Focus on prostate cancer

William Isaacs,[1,4] Angelo De Marzo,[2] and William G. Nelson[3]

[1]Department of Urology
[2]Department of Pathology
[3]Department of Oncology
The Johns Hopkins University School of Medicine, Baltimore, Maryland 21205
[4]Correspondence: wisaacs@jhmi.edu

Introduction and clinical epidemiology

In 1990, prostate cancer surpassed lung cancer as the most common noncutaneous malignancy diagnosed in men in the U.S. This year prostate cancer will be responsible for over 31,000 deaths in this country, resulting in an annual loss of almost 300,000 years of life. The incidence of prostate cancer shows strong age, race, and geographical dependence. Less than 1% of cases are diagnosed under the age of 40, although this may represent an underestimate as screening for disease in young men is rare. Prostate cancer is relatively uncommon in Asian populations and prevalent in Scandinavian countries, and the highest incidence (and mortality) rates known are in African Americans, being ~2-fold higher than in Caucasian Americans (Figure 1). Mortality rates vary significantly by country, ranging from over 32 per 100,000 in Trinidad, to 23 per 100,000 for Caucasians in the U.S., to 4 per 100,000 in Japan (Boring et al., 1992).

Like most common cancers, the etiologic factors associated with prostate cancer are varied, encompassing both host genetic and environmental influences. Environmental factors are clearly indicated by migration studies; e.g., large increases in risk in Japanese men occur when they move to the United States. Etiologic factors include aging, familial clustering, race, hormonal influences, diet (both inductive and preventive factors), and lifestyle factors (Hsing and Devesa, 2001). Age, familial clustering, and race are clearly important, well-documented risk factors, and dietary influences such as red meat, high fat (elevated risk), antioxidants (e.g., selenium, lycopene [lowered risk]), and hormone levels are most likely critical factors as well. The finding of increased risk associated with increased serum levels of insulin-like growth factor 1 (IGF-1) (Chan et al., 1998) is an example clearly implicating nonandrogenic growth regulatory pathways as potentially important in determining prostate cancer risk.

Natural history and diagnostics

The initiation of prostate cancer, i.e., the formation of a histologically identifiable lesion, is a common event, being detected at autopsy series in nearly one-third of men over age 45. Fortunately, the majority of such lesions do not progress to clinically detectable tumors within the lifetime of these men. Clinically, prostate cancers are diagnosed upon histological evaluation of needle biopsy samples of prostate tissue, taken because of an abnormal physical examination, an elevated serum PSA level, or both. Due to the common morphological heterogeneity of prostate cancer, two different grades are given for the first and second most prevalent patterns, and the sum of these two grades is added to give the Gleason score. Staging is categorized using a TNM (tumor, node, metastasis) classification, with lymph nodes and bone being the most common sites of metastatic spread. Prostate cancer develops in two different regions of the gland, with most lesions (~80%) being found in the periphery, and most of the remaining cancers found in a periurethral region termed the transition zone. Curiously, the virtually ubiquitous process of benign prostatic hyperplasia (BPH) originates in the transition zone of the prostate (McNeal, 1978). Based primarily on this regional difference in the incidence of benign and malignant growth, and the fact that stromal cell proliferation is typically a major component of BPH, these benign lesions are not thought to be the precursors of invasive adenocarcinoma in the prostate. Instead, prostatic intraepithelial neoplasia, or PIN, is the term given to characteristic foci of dysplastic ductal and acinar cells thought to be the precursor lesions of this disease (Bostwick, 1989).

Prior to the widespread study of PIN, various atrophic lesions have been described as potential prostate cancer precursors. More recently, this notion has become reinvigorated, since focal "atrophy" lesions are highly proliferative, occur predominantly in the peripheral zone, are found at times to merge directly with high-grade PIN, are often found near small can-

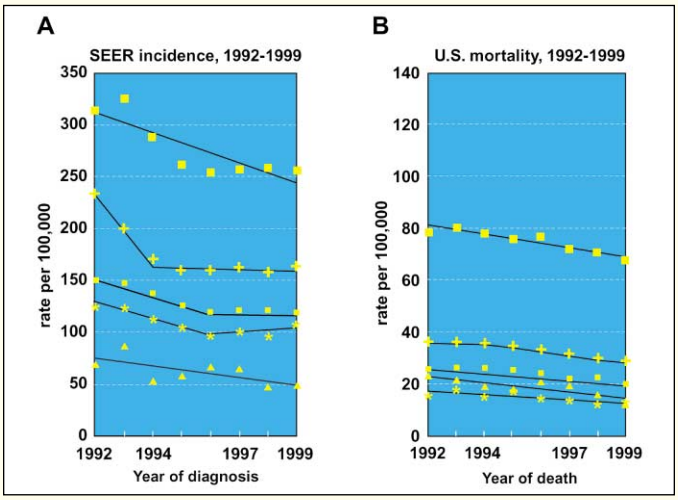

Figure 1. SEER incidence and mortality rates for prostate cancer in the U.S.

