Published in final edited form as:

Prostate. 2010 December 1; 70(16): 1739–1745. doi:10.1002/pros.21209.

p53 Pro72Arg Polymorphism and Prostate Cancer in Men of African Descent

L. Ricks-Santi^{1,2,*}, T. Mason², V. Apprey³, C. Ahaghotu⁴, A. McLauchlin^{2,5}, D. Josey^{1,2}, G. Bonney^{3,6}, and G.M. Dunston^{2,7}

¹Howard University Cancer Center, College of Medicine, Washington, District of Columbia

²Molecular Genetics Unit, National Human Genome Center, Washington, District of Columbia

³Statistical Genetics and Bioinformatics Unit, National Human Genome Center, Washington, District of Columbia

⁴Department of Urology, College of Medicine, Howard University, Washington, District of Columbia

⁵Department of Genetics, Graduate School, Howard University, Washington, District of Columbia

⁶Department of Community and Family Medicine, College of Medicine, Howard University, Washington, District of Columbia

⁷Department of Microbiology, College of Medicine, Howard University, Washington, District of Columbia

Abstract

BACKGROUND—p53 is a transcription factor that regulates the cell cycle, DNA repair, and apoptosis. A variant at codon 72, rs1042522, results in altered activities for p53 and is, notably, differentially distributed among different ethnic populations. However, associations of this variant with cancer in men of African descent have not been explored. Herein, we tested the hypothesis that rs1042522 was associated with prostate cancer (PCa) risk.

MATERIALS AND METHODS—Genotypes were determined by PCR-RFLP methods in a study population of African descent consisting of 266 PCa patients and 196 male controls.

RESULTS—Our results indicate that the p53 polymorphism may be associated with increased risk of PCa. Genotypes were significantly and marginally associated with PCa risk using the dominant and log-additive genetic models (OR = 1.53, 95% CI: 1.02–2.29, $P = 0.04$; OR = 1.33, 95% CI: 0.99–1.78, $P = 0.06$, respectively). After adjusting for age, the associations with PCa remained, but results were not statistically significant (OR = 1.48, 95% CI: 0.95–2.31, $P = 0.08$; OR = 1.30, 95% CI: 0.95–1.80, $P = 0.10$, respectively).

CONCLUSIONS—The present study demonstrates that population-dependent differences in allele frequencies associated with health disparities provide a valuable framework for the interrogation of complex diseases in all populations.

Keywords

prostate cancer; p53; health disparities

INTRODUCTION

The p53 transcription factor, encoded by the TP53 gene, plays a central role in regulating the cell cycle, DNA repair, and apoptosis, thus it can function as a tumor suppressor [1]. Specifically, p53 is activated by phosphorylation in response to stressors such as oxidative stress, DNA damaging agents, and temperature change. Because of p53's role in preventing cancers, it is one of the most intensely studied human genes and is often called the “guardian of the genome” [2]. Although mutations in p53 have been implicated in ~50% of human cancers and represent the most common somatic alteration in human cancers [3,4], several common polymorphic variants in the germline also appear to have functional effects related to cancer development [5–24].

One common variant, rs1042522, a single-nucleotide polymorphism (SNP) at codon 72 (CGC to CCC in exon 4), results in altered activities for p53. The C to G change also results in a proline (Pro) to arginine (Arg) amino acid alteration in the proline-rich region essential for p53-mediated apoptosis [25,26]. The Pro variant has increased transcriptional transactivation activities and appears to induce a higher level of G1 cell-cycle arrest, while the arginine allele has been associated with induction of apoptosis and suppression of cellular transformation by binding more efficiently to the promoters of pro-apoptotic genes such as Bax. Additionally, the Arg increases the ability to localize to the mitochondria [25,27–35].

Several studies have shown that there are population-dependent allele frequency differences in the p53 P72R SNP and that Pro (C allele) is less prevalent in Europeans (minor allele frequency (MAF) = 0.23) compared to people of African descent (MAF = 0.67 and 0.54, Yorubans and African Americans, respectively) [5,36,37]. Some have suggested that selection for the Arg allele is latitude or temperature dependent and that the further a population is from the equator, the more likely they are to have the Arg allele [5,36–38].

