Published in final edited form as:
Prostate. 2010 May 1; 70(6): 646–653. doi:10.1002/pros.21098.

Association of *CASP8 D302H* Polymorphism with Reduced Risk of Aggressive Prostate Carcinoma

Jessica Lubahn[1], **Sonja I. Berndt**[5], **Carol H. Jin**[2], **Aleksandra Klim**[1], **Jason Luly**[1], **William S. Wu**[1], **Sarah Isaacs**[6], **Kathleen Wiley**[6], **William B. Isaacs**[6], **Brian K. Suarez**[2,3,4], **Richard B. Hayes**[5], and **Adam S. Kibel**[1,3,4]

[1] Department of Surgery, Washington University School of Medicine, St. Louis MO

[2] Department of Psychiatry, Washington University School of Medicine, St. Louis MO

[3] Department of Genetics, Washington University School of Medicine, St. Louis MO

[4] Alvin J. Siteman Cancer Center, Washington University School of Medicine, St. Louis MO

[5] Division of Epidemiology, Department of Environmental Medicine, New York University Langone Medical Center, NY NY, 10016

[6] Department of Urology, Johns Hopkins Medical Institutions, Baltimore, MD

Abstract

BACKGROUND—Because of the dramatically different clinical course of aggressive and indolent prostate carcinoma (PCa), markers that distinguish between these phenotypes are of critical importance. Apoptosis is an important protective mechanism for unrestrained cellular growth and metastasis. Therefore, dysfunction in this pathway is a key step in cancer progression. As such, genetic variants in apoptosis genes are potential markers of aggressive PCa. Recent work in breast carcinoma has implicated the histidine variant of CASP8 D302H (rs1045485) as a protective risk allele.

METHODS—We tested the hypothesis that the Hvariant was protective for aggressive PCa in a pooled analysis of 796 aggressive cases and 2,060 controls. RESULTS. The H allele was associated with a reduced risk of aggressive PCa (ORper allele = 0.67, 95% CI: 0.54–0.83, Ptrend = 0.0003). The results were similar for European-Americans (ORper allele = 0.68; 95% CI: 0.54–0.86) and African-Americans (ORper allele = 0.61; 95% CI: 0.34–1.10). We further determined from the full series of 1,160 cases and 1,166 controls in the Prostate, Lung, Colorectal, Ovarian (PLCO) population that the protective effect of the H allele tended to be limited to high-grade and advanced PCa (all cases ORper allele = 0.94; 95% CI: 0.79–1.11; localized, low-grade disease ORper allele = 0.98; 95% CI: 0.79–1.23; and aggressive disease ORper allele = 0.73; 95% CI: 0.50–1.07).

CONCLUSION—These results suggest that histidine variant of CASP8 D302H is a protective allele for aggressive PCa with potential utility for identification of patients at differential risk for this clinically significant phenotype.

Keywords

Prostate Carcinoma; Apoptosis; Risk Assessment; Cancer Susceptibility; Metastatic Disease

Correspondence to: Adam S. Kibel.

INTRODUCTION

Multiple polymorphic variants have been associated with prostate cancer risk [1–5]. With an estimated 186,320 cases and 28,660 deaths from prostate cancer (PCa) in 2008 [6], identification of men at increased risk for the disease has the potential to profoundly affect management. However, since many patients are diagnosed with PCa unlikely to result in mortality from the disease [7,8] and could possibly be managed without aggressive therapy [9], markers that correlate with disease aggressiveness would be of great clinical utility. Few candidate genetic markers of aggressive PCa have been identified, with recent work implicating regions of 8q24 and 10q11 [3,10]. Apoptosis or programmed cell death is an important protective mechanism for unrestrained cellular growth and metastasis. Since the unrestrained growth characteristic of cancer commonly triggers apoptotic cell death, there is a clear survival advantage for the advanced cancer cell that can protect itself from apoptosis. Caspase 8 (CASP8 or FLICE) functions centrally in the apoptic pathway. Apoptotic signal transduction is initiated by death receptors. Activation leads to aggregation of death effector domain (DED) proteins, such as FADD, which in turn activate downstream caspases such as CASP8 and CASP10 by proteolytic cleavage. This results in activation of executioner caspases, such as caspase 3 and subsequent cell death by proteolysis of multiple substrates [11,12]. Importantly, other DED-containing proteins such as c-FLIP inhibit apoptosis by binding CASP8 [13,14]. As such, caspases in general and caspase 8 specifically play a central role in determining if a cell undergoes apoptosis or not [15].

