancel-Tassin G, Cussenot O, Valeri A, Andriole GL, Crawford ED, Haiman CA, Henderson BE, Kolonel L, Le ML, Siddiq A, Riboli E, Travis R, Kaaks R, Isaacs WB, Isaacs SD, Gronberg H, Wiklund F, Xu J, Vatten LJ, Hveem K, Kumle M, Tucker M, Hoover RN, Fraumeni JF Jr, Hunter DJ, Thomas G, Chatterjee N, Chanock SJ, Yeager M. Refining the Prostate Cancer Genetic Association within the *JAZF1* Gene on Chromosome 7p15.2. *Cancer Epidemiol Biomarkers Prev.* 2010
7. Hanas JS, Gunn CG. Inhibition of transcription factor IIIA-DNA interactions by xenobiotic metal ions. *Nucleic Acids Res.* 1996; 24(5):924–930. [PubMed: 8600461]

8. Hanas JS, Rodgers JS, Bantle JA, Cheng YG. Lead inhibition of DNA-binding mechanism of Cys(2)His(2) zinc finger proteins. *Mol Pharmacol*. 1999; 56(5):982–988. [PubMed: 10531404]
9. Asmuss M, Mullenders LH, Hartwig A. Interference by toxic metal compounds with isolated zinc finger DNA repair proteins. *ToxicolLett*. 2000; 112-113:227–231.
10. Beyersmann D, Hartwig A. Carcinogenic metal compounds: recent insight into molecular and cellular mechanisms. *Arch Toxicol*. 2008; 82(8):493–512. [PubMed: 18496671]
11. Koedrith P, Seo YR. Advances in carcinogenic metal toxicity and potential molecular markers. *Int J Mol Sci*. 2011; 12(12):9576–9595. [PubMed: 22272150]
12. Meplan C, Mann K, Hainaut P. Cadmium induces conformational modifications of wild-type p53 and suppresses p53 response to DNA damage in cultured cells. *J Biol Chem*. 1999; 274(44): 31663–31670. [PubMed: 10531375]
13. Hartwig A, Asmuss M, Ehleben I, Herzer U, Kostelac D, Pelzer A, Schwerdtle T, Burkle A. Interference by toxic metal ions with DNA repair processes and cell cycle control: molecular mechanisms. *Environ Health Perspect*. 2002; 110(Suppl 5):797–799. [PubMed: 12426134]
14. Wirth JJ, Mijal RS. Adverse effects of low level heavy metal exposure on male reproductive function. *Syst Biol ReprodMed*. 2010; 56(2):147–167.
15. Sahnoun AE, Case LD, Jackson SA, Schwartz GG. Cadmium and prostate cancer: a critical epidemiologic analysis. *Cancer Invest*. 2005; 23(3):256–263. [PubMed: 15945511]
16. Thun MJ, Schnorr TM, Smith AB, Halperin WE, Lemen RA. Mortality among a cohort of U.S. cadmium production workers--an update. *J Natl Cancer Inst*. 1985; 74(2):325–333. [PubMed: 3856046]
17. International Agency for Research on C. Overall evaluation of carcinogenicity:updating of IARC Monographs Vols. 1 to 42. IARC Monographs. 1987; 1-42:230–232.