Prostate cancer (PCa) is the second leading cause of cancer deaths in men after lung cancer. In the United States, African American men are affected by PCa 1.6 times more than European men and are 2.4 times more likely to die from PCa than their European counterparts [39]. Conflicting results of the rs1042522's association have been reported in several cancers, which include ovarian, lung, cervical, colon, and prostate [9,10,40–43] (Table I). Of the nine PCa studies, two reported that Pro was associated with decreased risk, while others reported no association or an association with Arg and decreased risk of PCa [44–51]. Furthermore, while the p53 Pro allele has been found to be protective in other populations (Caucasians and Taiwanese) [45,51], the role of this p53 polymorphism in contributing to risk in men of African descent has not been addressed. To this end, in this study we tested the hypothesis that this p53 SNP was associated with PCa risk. Given that the allele had differential prevalence between populations (Europeans vs. Africans) we also tested the hypothesis that allele frequency variation in populations could be used as a tool to interrogate the biology of PCa.

MATERIALS AND METHODS

Study Population

Unrelated men of African descent (i.e., self-reported African Americans, Afro-Caribbean, African-Latino, East and West Africans) were recruited from the Washington, DC area through the Division of Urology at the Howard University Hospital and/or PCa screening at the Howard University Cancer Center. PCa cases were between 40 and 85 years of age. All the cases were diagnosed within 1 year of enrollment. The study population of African descent consisted of 266 PCa patients and 196 male controls. Unaffected male volunteers

were enrolled among individuals undergoing regular physical exams in the Division of Urology at Howard University Hospital and/or men participating in screening programs for PCa at the Howard University Cancer Center. The screening program was demographically similar to the patient population seen in the Division of Urology clinics. The recruitment of controls occurred concurrently with the recruitment of PCa patients. Blood samples were collected from each subject. Clinical characteristics including Gleason grade, prostate-specific antigen (PSA), and diagnosis of prostatitis were obtained from medical records. The mean age of cases (69 ± 9.7) was significantly greater than controls (57 ± 11.4). All control subjects had PSA levels <4.0 ng/ml and normal digital rectal exams. The clinical profile of the study population is shown in Table I. Individuals diagnosed with benign prostatic hyperplasia were not considered in this analysis ($n = 99$). PCa cases were diagnosed by transrectal ultrasound-guided biopsy using standard saturation technique. Biopsy cores were reviewed by members of the Department of Pathology Howard University College of Medicine. PCa cases were classified according to the well-established parameters of the Gleason Scoring System [52,53]. Howard University Institutional Review Board approved the study and written consent was obtained from all participants.

Genotyping

Genotyping of P72R of TP53 (rs1042522) was determined by PCR-restriction fragment length polymorphism (RFLP) methods. The PCR fragment was amplified using 5'-CTG TCC CCG GAC GAT ATT G-3' (forward) and p53 5'-AAT GCA AGA AGC CCA GAC G-3' (reverse) primers. The restriction enzyme *BSTU1* was used to discriminate the Arg allele from the Pro allele. The expected fragment sizes were as follows: the Arg allele, which is recognized by *BSTU1*, resulted in 131 and 82 bp bands, whereas the uncut Pro allele had a band at 213 bp; the heterozygote had all three bands. For quality control, 20% samples were repeated. The concordance was 98.9%.

Statistical Methods

Prior data indicate that the MAF if African Americans is 0.54. If the true odds ratio (OR) for disease in subjects with the G allele compared to subjects with the C allele is 1.8, we will be able to reject the null hypothesis that this OR equals 1.0 with probability (β -power) 0.83 in a study consisting of 266 cases and 189 control subjects. The type I error (α) probability associated with this test of the null hypothesis is 0.05. We used a continuity-corrected chi-squared statistic or Fisher's exact test to evaluate the null hypothesis.

The statistical analyses for the case-control study were done with the SAS/STAT® software, version 9.1 (SAS Institute, Inc., Cary, NC). Differences in subject characteristics were compared by the chi-square or Fisher's exact test for categorical values or by Student's *t*-test for continuous variables. Hardy-Weinberg equilibrium (HWE) was calculated using control subjects by comparing expected genotype frequencies to observed genotype frequencies using chi-square.

Unconditional logistic regression models were used to calculate ORs with 95% confidence intervals for genotypes to estimate the effect of the SNP presence on PCa risk controlling for age. Two-sided *P*-values ≤ 0.05 were considered as statistically significant. Participants with missing values were omitted from the analysis. Genetic modeling was performed using the statistical analysis package R (Lucent Technologies, Murray Hill, NJ).

Electronic Database Information

dbSNP: <http://www.ncbi.nlm.nih.gov/projects/SNP/> (for human SNP allele frequencies).

RESULTS

As seen in Table II, subjects were predominantly African American, which reflects the population served by the Howard University Hospital. Because men of non-African descent made up <5 (or 3% as listed below in the Discussion Section) of the either the case or control populations, they were included in overall the analysis. In this study set, controls tended to be younger than cases ($57.36 \pm \text{SD}$ vs. $65.58 \pm \text{SD}$; $P < 0.01$). The age range for cases and controls was 41–95 and 35–89, respectively. PSA was also significantly higher in PCa patients compared to controls ($P < 0.0001$).