The role of CASP8 variants as a cancer susceptibility locus has recently been explored by Sun et al. [16] They examined a 6-bp deletion polymorphism (652 6N del) in the promoter of the CASP8 gene studied in 4,995 Chinese cancer patients and 4,972 controls. The variant was associated with multiple non-prostate cancers, including lung, esophageal, gastric, colorectal, cervical, and breast cancers. A follow-up study by Haiman et al. [17] examined 2,825 prostate cancer cases and 2,548 controls and failed to demonstrate an association between the deletion polymorphism and PCa in the Multiethnic Cohort Study. A second variant in CASP8 gene (D302H, rs1045485), which is in weak linkage disequilibrium with the deletion polymorphism (r2=0.19) [18], has been previously associated with a reduced risk of breast cancer. MacPherson et al. examined polymorphic variants of DR4, CASP8, and CASP10 in a population of 999 breast cancer cases and 996 controls and validated their findings in a second, independent population of 2,192 breast cancer cases and 2,262 controls. The CASP8 D302H variant was the only variant associated with a reduced risk of breast cancer in both cohorts [19]. A second study incorporated data from 14 separate studies encompassing 16,423 breast cancer cases and 17,109 controls and demonstrated a similar statistically significant risk reduction in breast cancer risk for the histidine variant [20].

Our interest was to determine if this variant was related to aggressive prostate cancer, in materials from two case control studies of aggressive prostate cancer at Washington University and Johns Hopkins University and in aggressive cases of this disease identified in the Prostate, Lung, Colorectal, Ovarian (PLCO) Cancer Screening Trial. Because the PLCO trial identified a spectrum of prostate cancer cases, we could also evaluate the association of CASP8 gene D302H with non-aggressive disease.

MATERIALS AND METHODS

Patient Populations

The Washington University (WU) cases consisted of 185 European-American (EA) patients and 73 African-Americans (AA) with aggressive PCa recruited from the St. Louis metropolitan area. Criteria for case selection in the WU population were as follows: patient

must (1) be receiving androgen ablation therapy for PCa and (2) have either pathologic or radiologic evidence of metastasis or a PSA of greater than 50 ng/ml. These criteria were designed to ensure that all patients had clinically significant PCa. The average age at diagnosis was 64.7 (±9.3) years. Criteria for enrollment: 33 (12.8%) patients had PSA greater than 50 ng/ml with no evidence of metastasis, 111 (43.0%) had metastatic disease, and 114 (43.8%) had androgen-independent metastatic disease of which 20 eventually (10.8%) progressed to death during follow-up. The control group consisted of 236 EA males and 206 AA males all from the St. Louis metropolitan area. The criteria for the control population were age > 75 years for EA and > 65 years for AA with no history of PCa, PSA <4.0 ng/ml, and a benign digital rectal examination. These criteria were designed so that controls were at minimal risk of developing clinically important PCa. The average age of the control population was 75.4 [±5.8] years.

The cases from the Johns Hopkins University (JHU) consisted of 305 EA and 79 AA patients with advanced PCa recruited from the Baltimore metropolitan area. Criteria for case selection in the JHU population were either pathologic or radiologic evidence of metastatic disease, a PSA of greater than 50 ng/ml, or a Gleason score of 8–10. Again, the criteria were designed to ensure that all patients had clinically significant PCa. The average age at diagnosis was 60.8 (±7.4) years. Criteria for enrollment; 88 (48.9%) had Gleason sum 8–10 cancer, 39 (10.2%) had PSA greater than 50 ng/ml, and 257 (66.9%) had metastatic disease. Two hundred eighty-six (74.5%) were treated with curative intent of which 206 (72.0%) progressed to metastatic disease. The control group consisted of 305 EA and 158 AA all from the Baltimore metropolitan area. Controls were matched 1:1 to cases for EA and 2:1 for AA by age and ethnicity. Controls had no history of PCa, PSA less than 4.0 ng/ml, and a benign digital rectal examination. These criteria were designed so that controls were at minimal risk of having clinically important PCa at the time of enrollment. The average age in the matched control population was 60.9 (±7.8) years.