18. International Agency For Research On C. Inorganic and Organic Lead Compounds: Summary of Data Reported and Evaluation. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. 2006; 87
19. Telisman S, Colak B, Pizent A, Jurasovic J, Cvitkovic P. Reproductive toxicity of low-level lead exposure in men. *Environ Res*. 2007; 105(2):256–266. [PubMed: 17632096]
20. Zaichick VY, Sviridova TV, Zaichick SV. Zinc concentration in human prostatic fluid: normal, chronic prostatitis, adenoma and cancer. *Int Urol Nephrol*. 1996; 28(5):687–694. [PubMed: 9061429]
21. Zaichick VY, Sviridova TV, Zaichick SV. Zinc in the human prostate gland: normal, hyperplastic and cancerous. *Int Urol Nephrol*. 1997; 29(5):565–574. [PubMed: 9413764]
22. Costello LC, Franklin RB. Zinc is decreased in prostate cancer: an established relationship of prostate cancer! *J Biol InorgChem*. 2011; 16(1):3–8.
23. Hogervorst J, Plusquin M, Vangronsveld J, Nawrot T, Cuypers A, Van HE, Roels HA, Carleer R, Staessen JA. House dust as possible route of environmental exposure to cadmium and lead in the adult general population. *Environ Res*. 2007; 103(1):30–37. [PubMed: 16843453]
24. Nriagu J, Burt B, Linder A, Ismail A, Sohn W. Lead levels in blood and saliva in a low-income population of Detroit, Michigan. *Int J HygEnviron Health*. 2006; 209(2):109–121.
25. Dye BA, Hirsch R, Brody DJ. The relationship between blood lead levels and periodontal bone loss in the United States, 1988-1994. *Environ Health Perspect*. 2002; 110(10):997–1002. [PubMed: 12361924]
26. Muntner P, Menke A, DeSalvo KB, Rabito FA, Batuman V. Continued decline in blood lead levels among adults in the United States: the National Health and Nutrition Examination Surveys. *Arch Intern Med*. 2005; 165(18):2155–2161. [PubMed: 16217007]
27. Krieger N, Chen JT, Waterman PD, Soobader MJ, Subramanian SV, Carson R. Choosing area based socioeconomic measures to monitor social inequalities in low birth weight and childhood lead poisoning: The Public Health Disparities Geocoding Project (US). *J Epidemiol Community Health*. 2003; 57(3):186–199. [PubMed: 12594195]
28. Krieger N, Chen JT, Waterman PD, Rehkopf DH, Subramanian SV. Race/ethnicity, gender, and monitoring socioeconomic gradients in health: a comparison of area-based socioeconomic measures--the public health disparities geocoding project. *Am J Public Health*. 2003; 93(10): 1655–1671. [PubMed: 14534218]

