

















PSA PARAMETER and HEREDITY FACTORS

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Pathological features of hereditary prostate cancer.

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J Urol 1995 Mar;153(3 Pt 2):987-92

The aim of this study was to characterize the pathological features of hereditary prostate cancer, a recently recognized variant of prostate cancer with an autosomal dominant inheritance of a rare highly penetrant gene associated with early onset of disease. We compared the histology at radical prostatectomy of clinical stage T2 prostate cancer, including its relationship to prostatic intraepithelial neoplasia, in men with a family history of prostate cancer to those without a family history of prostate cancer. Three cohorts (hereditary, familial and sporadic) were identified based on pedigree analysis. A hereditary subgroup (28 patients) met 1 of the following 3 criteria: 1) cluster of greater than 3 affected relatives within the nuclear family, 2) occurrence of prostate cancer in each of 3 generations in either the proband paternal or maternal lineage, or 3) a cluster of 2 relatives affected at an early age of less than 55 years. This subgroup was compared to an age-matched subgroup with family history of prostate cancer (26 patients) yet the aforementioned conditions for inclusion within the hereditary subgroup were not met and to a sporadic subgroup without a family history of prostate cancer (27 patients). All parameters were statistically similar among the groups except that hereditary and familial group multifocal tumors were of lower grade ($p = 0.0001$), sporadic cases had a greater proportion of small multifocal cancers associated with prostatic intraepithelial neoplasia ($p = 0.02$) and the familial group had a weaker correlation between total tumor volume and grade. In conclusion, our analysis failed to demonstrate substantial pathological differences among hereditary, familial and sporadic forms of prostate cancer. Rather, our data are remarkable for the wide range of all parameters studied in each group. Even the sporadic cases had features, such as increased numbers of precursor lesions and tumor multifocality, which in other organs are commonly associated with either hereditary cancer or cancer arising in a field effect due to diffuse exposure to a carcinogen.

Familial risk factors for prostate cancer.

Carter BS, Steinberg GD, Beaty TH, Childs B, Walsh PC
Department of Epidemiology, School of Hygiene and Public Health, Johns Hopkins Medical Institutions, Baltimore, Maryland 21205.
Cancer Surv 1991;11:5-13

This chapter describes the application of the genetic epidemiological approach to the study of human prostate cancer. We review the evidence for the familial clustering of prostate cancer and the Mendelian nature of this aggregation. The nature of this clustering is such that the closer genetically a man is to an affected relative and the greater number of relatives affected in a man's family, the greater his risk of prostate cancer. A complex segregation analysis of the 691 prostate cancer families showed that prostate cancer clustering can be explained by Mendelian inheritance of a rare autosomal gene producing prostate cancer at an early age. A model of inherited prostate cancer in the setting of multistep carcinogenesis is presented. The implications of these data for clinicians who diagnose and treat prostate cancer are also discussed.

Mendelian inheritance of familial prostate cancer.

Carter BS, Beaty TH, Steinberg GD, Childs B, Walsh PC
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Proc Natl Acad Sci U S A 1992 Apr 15;89(8):3367-71

Previous studies have demonstrated familial clustering of prostate cancer. To define the nature of this familial aggregation and to assess whether Mendelian inheritance can explain prostate cancer clustering, proportional hazards and segregation analyses were

performed on 691 families ascertained through a single prostate cancer proband. The proportional hazards analyses revealed that two factors, early age at onset of disease in the proband and multiple affected family members, were important determinants of risk of prostate cancer in these families. Furthermore, segregation analyses revealed that this clustering can be best explained by autosomal dominant inheritance of a rare ($q = 0.0030$) high-risk allele leading to an early onset of prostate cancer. The estimated cumulative risk of prostate cancer for carriers revealed that the allele was highly penetrant: by age 85, 88% of carriers compared to only 5% of noncarriers are projected to be affected with prostate cancer. The best fitting autosomal dominant model further suggested that this inherited form of prostate cancer accounts for a significant proportion of early onset disease but overall is responsible for a small proportion of prostate cancer occurrence (9% by age 85). These data provide evidence that prostate cancer is inherited in Mendelian fashion in a subset of families and provide a foundation for gene mapping studies of heritable prostate cancer. Characterization of genes involved in inherited prostate cancer could provide important insight into the development of this disease in general.

Family history and the risk of prostate cancer.