Regression lines are calculated using the Joinpoint regression program. +, White; ■, Black; ●, Hispanic; *, Asian/Pacific Islander; ▲, American Indian/Alaskan Native.

A: Source: SEER 12 areas (San Francisco, Connecticut, Detroit, Hawaii, Iowa, New Mexico, Seattle, Utah, Atlanta, San Jose-Monterey, Los Angeles, and Alaska). Incidence data for Hispanics does not include cases from Detroit and Hawaii.

B: Source: NCHS public use data file. Mortality data for Hispanics does not include cases from Connecticut, Oklahoma, New York, and New Hampshire. Mortality data from all other races are from all U.S. states.

cers, and at times have genetic alterations similar to those detected in high-grade PIN and adenocarcinoma (reviewed in De Marzo et al., 2001). Since these atrophy lesions are usually associated with an inflammatory component and exhibit phenotypic signs of incurring oxidant stress, they have been termed proliferative inflammatory atrophy (PIA). It has been suggested that similar to other major epithelial cancers, such as those in the liver and stomach, inflammatory cell mediated oxidant stress may be a key pathogenetic mechanism driving prostate carcinogenesis (De Marzo et al., 2001).

Prostate cancer is commonly multifocal, e.g., the prostate of a man diagnosed with prostate cancer contains an average of 5 apparently independent cancer lesions and many more high-grade PIN lesions (Bastacky et al., 1995). These lesions are genetically heterogeneous, both inter- and intratumorally; interestingly, this multifocality is independent of family history of prostate cancer (Bastacky et al., 1995). The tendency for prostate cancers to have a long natural history is emphasized by tumor doubling times often measured in months and years (Berges et al., 1995), although there are certainly exceptions.

The introduction of serum prostate-specific antigen (PSA) as a screening tool is primarily responsible for the >2-fold increase in incidence rates observed between 1986 and 1992 (Stanford et al., 1999), as well as the substantial decline in the percentage of cases diagnosed annually with disseminated disease. The absolute mortality rates for prostate cancer declined in the U.S. for the first time in 1995 (Stanford et al., 1999), most likely as a result of early detection and treatment resulting from increased screening, although there is debate over this issue.

PSA is a serine protease with a chymotrpysin-like substrate specificity, which is normally secreted by the prostate in large amounts into the seminal plasma, with only small amounts entering the bloodstream. While highly elevated serum PSA levels are most often associated with prostate cancer, a current focus of intense research effort is on the ability to accurately interpret moderately elevated PSA levels (e.g., 4–10 ng/ml), which can be indicative of either benign or malignant disease (reviewed in Bunting, 2002). The measurement of more cancer-specific forms of PSA offers the promise of discrimination to address this problem. Interestingly, baseline PSA levels in young men are strong predictors of the likelihood of eventual prostate cancer diagnosis (Fang et al., 2001).

While PSA is a useful tool for screening for prostate cancer and as a monitor of disease progression after therapy, it is not as useful in determining prognosis. In fact, the inability to determine, at diagnosis, which prostate cancers will progress or already have progressed to disseminated disease is one of the foremost problems in the clinical management of this disease. This problem in staging prostate cancer accurately is emphasized by two observations: (1) between 15% and 40% of men who are thought to have clinically localized disease at diagnosis in fact have disseminated disease, for which there is currently no curative treatment; and (2) a substantial but unknown fraction of prostate cancers will not progress or will progress so slowly that they pose little threat to the patients in whom they are diagnosed. New prognostic indicators and methodologies that can assist in these distinctions are urgently needed.

Therapeutics and androgen independence

Early stage prostate cancer is typically treated with either surgical removal or localized radiotherapy, and in some cases is just followed without treatment ("watchful waiting").

The effectiveness of these treatments, while still largely unproven, is suggested by decreasing mortality rates observed over the past several years. Increasing serum PSA levels after prostatectomy or other treatment for prostate cancer is a very reliable indication of disease progression, although the development of clinically detectable metastases typically takes years to become apparent (Pound et al., 1999).

The prostate gland is an androgen-dependent organ, and thus undergoes involution upon androgen deprivation. Similarly, prostate cancers generally respond to androgen ablation, triggering programmed cell death and forming the basis for the most common therapies currently used for treatment of advanced prostate cancer. Although very effective in a palliative sense, such androgen ablation therapy is almost never curative, as the disease invariably progresses to an androgen-independent state. This transition to a hormone refractory stage remains a foremost challenge, both therapeutically and experimentally (Feldman and Feldman, 2001). While the mechanisms underlying this transition are not fully understood, significant progress has been made in this area. Molecular mechanisms implicated in progression to androgen independence include *AR* gene amplification, steroid coactivator upregulation, *AR* mutations which alter ligand specificity and/or sensitivity (most commonly seen in patients on long term antiandrogen therapy), and altered dependence upon nonandrogen mediated growth factor and signaling pathways (e.g., ErbB2 and NFκB [Chen and Sawyers, 2002]).