29. Sargent JD, Bailey A, Simon P, Blake M, Dalton MA. Census tract analysis of lead exposure in Rhode Island children. *Environ Res.* 1997; 74(2):159–168. [PubMed: 9339229]
30. Update: blood lead levels--United States, 1991-1994. *MMWR MorbMortalWklyRep.* 1997; 46(7): 141–146.
31. Bako G, Smith ES, Hanson J, Dewar R. The geographical distribution of high cadmium concentrations in the environment and prostate cancer in Alberta. *CanJ Public Health.* 1982; 73(2): 92–94. [PubMed: 7104934]
32. Platz EA, Helzlsouer KJ, Hoffman SC, Morris JS, Baskett CK, Comstock GW. Prediagnostic toenail cadmium and zinc and subsequent prostate cancer risk. *Prostate.* 2002; 52(4):288–296. [PubMed: 12210489]
33. Vinceti M, Venturelli M, Sighinolfi C, Trerotoli P, Bonvicini F, Ferrari A, Bianchi G, Serio G, Bergomi M, Vivoli G. Case-control study of toenail cadmium and prostate cancer risk in Italy. *Sci Total Environ.* 2007; 373(1):77–81. [PubMed: 17175009]
34. Chen YC, Pu YS, Wu HC, Wu TT, Lai MK, Yang CY, Sung FC. Cadmium burden and the risk and phenotype of prostate cancer. *BMC Cancer.* 2009; 9:429. [PubMed: 20003241]
35. Lam TV, Agovino P, Niu X, Roche L. Linkage study of cancer risk among lead-exposed workers in New Jersey. *Sci Total Environ.* 2007; 372(2-3):455–462. [PubMed: 17129599]
36. Rousseau MC, Parent ME, Nadon L, Latreille B, Siemiatycki J. Occupational exposure to lead compounds and risk of cancer among men: a population-based case-control study. *Am J Epidemiol.* 2007; 166(9):1005–1014. [PubMed: 17690218]
37. Rybicki BA, Neslund-Dudas C, Nock NL, Schultz LR, Eklund L, Rosbalt J, Bock CH, Monaghan KG. Prostate cancer risk from occupational exposure to polycyclic aromatic hydrocarbons interacting with the GSTP1 Ile105Val polymorphism. *Cancer DetectPrev.* 2006; 30(5):412–422.
38. Tang D, Liu JJ, Rundle A, Neslund-Dudas C, Savera AT, Bock CH, Nock NL, Yang JJ, Rybicki BA. Grilled meat consumption and PhIP-DNA adducts in prostate carcinogenesis. *Cancer Epidemiol Biomarkers Prev.* 2007; 16(4):803–808. [PubMed: 17416774]
39. Umbach DM, Weinberg CR. Designing and analysing case-control studies to exploit independence of genotype and exposure. *Stat Med.* 1997; 16(15):1731–1743. [PubMed: 9265696]
40. Chang BL, Spangler E, Gallagher S, Haiman CA, Henderson BE, Isaacs WB, Benford ML, Kidd LR, Cooney K, Strom SS, Ingles SA, Stern MC, Corral R, Joshi AD, Xu J, Giri VN, Rybicki BA, Neslund-Dudas C, Kibel AS, Thompson IM Jr. Leach RJ, Ostrander EA, Stanford J, Witte JS, Casey G, Eeles R, Hsing AW, Chanock SJ, Hu JJ, John EM, Park JY, Stefflova K, Zeigler-Johnson C, Rebbeck TR. Validation of Genome-Wide Prostate Cancer Associations in Men of African Descent. *Cancer Epidemiol Biomarkers Prev.* 2010
41. Bock CH, Schwartz AG, Ruterbusch JJ, Levin AM, Neslund-Dudas C, Land SJ, Wenzlaff AS, Reich D, McKeigue P, Chen W, Heath EI, Powell IJ, Kittles RA, Rybicki BA. Results from a prostate cancer admixture mapping study in African-American men. *Hum Genet.* 2009; 126(5): 637–642. [PubMed: 19568772]
42. Bress WC, Bidanset JH. Percutaneous in vivo and in vitro absorption of lead. *Vet Hum Toxicol.* 1991; 33(3):212–214. [PubMed: 1858297]
43. Stauber JL, Florence TM, Gulson BL, Dale LS. Percutaneous absorption of inorganic lead compounds. *Sci Total Environ.* 1994; 145(1-2):55–70. [PubMed: 8016629]
44. Sun CC, Wong TT, Hwang YH, Chao KY, Jee SH, Wang JD. Percutaneous absorption of inorganic lead compounds. *AIHAJ (Fairfax, Va).* 2002; 63(5):641–646.
45. Filon FL, Boeniger M, Maina G, Adami G, Spinelli P, Damian A. Skin absorption of inorganic lead (PbO) and the effect of skin cleansers. *J Occup Environ Med.* 2006; 48(7):692–699. [PubMed: 16832226]
46. Pan J, Plant JA, Voulvoulis N, Oates CJ, Ihlenfeld C. Cadmium levels in Europe: implications for human health. *Environ GeochemHealth.* 2010; 32(1):1–12.
47. Khoury MJ, Flanders WD. Nontraditional epidemiologic approaches in the analysis of gene-environment interaction: case-control studies with no controls! *Am J Epidemiol.* 1996; 144(3): 207–213. [PubMed: 8686689]
48. Frazer KA, Ballinger DG, Cox DR, Hinds DA, Stuve LL, Gibbs RA, Belmont JW, Boudreau A, Hardenbol P, Leal SM, Pasternak S, Wheeler DA, Willis TD, Yu F, Yang H, Zeng C, Gao Y, Hu