Steinberg GD, Carter BS, Beaty TH, Childs B, Walsh PC
Brady Urological Institute, Johns Hopkins Hospital, Baltimore, MD 21205.
Prostate 1990;17(4):337-47

A case-control study was performed to estimate the relative risk of developing prostate cancer for men with a positive family history. Extensive cancer pedigrees were obtained on 691 men with prostate cancer and 640 spouse controls. Fifteen percent of the cases but only 8% of the controls had a father or brother affected with prostate cancer (P less than .001). Men with a father or brother affected were twice as likely to develop prostate cancer as men with no relatives affected. In addition, there was a trend of increasing risk with increasing number of affected family members such that men with two or three first degree relatives affected had a five and 11-fold increased risk of developing prostate cancer. Recognizing that 9-10% of U.S. men will develop prostate cancer in their lifetime, men with a family history of prostate cancer should be advised of their significantly increased prostate cancer risk and should undergo appropriate screening measures for this disease.

Familial patterns of prostate cancer: a case-control analysis.

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Department of Cancer Prevention and Control, University of Texas M.D. Anderson Cancer Center, Houston.
J Urol 1991 Nov;146(5):1305-7

Epidemiological data have not yet enabled physicians to look beyond age and race to identify men at increased risk for prostate cancer. We conducted a hospital-based case-control study of familial patterns of prostate cancer with self-reported data from a risk-factor questionnaire. There were 385 patients with histologically confirmed prostate cancer, and 385 race and age-matched (± 5 years) controls with other cancers. Family history, available for 378 patients and 383 controls, was positive for prostate cancer in 13.0% versus 5.7%, respectively. The difference was significant at $p = 0.01$. The over-all age-adjusted risk estimate for men with a first-degree relative with prostate cancer was significantly elevated (odds ratio of 2.41), as were the individual risk estimates for having a father or brother with prostate cancer (odds ratio of 2.24 and 2.66). Having a second-degree relative (grandfather or uncle) with prostate cancer also conferred elevated but not statistically significant risk. These data accord well with the few previously published case-control studies of familiarity of prostate cancer. On the basis of these findings, one should consider recommending participation in early detection programs for prostate cancer in a man whose father or brother has had the disease.

Family history and prostate cancer risk.

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Am J Epidemiol 1996 Dec 1;144(11):1041-7

The authors examined the relation between family history of prostate cancer and the risk of this cancer in a population-based case-control study conducted in Massachusetts between December 1992 and October 1994. Cases were all incident cases of prostate cancer in men younger than 70 years ($n = 563$); controls were men with no history of the disease matched to the cases on age and town of residence ($n = 703$). Prostate cancer risk was increased among men who reported a history of this cancer in either

their fathers or brothers (odds ratio (OR) = 2.3, 95% confidence interval (CI) 1.7-3.3). Risk varied with the number of relatives affected and their relationship to the case. For a history of prostate cancer in one relative, the OR was 2.2 (95% CI 1.5-3.2); if two or more relatives were affected, it was 3.9 (95% CI 1.7-5.2). For prostate cancer in the father, the OR was 1.9 (95% CI 1.2-3.0); for prostate cancer in a brother, it was 3.0 (95% CI 1.8-4.9). Risk was inversely related to the subject's age and to age at diagnosis of prostate cancer in his affected relative. Among probands younger than 60 years, the OR was 5.3 (95% CI 2.5-12); for those 60-64 years of age, the OR was 2.7 (95% CI 1.3-5.5); and for those 65 years of age and older, the OR was 1.6 (95% CI 1.0-2.5). For prostate cancer diagnosed in a relative before age 65, the OR was 4.1 (95% CI 2.3-7.3); for detection of the disease after age 74, the OR was 0.76 (95% CI 0.38-1.5). The association was present both among men with local and advanced stage disease and among men whose prostate cancer was detected either by screening or because of symptoms. These data provide evidence that after controlling for diet and other potential confounders, familial factors are significantly associated with the risk of prostate cancer.

Combination of screening and preoperative endocrine therapy: the potential for an important decrease in prostate cancer mortality.