The PLCO Cancer Screening Trial is described previously [21]. Between 1993 and 2001, over 150,000 men and women aged 55–74 years were recruited from 10 centers in the United States to participate in the PLCO Cancer Screening Trial, a randomized trial to evaluate screening methods for the early detection of cancer. Men randomized to the screening arm of the trial receive PSA screening and digital rectal exam annually. As described elsewhere [5], 1,163 EA PCa cases and 1,167 matched EA controls were selected from the screening arm of the trial for a genome-wide association study of prostate cancer (CGEMS). Unlike the previous cohorts, no data on metastasis were available. For our evaluation of aggressive prostate cancer risk, we limited cases to the 163 patients with Gleason 7–10 and Stage cT3–4 at the time of diagnosis. Again, criteria were designed to ensure that all patients had clinically significant PCa. Controls consisted of men without a diagnosis of prostate cancer and matched to the larger set of cases on age, year of randomization, and study year of the trial. The average age of the controls was 66.1 (±5.5) years.

In order to determine if variant was a general risk allele or associated with risk of aggressive disease, subsets by Gleason grade and stage were selected from the PLCO cohort for additional analysis: Gleason <7 AND Stage cT1–2 [n = 472]; Gleason 7–10 or Stage cT3–4 [n = 688]; Gleason 8–10 OR Stage cT3–4 [n = 314]; Gleason 7–10 AND Stage cT3–4 [n = 163], and Gleason 8–10 AND Stage cT3–4 (n = 47).

Table I outlines clinical data at time of diagnosis, initial treatment, and progression for all subjects. All study subjects in all three cohorts provided informed consent under a protocol approved by Institutional Review Board.

Genotyping

For WU and JHU populations, genomic DNA was prepared from peripheral blood leukocytes. Pyrosequencing TM assays were designed and performed as per manufacturer's recommendations using a forward primer 50-AATTTCACTTTTCAGGGGCTTTG-30, biotin-labeled reverse primer 50-TACTGTGGTCCATGAGTTGGTAGA-30 and internal sequencing primer 50-TTGCTCTACTGTGCAGTC-30. All samples were visually reviewed blinded to phenotype to confirm results. The assay was repeated in 10% of samples to confirm results. In the WUcohort, 254 patients and 441 controls had valid genotyping data. In the Johns Hopkins Cohort, 379 patients and 453 controls had valid genotyping data.

The PLCO population was genotyped using the Illumina HumanHap300 and HumanHap240 platforms as part of the Cancer Genetic Markers of Susceptibility (CGEMS) prostate cancer genome-wide association scan. The D302H genotype was imputed using the observed genotypes from the genome-wide scan and the HapMap CEPHEuropean reference panel with the MACH imputation program (http://sph.umich.edu/csg/abecasis/MACH/). The quality control r2 for the imputation of the polymorphism was 0.996. Of the PLCO subjects, 1,160 cases and 1,166 controls had valid genotype data. In total, genotype data were available for 796 aggressive prostate cancer cases and 2,060 controls.

Statistical Analysis

Allele frequencies between cases and controls were tested using a proportion test. Deviations from Hardy– Weinberg proportions were assessed for controls by ethnicity using a chi-square test with 1 degree of freedom or exact test (if cell counts were small). No significant deviations from Hardy–Weinberg proportions were observed (P>0.05) for either EA or AA. Odds ratios (OR) and 95% confidence intervals (95% CIs) were calculated using logistic regression, adjusting for age, race, and study as appropriate in SAS 8.2 (SAS Institute, Inc., Cary, NC).

RESULTS

The pooled analysis (Table II) of all aggressive cases (n=796 cases) and controls (n=2,060) controlling for age, race, and study demonstrated a strong protective effect for aggressive PCa for the H allele (ORper allele=0.67, 95% CI: 0.54–0.83, Ptrend=0.0003). The association was statistically significant in EA population (ORper allele=0.68, 95% CI: 0.54–0.86, Ptrend=0.001), with similar patterns of risk for African-Americans (ORper allele=0.61, 95% CI: 0.34–1.10, Ptrend=0.10) and across the three studies (WU: ORper allele=0.52, 95% CI: 0.30–0.89, Ptrend=0.02; JHU: ORper allele=0.71, 95% CI: 0.51–0.97, Ptrend=0.03; PLCO: ORper allele=0.73, 95% CI: 0.50–1.07, Ptrend=0.11).