- H, Hu W, Li C, Lin W, Liu S, Pan H, Tang X, Wang J, Wang W, Yu J, Zhang B, Zhang Q, Zhao H, Zhou J, Gabriel SB, Barry R, Blumenstiel B, Camargo A, Defelice M, Faggart M, Goyette M, Gupta S, Moore J, Nguyen H, Onofrio RC, Parkin M, Roy J, Stahl E, Winchester E, Ziaugra L, Altshuler D, Shen Y, Yao Z, Huang W, Chu X, He Y, Jin L, Liu Y, Sun W, Wang H, Wang Y, Xiong X, Xu L, Wayne MM, Tsui SK, Xue H, Wong JT, Galver LM, Fan JB, Gunderson K, Murray SS, Oliphant AR, Chee MS, Montpetit A, Chagnon F, Ferretti V, Leboeuf M, Olivier JF, Phillips MS, Roumy S, Sallee C, Verner A, Hudson TJ, Kwok PY, Cai D, Koboldt DC, Miller RD, Pawlikowska L, Taillon-Miller P, Xiao M, Tsui LC, Mak W, Song YQ, Tam PK, Nakamura Y, Kawaguchi T, Kitamoto T, Morizono T, Nagashima A, Ohnishi Y, Sekine A, Tanaka T, Tsunoda T, Deloukas P, Bird CP, Delgado M, Dermitzakis ET, Gwilliam R, Hunt S, Morrison J, Powell D, Stranger BE, Whittaker P, Bentley DR, Daly MJ, de Bakker PI, Barrett J, Chretien YR, Maller J, McCarroll S, Patterson N, Pe'er I, Price A, Purcell S, Richter DJ, Sabeti P, Saxena R, Schaffner SF, Sham PC, Varilly P, Stein LD, Krishnan L, Smith AV, Tello-Ruiz MK, Thorisson GA, Chakravarti A, Chen PE, Cutler DJ, Kashuk CS, Lin S, Abecasis GR, Guan W, Li Y, Munro HM, Qin ZS, Thomas DJ, McVean G, Auton A, Bottolo L, Cardin N, Eyheramendy S, Freeman C, Marchini J, Myers S, Spencer C, Stephens M, Donnelly P, Cardon LR, Clarke G, Evans DM, Morris AP, Weir BS, Mullikin JC, Sherry ST, Feolo M, Skol A, Zhang H, Matsuda I, Fukushima Y, Macer DR, Suda E, Rotimi CN, Adebamowo CA, Ajayi I, Aniagwu T, Marshall PA, Nkwodimmah C, Royal CD, Leppert MF, Dixon M, Peiffer A, Qiu R, Kent A, Kato K, Niikawa N, Adewole IF, Knoppers BM, Foster MW, Clayton EW, Watkin J, Muzny D, Nazareth L, Sodergren E, Weinstock GM, Yakub I, Birren BW, Wilson RK, Fulton LL, Rogers J, Burton J, Carter NP, Clee CM, Griffiths M, Jones MC, McLay K, Plumb RW, Ross MT, Sims SK, Willey DL, Chen Z, Han H, Kang L, Godbout M, Wallenburg JC, L'Archeveque P, Bellemare G, Saeki K, An D, Fu H, Li Q, Wang Z, Wang R, Holden AL, Brooks LD, McEwen JE, Guyer MS, Wang VO, Peterson JL, Shi M, Spiegel J, Sung LM, Zacharia LF, Collins FS, Kennedy K, Jamieson R, Stewart J. A second generation human haplotype map of over 3.1 million SNPs. *Nature*. 2007; 449(7164):851–861. [PubMed: 17943122]