Labrie F, Cusan L, Gomez JL, Diamond P, Candas B
Prostate Cancer Research Unit, CHUL Research Center, Le Centre Hospitalier de l'Universite Laval, Quebec, Canada.
J Clin Endocrinol Metab 1995 Jul;80(7):2002-13

Prostate cancer is the second cause of cancer death in men in the Western world; its medical and social impact is comparable to that of breast cancer in women. Although it is well recognized that early treatment is the only possibility for reducing the high rate of death from prostate cancer, screening and even early treatment are controversial issues due mainly to arguments based upon old literature and lack of awareness of the significant advances recently made in this field. As it is well known that surgical removal of organ-confined prostate cancer cures the disease, and it has been demonstrated that annual screening with prostate-specific antigen coupled with digital rectal examination followed, when indicated, by transrectal ultrasonography of the prostate more than doubles the proportion of organ-confined disease, screening alone offers the possibility of at least doubling the number of patients curable from prostate cancer or the potential for a cure to an estimated 45% of prostate cancer patients compared to a maximum of 20% in the absence of screening. It is important to mention that screening does not detect small and insignificant cancers, especially when random biopsies are not performed routinely. The critical volume of prostate cancer is estimated at 0.3 cm or a tumor 7.5 mm in diameter, if spherical. Such a tumor should increase serum prostate-specific antigen by 0.5 ng/mL. Contrary to the belief that screening detects cancers that are too small, the fact is that screening detects prostate cancer too late or nonorgan- or nonspecimen-confined cancer in 35-50% of cases. There is, thus, a narrow window when prostate cancer can be detected at a curable stage, and even the best available screening techniques cannot succeed in all cases. It should be mentioned that the recent improvements of the technique of radical prostatectomy have markedly improved the acceptability of surgery. Concerning the recent publicity related to watchful waiting, it is essential to indicate that all such reports support the notion that prostate cancer grows slowly, but steadily and irremediably, with increasing malignancy and risk of distant metastases and death if sufficient time is allowed. Another serious limitation of watchful waiting is that the available prognostic factors have a large margin of error and cannot predict with certainty the rate of progression of the tumor.

Diagnosis of advanced or noncurable prostate cancer can be practically eliminated by prostate-specific antigen.

Labrie F, Candas B, Cusan L, Gomez JL, Diamond P, Suburu R, Lemay M
Prostate Cancer Clinical Research Unit, CHUL Research Center, Quebec, Canada.
Urology 1996 Feb;47(2):212-7

OBJECTIVES: To determine the percentage of localized and potentially curable prostate cancers diagnosed at follow-up screening visits compared with the first screening visit.

METHODS: Within the context of a prospective screening study performed in randomly chosen men aged between 45 and 80 years, up to 6-year follow-up screening visits have been performed with serum prostate-specific antigen (PSA) measurement and digital rectal examination (DRE) followed by transrectal ultrasonography of the prostate when PSA or DRE is abnormal.

RESULTS: Of the 117 prostate cancers diagnosed at 14,554 annual follow-up visits, only 1 cancer (0.9%) was metastatic compared with 8% (26/322) at 8029 first visits. Moreover, 97% of the cancers detected at follow-up visits could be identified by PSA alone compared with 86% at first visit. The incidence of 0.8% per year during 15 years of screening between the ages of 55 and 70 years would diagnose localized prostate cancer in 12% of the population, a value not too different from the 10% diagnosed with prostate cancer during life-time in the absence of screening.

CONCLUSIONS: The present data show that annual screening with PSA diagnoses clinically localized prostate cancer in more than 95% of cases, thus almost completely eliminating the diagnosis of metastatic prostate cancer. Moreover, the number of prostate cancers diagnosed is not significantly increased by screening.

Evaluation of prostASURE index in the detection of prostate cancer: a preliminary report.

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Urology 1998 Jan;51(1):132-6

OBJECTIVES: Although prostate-specific antigen (PSA) has revolutionized the detection of prostate cancer, it has definite limitations with respect to its clinical sensitivity and specificity. Because a substantial number (20% to 40%) of men undergoing radical prostatectomy have a PSA level of 4.0 ng/mL or less, any new test offering diagnostic improvement must perform well in patients whose PSA level is less than or equal to 4.0 ng/mL, as well as in patients whose PSA is greater than 4.0 ng/mL. The performances of two tests, the ProstASURE index and the percent free PSA test, were evaluated in detecting cancer.

METHODS: We retrospectively analyzed serum samples from 225 men who were grouped into three categories: 94 men who had a normal digital rectal examination and a serum PSA level of 4.0 ng/mL or less, 77 men who were clinically suspected of having benign prostatic hyperplasia (BPH) with a serum PSA level of 4.0 ng/mL or less, and 54 men with localized prostate cancer. The PSA assays were performed using the Hybritech and Tosoh assays and the ProstASURE index was determined by Global Health Net, Savannah, Ga. Receiver operator characteristic (ROC) curves were constructed to evaluate the performance of these two tests, and the areas under the curve were compared for significance.