In controls, genotypes were in HWE ($P = 0.63$). Allele and genotype distributions in all men are shown in Table III. Results of the chi-square analysis are also shown in Table III. Logistic regression was used to evaluate p53 SNP association with PCa risk. In the dominant model, CG/GG genotypes were significantly associated with PCa risk (OR = 1.53, 95% CI: 1.02–2.29; $P = 0.04$) and in the log-additive model, the OR was 1.33 (95% CI: 0.99–1.78; $P = 0.06$) with increasing number of G alleles. In the co-dominant model, the GG genotype was not significantly associated with PCa risk (OR = 1.61, 95% CI: 0.87–3.00; $P = 0.12$). Since in this population, older age was associated with increased risk of PCa ($P < 0.01$), ORs were also adjusted for age. After this adjustment, the dominant model only showed a marginally significant association with PCa (OR = 1.48, 95% CI: 0.95–2.31; $P = 0.08$). Furthermore, the log-additive model only showed a marginal association with PCa as well (OR = 1.30, 95% CI: 0.95–1.80; $P = 0.10$). Additionally, in the co-dominant model, the GG genotype was associated with increased risk of PCa (OR=1.57, 95% CI: 0.80–3.09), although not statistically significant ($P = 0.21$).

DISCUSSION

PCa is a common malignancy and a leading cause of cancer death among men in the United States. There are three well-established risk factors for PCa: age, ethnicity, and family history [54], but the molecular mechanisms underlying its development and progression remain poorly understood. With regard to ethnicity, the incidence of PCa among African American (AA) men is 60% higher and the mortality is approximately twofold higher compared to their European counterparts. To date, the mechanisms for increased risk of PCa, in this group, have yet to be elucidated. To determine if genetic susceptibility to PCa, a health disparity, was associated with common SNPs in the critical tumor suppressor gene, p53, we genotyped the P72A SNP (rs1042522) in a PCa case–control study of men at the Howard University Hospital. Because men of ethnicities other than of African descent (i.e., European, Hispanic/Latino, etc.) comprised <5% of our population and when limiting the analysis to men of African descent, similar ORs were observed, we present data that include all study individuals.

In this study of the p53 Pro72Arg SNP and risk for PCa, our results indicate that the G allele coding for Arg was found to be significantly associated with prevalence of PCa in our Howard University Hospital population of mostly men of African descent (97.2%). However, after adjusting for age, only marginal significance remained. To our knowledge, our study is the first to test the association of this p53 polymorphism and PCa in African American men. The p53 C allele frequency in this study was similar to previously published frequencies (0.63 vs. 0.67 and 0.54, this study, Yorubans, and African Americans, respectively) (<http://www.ncbi.nlm.nih.gov/projects/SNP/>). Specifically, we performed regression analysis of the data using several models to determine which allele was associated with PCa risk. The co-dominant and log-additive models revealed a non-significant association between the three p53 genotypes and PCa risk ($P = 0.12$ and 0.06 , respectively). However, the dominant model showed a significant association between the

CG and GG genotypes and PCa risk ($P = 0.04$). After adjusting for age, the dominant model's association between CG and GG genotypes became insignificant ($P = 0.08$). The other models also remained insignificant ($P = 0.21$ and 0.10 , co-dominant and log-additive models, respectively).

The rs1042522 p53 SNP appears to be related to changes in the efficiency and function of p53 [28–38]. For instance, Thut et al. [55] demonstrated that Pro has increased transcriptional transactivation activities resulting in induction of a higher level of G1 cell-cycle arrest. On the other hand, Dumont et al. [29] showed that Arg is associated with greater efficiency in the induction of apoptosis. Notably, Khoo et al. [56] revealed that the Arg residue denatures at high temperatures and has evolved to be less thermodynamically stable. Many have hypothesized that this allele was under selective pressure [5,36–38]. Shi et al. proposed that selection of the Arg allele could have provided selective advantage in populations living in cold climates by reducing implantation failure [57], providing a greater ability to induce cell-cycle arrest in response to low glucose concentrations [58], and by decreasing the rate of glycolysis [59]. Conversely, Khoo et al. [56] that thermodynamically stable Pro has been selected for, as in the case for populations of African descent, which allows for increased induction of p53 necessary for repair of oxidative damage. We speculate that exposure to parasitic infections such as malaria (*Plasmodium falciparum*) may have also acted as a selection factor as oxidative stress can also occur as a residual effect of fighting malarial infections [61].