To determine if the association was limited to patients with aggressive prostate cancer or was a general risk allele for prostate cancer, analysis of the entire PLCO population (1,160 EA patients and 1,166 controls) were carried out, with consideration for cases of the spectrum of Gleason sum and stage (Table III). CASP 302H was not associated with PCa overall (ORper allele=0.94, 95% CI: 0.79–1.11, Ptrend=0.46), nor was any association noted for localized and low grade disease (Gleason sum <7 AND Stage cT1–2): ORper allele=0.98, 95% CI: 0.79–1.23, Ptrend=0.88); only with cases exhibiting either high-grade histology (Gleason sum 8–10) or clinically advanced disease (Stage cT3–4) was there a tendency toward a protective association. While not statistically significant these results were consistent with the statistically significant patterns shown for aggressive disease in Table II.

DISCUSSION

Our pooled analysis of three independent series of aggressive prostate cancer and controls demonstrates that the histidine allele of CASP8 D302H is associated with a decreased risk of aggressive PCa. Our analysis of PLCO cases and controls shows no evidence that this allele is associated with protection from indolent disease, supporting the hypothesis that the protective effect is not important in patients with indolent disease.

Increasing evidence points to an overdiagnosis of indolent PCa defined as cancer unlikely to cause harm. Studies examining surgical specimens have estimated that between 6% and 27% of patients undergoing radical prostatectomy have tumors similar to the tumors identified incidentally at autopsy [22,23]. While surgery has clearly altered the natural history of the disease, it is believed that many of these tumors were of no clinical significance. Clinical data from both the United States and Europe support this conclusion. Etzioni et al. [8] and Draisma et al. [7] used mathematical models to analyze PSA screening data and estimated the risk of over-detection was 18–66%. As such markers which indicate a patient's risk of developing aggressive disease would have clear clinical utility by identify patients which might benefit from aggressive screening or treatment.

While upwards of 42% of prostate cancer risk is attributed to heritable factors [24], the majority of genetic risk factors identified to date have been for general risk [1–5], not risk specifically associated with aggressive disease. Zheng et al. [25] examined 16 previously implicated variants and found a strong association between five SNPs and prostate cancer risk ($P=1.29\times10^{-8}$); importantly, none were linked to risk of aggressive PCa defined similarly to our study as spread to nearby lymph nodes and metastasis, a Gleason score of 8 or more, or a PSA level of more than 50 ng/ml. A meta-analysis of the 8q24 region recently demonstrated an association with advanced disease, using a somewhat wider definition of aggressive disease (Gleason sum _7, PSA >10 ng/ml, and stage >T2c) [10].

Haiman et al. [17] did not find a statistically significant association between a 6-bp deletion polymorphism (−652 6N del) in the promoter of the CASP8 gene and prostate cancer; however, the per allele OR approached statistical significance in Caucasians (OR=0.83; 95% CI: 0.68–1.01) and results for aggressive cases were not reported. MacPherson et al. demonstrated a reduction in breast cancer risk associated with this polymorphism (OR=0.83, 95% CI: 0.74–0.94 for DH and OR=0.58, 95% CI: 0.39–0.88 for HH). A second confirmatory breast cancer study determined a similar protective effect (OR=0.89, 95% CI: 0.85–0.94 for DH and OR=0.74, 95% CI: 0.62–0.87 for HH) [20]. In contrast, no association was found in a recent study of colorectal cancer [18].

The mechanism by which the D302H variant or another variant in linkage disequilibrium protects against aggressive prostate cancer is unknown. It may alter the ability of CASP8 to activate executioner caspases and therefore increase the likelihood that malignant cells undergo apoptosis. A second possibility is that the decreased risk is mediated through the immune system. The characterization of immunomodulatory genes associated with inherited susceptibility to prostate cancer [26], epidemiologic links between prostatitis and prostate cancer [27], and histologic evidence of inflammation in preneoplastic lesions [28] suggest that inflammation contributes to the development of prostate cancer [29]. Caspases are responsible for aspects of inflammation and immune cell death [15] and other genetic variants in CASP8 result in a blunted immune response to tumor cell antigens [16]. A third hypothesis is that the variants effect may be related to steroid signaling, as CASP8 directly interacts with the androgen receptor (AR) and inhibits AR-dependent gene expression [30]. Furthermore, the fact that this polymorphism has been implicated in breast and prostate

cancer, but not in colorectal carcinoma, lends some credence to hypothesis that CASP8 may affect risk by interacting with the hormonal axis.