RESULTS: The sensitivity and specificity of detecting prostate cancer using ProstASURE were 93% and 81%, respectively. Using a cutoff value of 15%, the sensitivity and specificity of detecting cancer for percent free PSA were 80% and 74%, respectively (sensitivity increased to 93% and specificity to 59% for free PSA at 19%). In men with a total serum PSA level of 4.0 ng/mL or less, ProstASURE had a lower false-positive rate compared to free PSA level at 19% for men with or without clinical BPH as well as for men without clinical BPH using a 15% free PSA threshold. ProstASURE left fewer cancers undetected (7%) compared to free PSA at the 15% cutoff (20%).

CONCLUSIONS: In this study of selected men, ROC curve analysis shows a statistically significant advantage in performance ($P = 0.0023$) for the ProstASURE index compared to free PSA in detecting prostate cancer.

Prostate cancer detection in men with serum PSA concentrations of 2.6 to 4.0 ng/mL and benign prostate examination. Enhancement of specificity with free PSA measurements.

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JAMA 1997 May 14;277(18):1452-5

OBJECTIVE: To determine the detection rate of prostate cancer in a screening population of men with prostate-specific antigen (PSA) concentrations of 2.6 to 4.0 ng/mL and a benign prostate examination, to assess the clinicopathological features of the cancers detected, and to assess the usefulness of measuring the ratio of free to total PSA to reduce the number of prostatic biopsies.

DESIGN: A community-based study of serial screening for prostate cancer with serum PSA measurements and prostate examinations.

SETTING: University medical center.

SUBJECTS: A total of 914 consecutive screening volunteers aged 50 years or older with serum PSA levels of 2.6 to 4.0 ng/mL who had a benign prostate examination and no prior screening tests suspicious for prostate cancer, 332 (36%) of whom underwent biopsy of the prostate.

MAIN OUTCOME MEASURES: Cancer detection rate, clinical and pathological features of cancers detected, and specificity for cancer detection using measurements of percentage of free PSA.

RESULTS: Cancer was detected in 22% (73/332) of men who underwent biopsy. All cancers detected were clinically localized, and 81% (42/52) that were surgically staged were pathologically organ confined. Ten percent of the cancers were clinically low-volume and low-grade tumors, and 17% of those surgically staged were low-volume and low-grade or moderately low-grade tumors (possibly harmless). Using a percentage of free PSA cutoff of 27% or less as a criterion for performing prostatic biopsy would have detected 90% of cancers, avoided 18% of benign biopsies, and yielded a positive predictive value of 24% in men who underwent biopsy.

CONCLUSIONS: There is an appreciable rate of detectable prostate cancer in men with serum PSA levels of 2.6 to 4.0 ng/mL. The great majority of cancers detected have the features of medically important tumors. Free serum PSA measurements may reduce the number of additional biopsies required by the lower PSA cutoff.

Prospective longitudinal evaluation of men with initial prostate specific antigen levels of 4.0 ng./ml. or less.

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Section of Urology, University of Arizona College of Medicine and Tucson Veterans Affairs Medical Center, USA.
J Urol 1997 May;157(5):1740-3

PURPOSE: We evaluated the 3-year longitudinal changes in serial serum prostate specific antigen (PSA) levels in men with an initial PSA of 4.0 ng./ml. or less and no suspicion of prostate cancer.

MATERIALS AND METHODS: A total of 760 men with an initial PSA of 4.0 ng./ml. or less plus a normal or suspicious digital rectal examination and a benign prostate biopsy was enrolled into an every 4-month PSA monitoring study.

RESULTS: Of the 559 men with an initial PSA of 2.0 ng./ml. or less only 3 (0.5%) had a persistently abnormal PSA for 3 years and 1 cancer (0.2%) was detected, and 48 men had a PSA velocity of 0.8 ng./ml. per year or more at year 1 but only 1 (2%) had a persistent rate of increase (2.4 ng./ml. Per year) at 3 years. Of the 201 men with a PSA of 2.1 to 4.0 ng./ml. 85 had an abnormal PSA but only 37 (43%) met the criteria for biopsy. Only 8 of 23 biopsies (35%) revealed cancer. Of the 201 men 24 had a PSA velocity of 0.8 ng./ml. Per year or more at year 1 but only 4 had persistence for 3 years. All 4 men had cancer but they were identified as at high risk by PSA criteria.