49. Muntner P, He J, Vupputuri S, Coresh J, Batuman V. Blood lead and chronic kidney disease in the general United States population: results from NHANES III. *Kidney Int*. 2003; 63(3):1044–1050. [PubMed: 12631086]
 50. Richter PA, Bishop EE, Wang J, Swahn MH. Tobacco smoke exposure and levels of urinary metals in the U.S. youth and adult population: the National Health and Nutrition Examination Survey (NHANES) 1999–2004. *Int J Environ Res Public Health*. 2009; 6(7):1930–1946. [PubMed: 19742163]
 51. O'Leary ES, Schoenfeld ER, Henderson K, Grimson R, Kabat GC, Kaune WT, Gammon MD, Leske MC. Wire coding in the EMF and Breast Cancer on Long Island Study: relationship to magnetic fields. *J ExpoAnalEnviron Epidemiol*. 2003; 13(4):283–293.
 52. Charles LE, Loomis D, Shy CM, Newman B, Millikan R, Nylander-French LA, Couper D. Electromagnetic fields, polychlorinated biphenyls, and prostate cancer mortality in electric utility workers. *Am J Epidemiol*. 2003; 157(8):683–691. [PubMed: 12697572]
 53. Haddow AD, Bixler D, Schuh AJ. The demographic and socioeconomic factors predictive for populations at high-risk for la crosse virus infection in West Virginia. *PLoS One*. 2011; 6(9):e25739. [PubMed: 21980533]
 54. Schootman M, Andresen EM, Wolinsky FD, Malmstrom TK, Morley JE, Miller DK. Adverse housing and neighborhood conditions and inflammatory markers among middle-aged African Americans. *J Urban Health*. 2010; 87(2):199–210. [PubMed: 20186494]
 55. Nakajima T, Fujino S, Nakanishi G, Kim YS, Jetten AM. TIP27: a novel repressor of the nuclear orphan receptor TAK1/TR4. *Nucleic Acids Res*. 2004; 32(14):4194–4204. [PubMed: 15302918]
 56. Lapointe J, Li C, Higgins JP, van de RM, Bair E, Montgomery K, Ferrari M, Egevad L, Rayford W, Bergerheim U, Ekman P, DeMarzo AM, Tibshirani R, Botstein D, Brown PO, Brooks JD, Pollack JR. Gene expression profiling identifies clinically relevant subtypes of prostate cancer. *Proc Natl Acad Sci USA*. 2004; 101(3):811–816. [PubMed: 14711987]
 57. Wallace TA, Prueitt RL, Yi M, Howe TM, Gillespie JW, Yfantis HG, Stephens RM, Caporaso NE, Loffredo CA, Ambs S. Tumor immunobiological differences in prostate cancer between African-American and European-American men. *Cancer Res*. 2008; 68(3):927–936. [PubMed: 18245496]