In summary, our results in three independent series indicate that the H allele of the CASP8 D302H polymorphism is associated with reduced risk for aggressive prostate cancer and is unassociated with less aggressive forms of the disease.

Acknowledgments

This work was supported by NCI - R01CA112028, R21CA098020, the St. Louis Men's Group Against Cancer, and the Intramural Research Program of the Division of Cancer Epidemiology and Genetics, National Cancer Institute, NIH

This work was supported by NCI (R01CA112028, R21CA098020), the St. Louis Men's Group Against Cancer, the Intramural Research Program of the Division of Cancer Epidemiology and Genetics, National Cancer Institute, NIH, and Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial.

References

1. 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, et al. Multiple newly identified loci associated with prostate cancer susceptibility. Nat Genet. 2008
2. Gudmundsson J, Sulem P, Rafnar T, Bergthorsson JT, Manolescu A, Gudbjartsson D, Agnarsson BA, Sigurdsson A, Benediktsdottir KR, Blondal T, Jakobsdottir M, Stacey SN, et al. Common sequence variants on 2p15 and Xp11.22 confer susceptibility to prostate cancer. Nat Genet. 2008
3. Thomas G, Jacobs KB, Yeager M, Kraft P, Wacholder S, Orr N, Yu K, Chatterjee N, Welch R, Hutchinson A, Crenshaw A, Cancel-Tassin G, et al. Multiple loci identified in a genome-wide association study of prostate cancer. Nat Genet. 2008
4. Amundadottir LT, Sulem P, Gudmundsson J, Helgason A, Baker A, Agnarsson BA, Sigurdsson A, Benediktsdottir KR, Cazier JB, Sainz J, Jakobsdottir M, Kostic J, et al. A common variant associated with prostate cancer in European and African populations. Nat Genet. 2006; 38:652–8. [PubMed: 16682969]
5. Yeager M, Orr N, Hayes RB, Jacobs KB, Kraft P, Wacholder S, Minichiello MJ, Fearnhead P, Yu K, Chatterjee N, Wang Z, Welch R, et al. Genome-wide association study of prostate cancer identifies a second risk locus at 8q24. Nat Genet. 2007; 39:645–9. [PubMed: 17401363]
6. Jemal A, Siegel R, Ward E, Hao Y, Xu J, Murray T, Thun MJ. Cancer statistics, 2008. CA Cancer J Clin. 2008; 58:71–96. [PubMed: 18287387]
7. Draisma G, Etzioni R, Tsodikov A, Mariotto A, Wever E, Gulati R, Feuer E, de Koning H. Lead time and overdiagnosis in prostate-specific antigen screening: importance of methods and context. J Natl Cancer Inst. 2009; 101:374–83. [PubMed: 19276453]
8. Etzioni R, Penson DF, Legler JM, di Tommaso D, Boer R, Gann PH, Feuer EJ. Overdiagnosis due to prostate-specific antigen screening: lessons from U.S. prostate cancer incidence trends. J Natl Cancer Inst. 2002; 94:981–90. [PubMed: 12096083]
9. Dall'era MA, Cooperberg MR, Chan JM, Davies BJ, Albertsen PC, Klotz LH, Warlick CA, Holmberg L, Bailey DE Jr, Wallace ME, Kantoff PW, Carroll PR. Active surveillance for early-stage prostate cancer: review of the current literature. Cancer. 2008
10. Cheng I, Plummer SJ, Jorgenson E, Liu X, Rybicki BA, Casey G, Witte JS. 8q24 and prostate cancer: association with advanced disease and meta-analysis. Eur J Hum Genet. 2008; 16:496–505. [PubMed: 18231127]
11. Zimmermann KC, Bonzon C, Green DR. The machinery of programmed cell death. Pharmacology & therapeutics. 2001; 92:57–70. [PubMed: 11750036]
12. Degterev A, Yuan J. Expansion and evolution of cell death programmes. Nat Rev Mol Cell Biol. 2008; 9:378–90. [PubMed: 18414491]
13. Budd RC, Yeh WC, Tschopp J. cFLIP regulation of lymphocyte activation and development. Nature reviews. 2006; 6:196–204.