CONCLUSIONS: Men with a PSA of 2.0 ng./ml. or less are at low risk for an abnormal PSA or cancer within 3 years and annual monitoring may not be necessary. However, annual monitoring is clinically useful in men with an initial PSA of 2.1 to 4.0 ng./ml. Also, serial monitoring with interval testing in men whose PSA becomes greater than 4.0 ng./ml. Is beneficial in identifying a high risk group requiring biopsy. Finally, PSA velocity did not add further to cancer detection in this population.

Systematic 5 region prostate biopsy is superior to sextant method for diagnosing carcinoma of the prostate.

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J Urol 1997 Jan;157(1):199-202; discussion 202-3

PURPOSE: The number of patients undergoing prostate biopsy has dramatically increased due to prostate specific antigen screening. The low specificity of this screening tool requires prostate biopsy for diagnosis of prostate cancer. The sextant biopsy technique has been used widely with success in diagnosing carcinoma of the prostate. However, concern has arisen that the original sextant method may not include an adequate sampling of the prostate. For many years we have used a method of prostate biopsy that, in addition to sextant biopsies, takes additional biopsies in a systematic fashion, which we call the 5 region prostate biopsy. We conducted a prospective study to determine if our 5 region prostate biopsy technique significantly increases the chances of finding carcinoma of the prostate compared to the sextant biopsy technique.

MATERIALS AND METHODS: A total of 119 patients underwent transrectal ultrasound guided needle biopsy of the prostate. In addition to sextant biopsies, cores were taken from the far lateral and mid regions of the gland. Pathological findings of the additional regions were compared to those of the sextant regions.

RESULTS: Of the 48 patients with prostate cancer 17 (35%) had carcinomas only in the additional regions, which would have remained undetected had the sextant biopsy technique been used alone ($p < 0.05$). Of these additional cancers 83% had Gleason scores of 6 or more.

CONCLUSIONS: We introduce the 5 region technique of prostate biopsy as a means of significantly increasing the diagnostic yield of prostate biopsy in finding carcinoma of the prostate. We have found this technique to be safe, efficacious and superior to the sextant method of biopsy in identifying prostate cancer at an early but significant stage. The greatest use of the 5 region biopsy technique is in patients who have prostate specific antigen levels between 4 and 10 ng./ml.

Family history of breast cancer as a predictor for fatal prostate cancer.

Rodriguez C, Calle EE, Tatham LM, Wingo PA, Miracle-McMahill HL, Thun MJ, Heath CW Jr
American Cancer Society, Epidemiology and Surveillance Research, Atlanta, GA 30329-4251, USA.
Epidemiology 1998 Sep;9(5):525-9

To examine the relation between family history of breast cancer in a mother or sister and a man's risk of fatal prostate cancer, we analyzed data from a prospective mortality study of adult men in the United States. During 12 years of follow-up, there were 3,141 deaths from prostate cancer in a cohort of 480,802 men who were cancer-free at study entry in 1982. Results from Cox proportional hazards models, adjusted for other risk factors, showed a modest increased risk of fatal prostate cancer associated with a family history of breast cancer (in the absence of a family history of prostate cancer) [rate ratio (RR) = 1.16; 95% confidence interval (CI) = 1.01-1.33]. The association was stronger among men younger than 65 years of age whose relatives were diagnosed with breast cancer before age 50 years (RR = 1.65; 95% CI = 0.88-3.10) and among Jewish men (RR = 1.73; 95% CI = 1.00-2.97). The increased risks observed in these subgroups may reflect genetic alterations underlying familial clustering of prostate and breast cancer.

Genetic epidemiology of prostate cancer in the Utah Mormon Genealogy.

Cancer Surv 1:47-69, 1982.

No abstract.

Dietary phytoestrogens and prostate cancer.

Proc Annu Meet Am Assoc Cancer Res 36:687, 1995.

No abstract

Familial clustering of cancers of the breast and prostate in a population-based sample of postmenopausal women.

Proc Annu Meet Am Assoc Cancer Res 35:A1724, 1994.

No abstract.

Hereditary prostate cancer: epidemiologic and clinical features.

Carter BS, Bova GS, Beaty TH, Steinberg GD, Childs B, Isaacs WB, Walsh PC
Department of Urology, Johns Hopkins Medical Institutions, Baltimore, Maryland 21287-2101.
J Urol 1993 Sep;150(3):797-802

No abstract.

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