58. Chang C, Da Silva SL, Ideta R, Lee Y, Yeh S, Burbach JP. Human and rat TR4 orphan receptors specify a subclass of the steroid receptor superfamily. *Proc Natl Acad Sci USA*. 1994; 91(13): 6040–6044. [PubMed: 8016112]
59. Lee YF, Shyr CR, Thin TH, Lin WJ, Chang C. Convergence of two repressors through heterodimer formation of androgen receptor and testicular orphan receptor-4: a unique signaling pathway in the steroid receptor superfamily. *Proc Natl Acad Sci USA*. 1999; 96(26):14724–14729. [PubMed: 10611280]
60. Liu NC, Lin WJ, Kim E, Collins LL, Lin HY, Yu IC, Sparks JD, Chen LM, Lee YF, Chang C. Loss of TR4 orphan nuclear receptor reduces phosphoenolpyruvate carboxykinase-mediated gluconeogenesis. *Diabetes*. 2007; 56(12):2901–2909. [PubMed: 17827404]
61. Soraham T, Waterhouse JA. Cancer of prostate among nickel-cadmium battery workers. *Lancet*. 1985; 1(8426):459. [PubMed: 2857832]
62. Enterline PE, Marsh GM. Mortality studies of smelter workers. *Am J Ind Med*. 1980; 1(3-4):251–259. [PubMed: 7342769]
63. McMichael AJ, Johnson HM. Long-term mortality profile of heavily-exposed lead smelter workers. *J Occup Med*. 1982; 24(5):375–378. [PubMed: 7086551]
64. Selevan SG, Landrigan PJ, Stern FB, Jones JH. Mortality of lead smelter workers. *Am J Epidemiol*. 1985; 122(4):673–683. [PubMed: 4025307]
65. Gerhardsson L, Lundstrom NG, Nordberg G, Wall S. Mortality and lead exposure: a retrospective cohort study of Swedish smelter workers. *Br J Ind Med*. 1986; 43(10):707–712. [PubMed: 3778840]
66. Fu H, Boffetta P. Cancer and occupational exposure to inorganic lead compounds: a meta-analysis of published data. *Occup Environ Med*. 1995; 52(2):73–81. [PubMed: 7757170]
67. Apostoli P, Kiss P, Porru S, Bonde JP, Vanhoorne M. Male reproductive toxicity of lead in animals and humans. ASCLEPIOS Study Group. *Occup Environ Med*. 1998; 55(6):364–374.
68. Woodruff TJ, Carlson A, Schwartz JM, Giudice LC. Proceedings of the Summit on Environmental Challenges to Reproductive Health and Fertility: executive summary. *FertilSteril*. 2008; 89(2): 281–300.
69. Mendiola J, Moreno JM, Roca M, Vergara-Juarez N, Martinez-Garcia MJ, Garcia-Sanchez A, Elvira-Rendueles B, Moreno-Grau S, Lopez-Espin JJ, Ten J, Bernabeu R, Torres-Cantero AM. Relationships between heavy metal concentrations in three different body fluids and male reproductive parameters: a pilot study. *Environ Health*. 2011; 10(1):6. [PubMed: 21247448]
70. Anis TH, ElKaraksy A, Mostafa T, Gadalla A, Imam H, Hamdy L, bu el-Alla O. Chronic lead exposure may be associated with erectile dysfunction. *J Sex Med*. 2007; 4(5):1428–1434. [PubMed: 17727353]
71. van WE, Singer EA, Palapattu GS. Prostate-specific antigen levels in relation to cadmium exposure and zinc intake: results from the 2001-2002 National Health and Nutrition Examination Survey. *Prostate*. 2008; 68(2):122–128. [PubMed: 18044729]
72. Pizent A, Colak B, Kljakovic Z, Telisman S. Prostate-specific antigen (PSA) in serum in relation to blood lead concentration and alcohol consumption in men. *Arh Hig Rada Toksikol*. 2009; 60(1):69–78.
73. Clayton D, McKeigue PM. Epidemiological methods for studying genes and environmental factors in complex diseases. *Lancet*. 2001; 358(9290):1356–1360. [PubMed: 11684236]
74. Bookman EB, McAllister K, Gillanders E, Wanke K, Balshaw D, Rutter J, Reedy J, Shaughnessy D, gurs-Collins T, Paltoo D, Atienza A, Bierut L, Kraft P, Fallin MD, Perera F, Turkheimer E, Boardman J, Marazita ML, Rappaport SM, Boerwinkle E, Suomi SJ, Caporaso NE, Hertz-Picciotto I, Jacobson KC, Lowe WL, Goldman LR, Duggal P, Gunnar MR, Manolio TA, Green ED, Olster DH, Birmbaum LS. Gene-environment interplay in common complex diseases: forging an integrative model-recommendations from an NIH workshop. *Genet Epidemiol*. 2011
75. Bhatti P, Stewart PA, Linet MS, Blair A, Inskip PD, Rajaraman P. Comparison of occupational exposure assessment methods in a case-control study of lead, genetic susceptibility and risk of adult brain tumours. *Occup Environ Med*. 2010