14. Condorelli G, Vigliotta G, Cafieri A, Trencia A, Andalo P, Oriente F, Miele C, Caruso M, Formisano P, Beguinot F. PED/PEA-15: an anti-apoptotic molecule that regulates FAS/TNFR1-induced apoptosis. Oncogene. 1999; 18:4409–15. [PubMed: 10442631]
15. Siegel RM. Caspases at the crossroads of immune-cell life and death. Nature reviews. 2006; 6:308–17.
16. Sun T, Gao Y, Tan W, Ma S, Shi Y, Yao J, Guo Y, Yang M, Zhang X, Zhang Q, Zeng C, Lin D. A six-nucleotide insertion-deletion polymorphism in the CASP8 promoter is associated with susceptibility to multiple cancers. Nat Genet. 2007; 39:605–13. [PubMed: 17450141]
17. Haiman CA, Garcia RR, Kolonel LN, Henderson BE, Wu AH, Le Marchand L. A promoter polymorphism in the CASP8 gene is not associated with cancer risk. Nat Genet. 2008; 40:259–60. author reply 60-1. [PubMed: 18305469]
18. Pittman AM, Broderick P, Sullivan K, Fielding S, Webb E, Penegar S, Tomlinson I, Houlston RS. CASP8 variants D302H and −652 6N ins/del do not influence the risk of colorectal cancer in the United Kingdom population. Br J Cancer. 2008; 98:1434–6. [PubMed: 18362937]
19. Cox A, Dunning AM, Garcia-Closas M, Balasubramanian S, Reed MW, Pooley KA, Scollen S, Baynes C, Ponder BA, Chanock S, Lissowska J, Brinton L, et al. A common coding variant in CASP8 is associated with breast cancer risk. Nat Genet. 2007; 39:352–8. [PubMed: 17293864]
20. MacPherson G, Healey CS, Teare MD, Balasubramanian SP, Reed MW, Pharoah PD, Ponder BA, Meuth M, Bhattacharyya NP, Cox A. Association of a common variant of the CASP8 gene with reduced risk of breast cancer. J Natl Cancer Inst. 2004; 96:1866–9. [PubMed: 15601643]
21. Prorok PC, Andriole GL, Bresalier RS, Buys SS, Chia D, Crawford ED, Fogel R, Gelmann EP, Gilbert F, Hasson MA, Hayes RB, Johnson CC, et al. Design of the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial. Control Clin Trials. 2000; 21:273S–309S. [PubMed: 11189684]
22. Humphrey PA, Keetch DW, Smith DS, Shepherd DL, Catalona WJ. Prospective characterization of pathological features of prostatic carcinomas detected via serum prostate specific antigen based screening. J Urol. 1996; 155:816–20. [PubMed: 8583583]
23. Epstein JI, Walsh PC, Carmichael M, Brendler CB. Pathologic and clinical findings to predict tumor extent of nonpalpable (stage T1c) prostate cancer. Jama. 1994; 271:368–74. [PubMed: 7506797]
24. Lichtenstein P, Holm NV, Verkasalo PK, Iliadou A, Kaprio J, Koskenvuo M, Pukkala E, Skytthe A, Hemminki K. Environmental and heritable factors in the causation of cancer--analyses of cohorts of twins from Sweden, Denmark, and Finland. N Engl J Med. 2000; 343:78–85. [PubMed: 10891514]
25. Zheng SL, Sun J, Wiklund F, Smith S, Stattin P, Li G, Adami HO, Hsu FC, Zhu Y, Balter K, Kader AK, Turner AR, et al. Cumulative Association of Five Genetic Variants with Prostate Cancer. N Engl J Med. 2008
26. Albertsen PC, Hanley JA, Fine J. 20-year outcomes following conservative management of clinically localized prostate cancer. Jama. 2005; 293:2095–101. [PubMed: 15870412]
27. Roehl KA, Han M, Ramos CG, Antenor JA, Catalona WJ. Cancer progression and survival rates following anatomical radical retropubic prostatectomy in 3,478 consecutive patients: long-term results. J Urol. 2004; 172:910–4. [PubMed: 15310996]
28. Bill-Axelson A, Holmberg L, Filen F, Ruutu M, Garmo H, Busch C, Nordling S, Haggman M, Andersson SO, Bratell S, Spangberg A, Palmgren J, et al. Radical prostatectomy versus watchful waiting in localized prostate cancer: the Scandinavian prostate cancer group-4 randomized trial. J Natl Cancer Inst. 2008; 100:1144–54. [PubMed: 18695132]
29. Carpten J, Nupponen N, Isaacs S, Sood R, Robbins C, Xu J, Faruque M, Moses T, Ewing C, Gillanders E, Hu P, Bujnovszky P, et al. Germline mutations in the ribonuclease L gene in families showing linkage with HPC1. Nat Genet. 2002; 30:181–4. [PubMed: 11799394]
30. Sarma AV, McLaughlin JC, Wallner LP, Dunn RL, Cooney KA, Schottenfeld D, Montie JE, Wei JT. Sexual behavior, sexually transmitted diseases and prostatitis: the risk of prostate cancer in black men. J Urol. 2006; 176:1108–13. [PubMed: 16890703]