Data on the association of this p53 SNP have been contradictory and inconclusive. Depending on the ethnicity of the population and the type of cancer being studied, both the Arg and the Pro alleles have both been found to be associated with increased cancer risk (Table I). However, this could be a function of the small sample sizes in most of the studies and is a limitation of our study as well. Another limitation is in the definition our eligibility criteria for our control group. We chose controls that had a PSA of ≤ 4.0 ng/ml and a negative DRE. In fact, PCa has been diagnosed in some men with a PSA level ≤ 4.0 ng/ml [62]. In addition, false negative DREs can occur. The inclusion criteria may have impacted our results negatively and may have resulted in the marginal associations found. Nevertheless, the association between rs1042522 and PCa should and will be pursued in larger follow-up studies given our marginal significance with an inclusion criteria that only includes men with the a PSA < 2.5 ng/ml in the control group.

In conclusion, we have examined the association between the p53 P72R polymorphism and PCa in a case–control study consisting predominantly of African American men. Our results indicate that the p53 polymorphism may be associated with PCa prevalence. Furthermore, given the environment-dependent function of the alleles, our results suggest that natural selection may have led to the preference of an allele advantageous in one environment, but disadvantageous in another environment. The present study demonstrates that population-dependent differences in allele frequencies associated with health disparities provide a valuable framework for the interrogation of complex diseases in all populations.

REFERENCES

1. Jin S, Levine AJ. The p53 functional circuit. *J Cell Sci* 2001;114:4139–4140. [PubMed: 11739646]
2. Read, AP.; Strachan, T. Cancer genetics. New York: Wiley; 1999. Human molecular genetics 2. Chapter 18.
3. Hollstein M, Sidransky D, Vogelstein B, Harris CC. p53 mutations in human cancers. *Science* 1991;253:49–53. [PubMed: 1905840]
4. Vousden KH, Lu X. Live or let die: The cell's response to p53. *Nat Rev Cancer* 2002;2:594–604. [PubMed: 12154352]