76. Mielke HW, Powell ET, Shah A, Gonzales CR, Mielke PW. Multiple metal contamination from house paints: consequences of power sanding and paint scraping in New Orleans. *Environ Health Perspect.* 2001; 109(9):973–978. [PubMed: 11673129]

Table 1

African American prostate cancer case and control characteristics

Characteristics		Controls (N= 82) N(%)	Cases (N= 228) N(%)	p-value
Age (years (s.d.))		61.0 (7.3)	62.1 (7.3)	0.24
African Ancestry (mean % (s.d.))		82.0 (0.9)	81.0 (0.11)	0.43
JAZF1 genotype				
	CC	41 (50.0)	132 (57.9)	0.40
	CT	33 (40.2)	81 (35.5)	
	TT	8 (9.8)	15 (6.6)	
Smoking				
	Never Smoker	20 (24.4)	73 (32.2)	0.25
	21 pack-years	28 (34.1)	82 (36.1)	
	> 21 pack-years	34 (41.5)	72 (31.7)	
Census Tract				
	Homes Built before 1950 (median %)	49.8	47.4	0.29
	Household income (median)	35,720	34,462	0.98
Occupational Metal Exposure				
	Cadmium			
	Any Exposure	10 (12.2)	41 (18.1)	0.22
	Cutaneous	2 (2.4)	20 (8.8)	0.22
	Respiratory	10 (12.2)	41 (18.1)	0.06
	Age first exposed (mean years (sd))	40.1 (14.1)	30.5 (10.3)	0.018
	Years of exposure (median (range))	16.0 (1-33)	5.0 (1-37)	0.28
Lead				
	Any Exposure	57 (69.5)	157 (68.9)	0.91
	Cutaneous	15 (18.3)	40 (17.6)	0.90
	Respiratory	56 (68.3)	153 (67.4)	0.88
	Age first exposed (mean years (sd))	26.8 (10.0)	24.9 (9.4)	0.26
	Years of exposure (median (range))	3.5 (1-43)	5.0 (1-38)	0.98
Clinical characteristics				
	BPH	13 (15.9)	75 (33.0)	0.003
	PSA > 10	-	48 (20.8)	
	Gleason 7	-	129 (57.3)	
	Stage T2c or greater	-	64 (28.2)	

p-value from t-test for means, chi-square test for categories, Mann-Whitney test for medians.

Table 2

Gene-environment interactions between JAZF1 rs10486567 (referent CT or TT) and sources of cadmium and lead exposure in African American prostate cancer cases and controls. (Case-only and Case-control)

Case-Only						Case-Control			
Exposure	JAZF1 rs10486567					JAZF1 rs10486567			
	CC N(%)	CT or TT N(%)	OR*	95% CI	p	IOR*	95% CI	p	
Smoking									
Never	45 (34.1)	28 (29.2)	ref			ref			
21 packyears	45 (34.1)	37 (38.5)	0.77	0.40-1.48	0.44	0.82	0.21-3.12	0.76	
>21 packyears	42 (31.8)	31 (32.3)	0.87	0.43-1.73	0.69	1.13	0.31-4.20	0.85	
Housing Built									
Before 1950 [†]									
Low	57 (43.5)	57 (59.4)	ref			ref			
High	74 (56.5)	39 (40.6)	1.81	1.04-3.16	0.04	2.33	0.77-7.03	0.13	
Occupational Metal									
Cadmium									
No Cd	106 (80.3)	81 (84.4)	ref			ref			
Any Cd	26 (19.7)	15 (15.6)	1.30	0.64-2.64	0.46	0.85	0.18-3.97	0.83	
Lead									
No Pb	40 (30.3)	34 (35.4)	ref			ref			
Low Pb	41 (31.1)	34 (35.4)	0.96	0.50-1.86	0.90	0.73	0.21-2.55	0.62	
High Pb	51 (38.6)	28 (29.2)	1.46	0.76-2.81	0.26	1.98	0.54-7.22	0.30	

Abbreviations: Interaction odds ratio (IOR), confidence interval (CI), Housing built before 1950, less than or equal median proportion (Low), greater than median proportion (High), Lead, less than or equal to median for those exposed (Low Pb), greater than median for those exposed (High Pb).

* OR and IOR adjusted for age and BPH.

[†] GEE used for models based on Census tracts.