31. De Marzo AM, Marchi VL, Epstein JI, Nelson WG. Proliferative inflammatory atrophy of the prostate: implications for prostatic carcinogenesis. Am J Pathol. 1999; 155:1985–92. [PubMed: 10595928]

32. Nelson WG, De Marzo AM, Isaacs WB. Prostate cancer. N Engl J Med. 2003; 349:366–81. [PubMed: 12878745]

33. Qi W, Wu H, Yang L, Boyd DD, Wang Z. A novel function of caspase-8 in the regulation of androgen-receptor-driven gene expression. Embo J. 2007; 26:65–75. [PubMed: 17170703]

Prostate. Author manuscript; available in PMC 2011 May 1.

Table 1

Baseline and clinical characteristics of the aggressive prostate cancer cases*

		Washington University (N = 258)	Johns Hopkins (N = 384)	PLCO (N = 163)	Total (N = 805)
Ethnicity	European American	185 (71.7%)	305 (79.4%)	163 (100%)	653 (81.1%)
	African American	73 (28.3%)	79 (20.6%)	0	152 (18.9%)
Age at Diagnosis (years)	Median	64	60	66	63
	Mean	64.7	60.8	65.6	63.1
	Range	39–86	37–85	55–79	37–86
Stage at Diagnosis	Localized	99 (38.4%)	286 (74.5%)	122 (74.8%)	507 (63.0%)
	Metastatic	153 (59.3%)	98 (25.5%)	41 (25.2%)	292 (36.3%)
	Unknown	6 (2.3%)	0	0	6 (0.7%)
Gleason Score at Diagnosis	<7	56 (21.7%)	46 (12.0%)	0	102 (12.7%)
	7	90 (34.9%)	117 (30.5%)	116 (71.2%)	323 (40.1%)
	>7	87 (33.7%)	188 (48.9%)	47 (28.8%)	322 (40.0%)
	Unknown	25 (9.7%)	33 (8.6%)	0	58 (7.2%)
1st Degree Relative with Prostate Cancer	Yes	53 (20.5%)	-	23 (14.1%)	76 (9.4%)
	No	204 (79.1%)	-	140 (85.9%)	344 (42.7%)
	Unknown	1 (0.4%)	384 (100%)	0	385 (47.8%)
Primary Treatment for Localized Disease	Radical Prostatectomy	61 (61.6%)	208 (72.7%)	-	269 (53.0%)
	Radiation Therapy	24 (24.2%)	78 (27.3%)	-	102 (20.1%)
	Watchful Waiting	11 (11.1%)	0	-	11 (2.2%)
	Primary Hormone therapy	3 (3.0%)	0	-	3 (0.6%)
	Unknown	0	0	122 (100%)	122 (24.1%)
Known to have Died of Disease		17	9	-	26

* Information regarding family history was unknown for the Johns Hopkins University cases and data on primary treatment and death from prostate cancer were unavailable for the PLCO cases.