5. Sjalander A, Birgander R, Saha N, Beckman L, Beckman G. p53 polymorphisms and haplotypes show distinct differences between major ethnic groups. *Hum Hered* 1996;46:41–48. [PubMed: 8825462]
6. Weston A, Pan CF, Ksieski HB, Wallenstein S, Berkowitz GS, Tartter PI, Bleiweiss IJ, Brower ST, Senie RT, Wolff MS. p53 haplotype determination in breast cancer. *Cancer Epidemiol Biomarkers Prev* 1997;6:105–112. [PubMed: 9037561]
7. Papadakis ED, Soultz N, Spandidos DA. Association of p53 codon 72 polymorphism with advanced lung cancer: The Arg allele is preferentially retained in tumours arising in Arg/Pro germline heterozygotes. *Br J Cancer* 2002;87:1013–1018. [PubMed: 12434294]
8. Papadakis EN, Dokianakis DN, Spandidos DA. p53 codon 72 polymorphism as a risk factor in the development of breast cancer. *Mol Cell Biol Res Commun* 2000;3:389–392. [PubMed: 11032762]
9. Mechanic LE, Bowman ED, Welsh JA, Khan MA, Hagiwara N, Enewold L, Shields PG, Burdette L, Chanock S, Harris CC. Commongenetic variation in TP53 is associated with lung cancer risk and prognosis in African Americans and somatic mutations in lung tumors. *Cancer Epidemiol Biomarkers Prev* 2007;16:214–222. [PubMed: 17301252]
10. Klug SJ, Rensing M, Koenig J, Abba MC, Agorastos T, Brenna SM, Ciotti M, Das BR, Del MA, Dybikowska A, Giuliano AR, Gudleviciene Z, Gyllenstein U, Haws AL, Helland A, Herrington CS, Hildesheim A, Humbey O, Jee SH, Kim JW, Madeleine MM, Menczer J, Ngan HY, Nishikawa A, Niwa Y, Pegoraro R, Pillai MR, Ranzani G, Rezza G, Rosenthal AN, Roychoudhury S, Saranath D, Schmitt VM, Sengupta S, Settheetham-Ishida W, Shirasawa H, Snijders PJ, Stoler MH, Suarez-Rincon AE, Szarka K, Tachezy R, Ueda M, van der Zee AG, von Knebel DM, Wu MT, Yamashita T, Zehbe I, Blettner M. TP53 codon 72 polymorphism and cervical cancer: Apooled analysis of individual data from 49 studies. *Lancet Oncol* 2009;10:772–784. [PubMed: 19625214]
11. Ashton KA, Proietto A, Otton G, Symonds I, McEvoy M, Attia J, Gilbert M, Hamann U, Scott RJ. Polymorphisms in TP53 and MDM2 combined are associated with high grade endometrial cancer. *Gynecol Oncol* 2009;113:109–114. [PubMed: 19193430]
12. Mechanic LE, Marrogi AJ, Welsh JA, Bowman ED, Khan MA, Enewold L, Zheng YL, Chanock S, Shields PG, Harris CC. Polymorphisms in XPD and TP53 and mutation in human lung cancer. *Carcinogenesis* 2005;26:597–604. [PubMed: 15564288]
13. Matakidou A, Eisen T, Houlston RS. TP53 polymorphisms and lung cancer risk: A systematic review and meta-analysis. *Mutagenesis* 2003;18:377–385. [PubMed: 12840112]
14. Liu G, Miller DP, Zhou W, Thurston SW, Fan R, Xu LL, Lynch TJ, Wain JC, Su L, Christiani DC. Differential association of the codon 72 p53 and GSTM1 polymorphisms on histological subtype of non-small cell lung carcinoma. *Cancer Res* 2001;61:8718–8722. [PubMed: 11751390]
15. Miller DP, Liu G, De Vivo I, Lynch TJ, Wain JC, Su L, Christiani DC. Combinations of the variant genotypes of GSTP1, GSTM1, and p53 are associated with an increased lung cancer risk. *Cancer Res* 2002;62:2819–2823. [PubMed: 12019159]
16. Schabath MB, Wu X, Wei Q, Li G, Gu J, Spitz MR. Combined effects of the p53 and p73 polymorphisms on lung cancer risk. *Cancer Epidemiol Biomarkers Prev* 2006;15:158–161. [PubMed: 16434604]
17. Hong Y, Miao X, Zhang X, Ding F, Luo A, Guo Y, Tan W, Liu Z, Lin D. The role of P53 and MDM2 polymorphisms in the risk of esophageal squamous cell carcinoma. *Cancer Res* 2005;65:9582–9587. [PubMed: 16230424]
18. Fan R, Wu MT, Miller D, Wain JC, Kelsey KT, Wiencke JK, Christiani DC. The p53 codon 72 polymorphism and lung cancer risk. *Cancer Epidemiol Biomarkers Prev* 2000;9:1037–1042. [PubMed: 11045785]
19. Siddique MM, Balram C, Fiszer-Maliszewska L, Aggarwal A, Tan A, Tan P, Soo KC, Sabapathy K. Evidence for selective expression of the p53 codon 72 polymorphs: Implications in cancer development. *Cancer Epidemiol Biomarkers Prev* 2005;14:2245–2252. [PubMed: 16172238]
20. Tommiska J, Eerola H, Heinonen M, Salonen L, Kaare M, Tallila J, Ristimäki A, von Smitten K, Aittomäki K, Heikkilä P, Blomqvist C, Nevanlinna H. Breast cancer patients with p53 Pro72 homozygous genotype have a poorer survival. *Clin Cancer Res* 2005;11:5098–5103. [PubMed: 16033823]