Table 3

Case-control associations between JAZF1 rs10486567 (referent CT or TT) and risk of prostate cancer stratified by sources of Cd and Pb exposure in African American men

	Control N	Case N	OR ^{a,b,c,d}	95% CI	p	OR ^{a,b,c,d}	95% CI	p
Smoking								
Never-CT or TT	9	28	ref					
Never-CC	11	45	1.26 ^a	0.76-2.12	0.37			
21 packyears-CT or TT	14	37	1.46 ^a	0.59-3.59	0.41	ref		
21 packyears-CC	14	45	1.14 ^a	0.48-2.72	0.77	1.03 ^a	0.42-2.50	0.95
>21 packyears-CT or TT	18	31	1.22 ^a	0.52-2.84	0.65	ref		
>21 packyears-CC	16	42	0.69 ^a	0.30-1.59	0.38	1.48 ^a	0.62-3.53	0.37
Census Tract Housing Built Before 1950								
Low-CT or TT	18	58	ref					
Low-CC	19	61	0.84 ^b	0.36-1.95	0.68			
High-CT or TT	23	38	0.46 ^b	0.21-0.97	0.05	ref		
High-CC	22	71	0.94 ^b	0.45-1.97	0.88	2.03 ^b	0.99-4.19	0.05
Occupational Metal								
Cadmium								
No Cd-CT or TT	37	81	ref					
No Cd-CC	35	106	1.28 ^c	0.73-2.24	0.38			
Any Cd-CT or TT	4	15	1.66 ^c	0.50-5.48	0.40	ref		
Any Cd-CC	6	26	1.86 ^c	0.47-1.49	0.22	1.05 ^c	0.24-4.66	0.95
Lead								
None-CT or TT	13	34	ref					
None-CC	13	40	1.13 ^d	0.46-2.79	0.79			
Low-CT or TT	13	34	1.05 ^d	0.41-2.70	0.92	ref		
Low-CC	17	41	0.91 ^d	0.37-2.25	0.83	0.79 ^d	0.32-1.95	0.62
High-CT or TT	15	28	0.57 ^d	0.23-1.46	0.24	ref		
High-CC	11	51	1.14 ^d	0.45-2.91	0.78	2.50 ^d	1.01-6.18	0.05

Abbreviations: odds ratio (OR), confidence interval (CI). Occupational lead low 3.2 and high > 3.2. Census tract housing built before 1950 low 48.4% and high > 48.4%. GEE used for all models.

^aOR adjusted for age, BPH, and occupational Cd. Adjusting for Pb in place of Cd did not change result.

^bOR adjusted for age, BPH, and occupational Pb.

^cOR adjusted for age, BPH, and smoking.

^dOR adjusted for age, BPH, and Census tract housing built before 1950.

Table 4

Case-only gene-environment interaction between JAZF1 rs10486567 (referent CT or TT) and overall Pb exposure (occupation and housing) in African American prostate cancer cases

Overall Pb Exposure*	JAZF1 rs10486567		OR**	95% CI	p
	CC	CT or TT			
No Occupational Pb &	N (%)	N (%)			
Low % Old Housing	18 (13.6)	22 (22.9)	ref		
High % Old Housing	22 (16.7)	12 (12.5)	2.17	0.85-5.56	0.11
Low Occupation Pb &					
Low % Old Housing	19 (14.4)	20 (20.8)	1.08	0.43-2.70	0.88
High % Old Housing	22 (16.7)	14 (14.6)	1.94	0.76-4.98	0.16
High Occupation Pb &					
Low % Old Housing	24 (18.2)	16 (16.7)	1.72	0.66-4.48	0.27
High % Old Housing	27 (20.5)	12 (12.5)	2.62	1.03-6.68	0.04

Abbreviations: Lead (Pb), gene-environment odds ratio (OR), confidence interval (CI).

* GEE used for all models. Occupational respiratory Pb (low 3.2 or high > 3.2), % of housing built before 1950 (low 48.4 or high > 48.4).

** OR adjusted for age and BPH.