Table 2

Risk of aggressive prostate cancer associated with the *CASP8 D302H* polymorphism

	Washington University		Johns Hopkins University		PLCO Cancer Screening Trial		Pooled	
	Cases/Controls	**OR (95% CI)***	**Cases/Controls**	**OR (95% CI)***	**Cases/Controls**	**OR (95% CI)***	**Cases/Controls**	**OR (95% CI)***
All subjects								
DD	218/352	1.0	312/349	1.0	131/874	1.0	661/1575	1.0
DH	35/84	0.48 (0.27–0.87)	62/96	0.67 (0.47–0.97)	31/273	0.76 (0.50–1.15)	128/453	0.66 (0.52–0.84)
HH	1/5	0.55 (0.05–5.96)	5/8	0.64 (0.20–1.99)	1/19	0.36 (0.05–2.69)	7/32	0.48 (0.20–1.18)
DH+HH		0.49 (0.27–0.87)		0.67 (0.47–0.95)		0.73 (0.49–1.10)		0.65 (0.52–0.82)
Per H allele		0.52 (0.30–0.89)		0.71 (0.51–0.97)		0.73 (0.50–1.07)		0.67 (0.54–0.83)
P_{trend}		0.02		0.03		0.11		0.0003
European American subjects								
DD	149/175	1.0	244/221	1.0	131/874	1.0	524/1270	1.0
DH	32/55	0.46 (0.20–1.08)	54/73	0.68 (0.46–1.02)	31/273	0.76 (0.50–1.15)	117/401	0.70 (0.54–0.91)
HH	0/5	-	4/6	0.56 (0.16–2.03)	1/19	0.36 (0.05–2.69)	5/30	0.35 (0.13–1.00)
DH+HH		0.44 (0.19–1.03)		0.67 (0.46–0.99)		0.73 (0.49–1.10)		0.68 (0.52–0.87)
Per H allele		0.44 (0.19–1.01)		0.70 (0.49–0.99)		0.73 (0.50–1.07)		0.68 (0.54–0.86)
P_{trend}		0.05		0.05		0.11		0.001
African American subjects								
DD	69/177	1.0	68/128	1.0		-	137/305	1.0
DH	3/29	0.31 (0.09–1.07)	8/23	0.65 (0.27–1.52)		-	11/52	0.45 (0.23–0.91)
HH	1/0	-	1/2	0.97 (0.09–10.89)		-	2/2	2.09 (0.28–15.47)
DH+HH		0.40 (0.13–1.20)		0.67 (0.30–1.52)		-		0.52 (0.27–0.99)
Per H allele		0.52 (0.20–1.38)		0.73 (0.35–1.52)		-		0.61 (0.34–1.10)
P_{trend}		0.19		0.40		-		0.10

*Odds ratios are adjusted for age, race, and study (as appropriate). P-values for heterogeneity between studies for the log-additive model were 0.77, 0.83, and 0.59 for all, white, and black subjects, respectively.

Table 3

Risk of any and increasingly advanced prostate cancer associated with *CASP8 D302H* in the PLCO Cancer Screening Trial

PLCO Population	MAF Controls	MAF Cases	Per Allele OR* (95% CI) [H vs D]	Heterozygous OR* (95% CI) [DH vs DD]	Homozygous OR* (95% CI) [HH vs DD]	Dominant OR* (95% CI) [DH, HH vs DD]	P_{trend}
Entire Cohort	0.133	0.126	0.94 (0.79–1.11)	0.91 (0.75–1.11)	1.03 (0.55–1.95)	0.92 (0.76–1.11)	0.46
Gleason ≤ 6 And Stage cT1–2	0.133	0.131	0.98 (0.79–1.23)	0.95 (0.74–1.23)	1.17 (0.52–2.60)	0.98 (0.75–1.24)	0.88
Gleason 7–10 OR Stage cT3–4	0.133	0.123	0.91 (0.74–1.11)	0.89 (0.71–1.11)	0.95 (0.45–2.01)	0.89 (0.71–1.11)	0.34
Gleason 8–10 OR Stage cT3–4	0.133	0.116	0.85 (0.65–1.12)	0.88 (0.65–1.19)	0.57 (0.11–1.95) †	0.86 (0.64–1.15)	0.25
Gleason 7–10 AND Stage cT3–4	0.133	0.101	0.73 (0.50–1.07)	0.76 (0.50–1.15)	0.35 (0.008–2.25) †	0.73 (0.49–1.10)	0.11
Gleason 8–10 AND Stage cT3–4	0.133	0.075	0.52 (0.24–1.14)	0.56 (0.25–1.27)	-	0.52 (0.23–1.18)	0.10

*Odds ratios are adjusted for age

†Exact confidence interval calculated