21. Bonafe M, Ceccarelli C, Farabegoli F, Santini D, Taffurelli M, Barbi C, Marzi E, Trapassi C, Storci G, Olivieri F, Franceschi C. Retention of the p53 codon 72 arginine allele is associated with a reduction of disease-free and overall survival in arginine/proline heterozygous breast cancer patients. *Clin Cancer Res* 2003;9:4860–4864. [PubMed: 14581358]
22. Wang NM, Tsai CH, Yeh KT, Chen SJ, Chang JG. P53 codon 72Arg polymorphism is not a risk factor for carcinogenesis in the Chinese. *Int J Mol Med* 1999;4:249–252. [PubMed: 10425273]
23. Wang YC, Lee HS, Chen SK, Chang YY, Chen CY. Prognostic significance of p53 codon 72 polymorphism in lung carcinomas. *Eur J Cancer* 1999;35:226–230. [PubMed: 10448264]
24. Starinsky S, Figer A, Ben-Asher E, Geva R, Flex D, Fidler HH, Zidan J, Lancet D, Friedman E. Genotype–phenotype correlations in Israeli colorectal cancer patients. *Int J Cancer* 2005;114:58–73. [PubMed: 15523694]
25. Sullivan A, Syed N, Gasco M, Bergamaschi D, Trigianti G, Attard M, Hiller L, Farrell PJ, Smith P, Lu X, Crook T. Polymorphism in wild-type p53 modulates response to chemotherapy in vitro and in vivo. *Oncogene* 2004;23:3328–3337. [PubMed: 15077186]
26. Sakamuro D, Sabbatini P, White E, Prendergast GC. The polyproline region of p53 is required to activate apoptosis but not growth arrest. *Oncogene* 1997;15:887–898. [PubMed: 9285684]
27. Bergamaschi G, Merante S, Orlandi E, Galli A, Bernasconi P, Cazzola M. TP53 codon 72 polymorphism in patients with chronic myeloid leukemia. *Haematologica* 2004;89:868–869. [PubMed: 15257943]
28. Murphy ME. Polymorphic variants in the p53 pathway. *Cell Death Differ* 2006;13:916–920. [PubMed: 16557270]
29. Dumont P, Leu JI, Della PA III, George DL, Murphy M. The codon 72 polymorphic variants of p53 have markedly different apoptotic potential. *Nat Genet* 2003;33:357–365. [PubMed: 12567188]
30. Thomas M, Kalita A, Labrecque S, Pim D, Banks L, Matlashewski G. Two polymorphic variants of wild-type p53 differ biochemically and biologically. *Mol Cell Biol* 1999;19:1092–1100. [PubMed: 9891044]
31. Chipuk JE, Kuwana T, Bouchier-Hayes L, Droin NM, Newmeyer DD, Schuler M, Green DR. Direct activation of Bax by p53 mediates mitochondrial membrane permeabilization and apoptosis. *Science* 2004;303:1010–1014. [PubMed: 14963330]
32. Leu JI, Dumont P, Hafey M, Murphy ME, George DL. Mitochondrial p53 activates Bak and causes disruption of a Bak-Mcl1 complex. *Nat Cell Biol* 2004;6:443–450. [PubMed: 15077116]
33. Pim D, Banks L. p53 polymorphic variants at codon 72 exert different effects on cell cycle progression. *Int J Cancer* 2004;108:196–199. [PubMed: 14639602]
34. Siddique M, Sabapathy K. Trp53-dependent DNA-repair is affected by the codon 72 polymorphism. *Oncogene* 2006;25:3489–3500. [PubMed: 16462765]
35. Whibley C, Pharoah PD, Hollstein M. p53 polymorphisms: Cancer implications. *Nat Rev Cancer* 2009;9:95–107. [PubMed: 19165225]
36. Beckman G, Birgander R, Sjalander A, Saha N, Holmberg PA, Kivela A, Beckman L. Is p53 polymorphism maintained by natural selection? *Hum Hered* 1994;44:266–270. [PubMed: 7927355]
37. Birgander R, Sjalander A, Saha N, Spitsyn V, Beckman L, Beckman G. The codon 31 polymorphism of the p53-inducible gene p21 shows distinct differences between major ethnic groups. *Hum Hered* 1996;46:148–154. [PubMed: 8860009]
38. Shi H, Tan SJ, Zhong H, Hu W, Levine A, Xiao CJ, Peng Y, Qi XB, Shou WH, Ma RL, Li Y, Su B, Lu X. Winter temperature and UV are tightly linked to genetic changes in the p53 tumor suppressor pathway in Eastern Asia. *Am J Hum Genet* 2009;84:534–541. [PubMed: 19344876]
39. Ries, LAG.; Melbert, D.; Krapcho, M. SEER cancer statistics review. Bethesda, MD: National Cancer Institute; 2009.
40. Shepherd T, Tolbert D, Benedetti J, Macdonald J, Stemmermann G, Wiest J, DeVoe G, Miller MA, Wang J, Noffsinger A, Fenoglio-Preiser C. Alterations in exon 4 of the p53 gene in gastric carcinoma. *Gastroenterology* 2000;118:1039–1044. [PubMed: 10833478]

41. Pegoraro RJ, Rom L, Lanning PA, Moodley M, Naiker S, Moodley J. P53 codon 72 polymorphism and human papillomavirus type in relation to cervical cancer in South African women. *Int J Gynecol Cancer* 2002;12:383–388. [PubMed: 12144687]
42. Pegoraro RJ, Moodley M, Rom L, Chetty R, Moodley J. p53 codon 72 polymorphism and BRCA 1 and 2 mutations in ovarian epithelial malignancies in black South Africans. *Int J Gynecol Cancer* 2003;13:444–449. [PubMed: 12911720]
43. Katkoori VR, Jia X, Shanmugam C, Wan W, Meleth S, Bumpers H, Grizzle WE, Manne U. Prognostic significance of p53 codon 72 polymorphism differs with race in colorectal adenocarcinoma. *Clin Cancer Res* 2009;15:2406–2416. [PubMed: 19339276]
44. Wu WJ, Kakehi Y, Habuchi T, Kinoshita H, Ogawa O, Terachi T, Huang CH, Chiang CP, Yoshida O. Allelic frequency of p53 gene codon 72 polymorphism in urologic cancers. *Jpn J Cancer Res* 1995;86:730–736. [PubMed: 7559095]
45. Henner WD, Evans AJ, Hough KM, Harris EL, Lowe BA, Beer TM. Association of codon 72 polymorphism of p53 with lower prostate cancer risk. *Prostate* 2001;49:263–266. [PubMed: 11746272]
46. Suzuki K, Matsui H, Ohtake N, Nakata S, Takei T, Nakazato H, Okugi H, Koike H, Ono Y, Ito K, Kurokawa K, Yamanaka H. A p53 codon 72 polymorphism associated with prostate cancer development and progression in Japanese. *J Biomed Sci* 2003;10:430–435. [PubMed: 12824702]
47. Figer A, Friedman T, Manguoglu AE, Flex D, Vazina A, Novikov I, Shtrieker A, Sidi AA, Tichler T, Sapir EE, Baniel J, Friedman E. Analysis of polymorphic patterns in candidate genes in Israeli patients with prostate cancer. *Isr Med Assoc J* 2003;5:741–745. [PubMed: 14719475]
48. Huang SP, Wu WJ, Chang WS, Wu MT, Chen YY, Chen YJ, Yu CC, Wu TT, Lee YH, Huang JK, Huang CH. p53 codon 72 and p21 codon 31 polymorphisms in prostate cancer. *Cancer Epidemiol Biomarkers Prev* 2004;13:2217–2224. [PubMed: 15598783]
49. Quinones LA, Irrarrazabal CE, Rojas CR, Orellana CE, Acevedo C, Huidobro C, Varela NE, Caceres DD. Joint effect among p53, CYP1A1, GSTM1 polymorphism combinations and smoking on prostate cancer risk: An exploratory genotype-environment interaction study. *Asian J Androl* 2006;8:349–355. [PubMed: 16625286]
50. Hirata H, Hinoda Y, Tanaka Y, Okayama N, Suehiro Y, Kawamoto K, Kikuno N, Majid S, Vejdani K, Dahiya R. Polymorphisms of DNA repair genes are risk factors for prostate cancer. *Eur J Cancer* 2007;43:231–237. [PubMed: 17196815]
51. Huang SP, Huang CY, Wang JS, Liu CC, Pu YS, Yu HJ, Yu CC, Wu TT, Huang CH, Wu WJ, Chou YH, Wu MT. Prognostic significance of p53 and X-ray repair cross-complementing group 1 polymorphisms on prostate-specific antigen recurrence in prostate cancer post radical prostatectomy. *Clin Cancer Res* 2007;13:6632–6638. [PubMed: 18006764]
52. Freedland SJ, Isaacs WB, Mangold LA, Yiu SK, Grubb KA, Partin AW, Epstein JI, Walsh PC, Platz EA. Stronger association between obesity and biochemical progression after radical prostatectomy among men treated in the last 10 years. *Clin Cancer Res* 2005;11:2883–2888. [PubMed: 15837737]
53. Platz EA, Rohrmann S, Pearson JD, Corrada MM, Watson DJ, De Marzo AM, Landis PK, Metter EJ, Carter HB. Nonsteroidal anti-inflammatory drugs and risk of prostate cancer in the Baltimore Longitudinal Study of Aging. *Cancer Epidemiol Biomarkers Prev* 2005;14:390–396. [PubMed: 15734963]
54. Rodriguez C, Calle EE, Miracle-McMahill HL, Tatham LM, Wingo PA, Thun MJ, Heath CW Jr. Family history and risk of fatal prostate cancer. *Epidemiology* 1997;8:653–657. [PubMed: 9345665]
55. Thut CJ, Chen JL, Klemm R, Tjian R. p53 transcriptional activation mediated by coactivators TAFII40 and TAFII60. *Science* 1995;267:100–104. [PubMed: 7809597]
56. Khoo KH, Andreeva A, Fersht AR. Adaptive evolution of p53 thermodynamic stability. *J Mol Biol* 2009;393:161–175. [PubMed: 19683006]
57. Hu W, Feng Z, Teresky AK, Levine AJ. p53 regulates maternal reproduction through LIF. *Nature* 2007;450:721–724. [PubMed: 18046411]

58. Jones RG, Plas DR, Kubek S, Buzzai M, Mu J, Xu Y, Birnbaum MJ, Thompson CB. AMP-activated protein kinase induces a p53-dependent metabolic checkpoint. *Mol Cell* 2005;18:283–293. [PubMed: 15866171]
59. Bensaad K, Tsuruta A, Selak MA, Vidal MN, Nakano K, Bartrons R, Gottlieb E, Vousden KH. TIGAR, a p53-inducible regulator of glycolysis and apoptosis. *Cell* 2006;126:107–120. [PubMed: 16839880]
60. Shigenaga MK, Gimeno CJ, Ames BN. Urinary 8-hydroxy-2'-deoxyguanosine as a biological marker of in vivo oxidative DNA damage. *Proc Natl Acad Sci USA* 1989;86:9697–9701. [PubMed: 2602371]
61. Postma NS, Mommers EC, Eling WM, Zuidema J. Oxidative stress in malaria; implications for prevention and therapy. *Pharm World Sci* 1996;18:121–129. [PubMed: 8873227]
62. Thompson IM, Pauler DK, Goodman PJ, Tangen CM, Lucia MS, Parnes HL, Minasian LM, Ford LG, Lippman SM, Crawford ED, Crowley JJ, Coltman CA Jr. Prevalence of prostate cancer among men with a prostate-specific antigen level ≤ 4.0 ng per milliliter. *N Engl J Med* 2004;350:2239–2246. [PubMed: 15163773]
63. Wu HC, Chang CH, Chen HY, Tsai FJ, Tsai JJ, Chen WC. p53 gene codon 72 polymorphism but not tumor necrosis factor- α gene is associated with prostate cancer. *Urol Int* 2004;73:41–46. [PubMed: 15263792]

TABLE I

Association of p53 Codon 72 Polymorphism With Prostate and Other Cancers

Refs.	Association with PCa	Allele	Population	Cases/controls
Wu et al. [44]	—	Pro	Japanese	28/56
Henner et al. [45]	0.23 (0.07–0.79)	Pro	US men (>Caucasian)	115/181
Suzuki et al. [46]	2.80 (1.04–7.53)	Pro	Japanese	114/105
Figer et al. [47]	—	Pro	Jewish Israeli men	224 cases
Huang et al. [48]	—	Pro	Taiwanese	200/247
Wu et al. [63]	2.6 (1.0–6.45)	Pro	Taiwanese	96/126
Quinones et al. [49]	+	Pro	Chile	
Hirata et al. [50]	+	Pro	Japanese	167/167
Huang et al. [51]	+	Arg	Taiwanese	126 cases
Refs.	Other cancer	Allele	Population	Cases/controls
Shepherd et al. [40]	+Antral cancer	Pro	US men (>Caucasian)	217 cases
Pegoraro et al. [41]	+Ovarian	Arg	Black South Africans	281/340
Pegoraro et al. [42]	+Ovarian	Arg	Black South Africans	75/340
Mechanic et al. [9]	+Lung cancer	Pro	US men (>Caucasian)	443/547
Klug et al. [10]	+Cervical cancer	Arg	All pops	7946/7888
Katkoori et al. [43]	+Colon cancer	Pro	US men (>Caucasian)	137 AAs, 236 Caucasians (cases)

TABLE II

Characteristics of Howard University Hospital Prostate Cancer Cases and Controls

	Controls	Cases	Total	P-value
Number of subjects	189 (34.11%)	266 (48%)	455	
Average age (mean $\pm$ SD)	57.355 ($\pm$ SD)	65.58 ($\pm$ SD)		<0.01
Age range (years)	35–89	41–95		
Average PSA (mean $\pm$ SD)	3.11 $\pm$ 12.18	85.01 $\pm$ 391.58		<0.0001
Ethnicity				
African descent	187 (33.75%)	257 (46.39%)	444 (97.6%)	
Non-African descent	2 (0.3%)	9 (1.62%)	11 (2.4%)	

TABLE III

Association Between p53 Codon 72 Polymorphism and Prostate Cancer

Genotypes (all ethnicities)	Controls	%	Cases	%	OR	Lower 95% CI	Upper 95% CI	P-value	OR ^a	Lower 95% CI	Upper 95% CI	P-value
HWE (<i>P</i>)	0.63		0.06									
C allele	226	0.63	281	0.57	1.00							
G allele	130	0.37	209	0.43	1.29	0.97	1.71	0.08				
CC	70	0.39	73	0.30	1.00				1.00			
CG	86	0.48	135	0.55	1.51	0.98	2.30		1.46	0.92	2.32	
GG	22	0.12	37	0.15	1.61	0.87	3.00	0.12	1.57	0.80	3.09	0.21
Co-dominant												
Dominant	108	0.61	172	11,720	1.53	1.02	2.29	0.04	1.48	0.95	2.31	0.08
Log-additive	178	0.42	245	0.58	1.33	0.99	1.78	0.06	1.30	0.95	1.80	0.10

^a Adjusted for age.