Current clinical challenges include the development of methodologies to more effectively stage prostate cancer (including development of more informative and sensitive imaging modalities), definition of better prognostic markers, particularly ones that are least effected by sampling bias, and efficient treatments for advanced, hormone refractory disease. Promising advances in this last area include prostate replication restricted adenoviruses (Rodriguez et al., 1997), cytotoxic drug activation by PSA (i.e., prodrug therapy) (Denmeade et al., 1998), antibodies targeted at prostate-specific membrane antigen (PSMA) (Gong et al., 1999), and signal transduction inhibitors which target *PTEN* null cells (Neshat et al., 2001).

Genetics of sporadic and familial prostate cancer

As with other commons adenocarcinomas, both numerical and structural chromosomal alterations are frequent somatic changes in prostate cancer cells. The most frequently affected chromosomes are 8, 10, 13, 16, and 17 (for review see Isaacs and Kainu, 2001). Loss of 8p appears to be an early event in prostate cancer development, since prostate intraepithelial neoplasia frequently shows LOH at this location, and more recently, chromosome 8 alterations have been detected in PIA. However, no unequivocal candidates for the specific genes involved have appeared, although several genes, including *NKX3.1* and *LZTS*, are promising.

Clearly, the initiating somatic genetic alterations driving prostate cancer development still remain to be uncovered. Intriguingly, hypermethylation of the *glutathione S transferase P1* promoter region is associated with prostate cancer, occurring in approximately 90% of cancer lesions and 70% of high-grade PIN lesions. Promoter methylation-mediated inactivation of this gene, which can detoxify environmental carcinogens, has been proposed as a prerequisite somatic genome alteration during prostate carcinogenesis. Attempts to reactivate this or similar pathways form the basis for novel approaches for

Table 1. Genes associated with prostate cancer

Gene	Alteration	Status	Location
PTEN	Somatic mutation	Inactivated/downregulated	10q23
p53	Somatic mutation	Inactivated	17p13
CTNNB1	Somatic mutation	Activated	3p21
AR	Somatic mutation	Altered specificity	Xq12
KLF6	Somatic mutation	Inactivated*	10p15
GSTP1	Altered expression-	Downregulated in PIN and cancer - hypermethylated	11q13
HPN, AMACR, TARP, FASN	Altered expression-	Upregulated	5p12, 19q12, 7p14, 17q25
PDGFR, PIM1, phospho-AKT, phospho-MAPK, c-myc	Altered expression-	Upregulated in high grade	5q31, 6p21, 14q32,22q11, 8q24
AR, NFkB, SRC1, ERBB2, S100P, IGFBP2	Altered expression-	Upregulated in advanced/ hormone refractory disease	Xq12, 4q23, 2p23, 17q21, 17q21, 2q33
Kai1, CDH1, MKK4	Altered expression-	Downregulated in high grade/metastasis	11p11, 16q22, 17p11
ELAC2/HPC2, RNAse L	Germline mutation/variation	Inactivated	17p11, 1q25
AR, CYPs, hOGG1	Germline variation	?	Xq12, multiple, 3p26
CAPB, PCAP, HPC20	Not yet cloned	?	1p36, 1q42, 20q13

*Not yet confirmed.

chemoprevention of prostate cancer, which may be particularly relevant given the putative role for oxidative stress in the etiology of this disease (see Nelson et al., 2001 for discussion).

Other sites of loss/deletion in prostate cancer mainly occur in the late stages of cancer progression. Genetic inactivation of such tumor suppressor genes as *p53*, *RB1*, *p16*, and *PTEN* is seen most commonly in advanced cases of prostate cancer, although nonmutational downregulation of these genes, particularly *PTEN*, may frequently occur earlier. Furthermore, the occurrence of pathogenic mutations in these genes in early prostate cancer may portend a less favorable outcome. As mentioned above, agents which target *PTEN* null prostate cancer cells have provided an important new avenue for therapeutic intervention. Gains of Xq and 8q are associated with progression of prostate cancer, and may reflect selection of cells containing extra copies of *AR* and *c-myc*, respectively. Activation of the wnt/β catenin pathway appears to play an important role in a subset of prostate cancers and activates or otherwise modifies androgen action in the prostate (Truica et al., 2000; Chesire et al., 2002). The *KLF6* gene at 10p15 has recently been reported to be inactivated by mutation and deletion in a high proportion of primary prostate cancers (Narla et al., 2001).

Regarding a potentially inherited form of prostate cancer, results from multiple studies provide evidence for aggregation of prostate cancer in families, and family history of prostate cancer remains one of the most consistent risk factors yet identified. Segregation analyses support the existence of high-risk alleles for prostate cancer, and twin studies have estimated that a substantial fraction (over 40%) of prostate cancer has a genetic component (reviewed by Stanford and Ostrander, 2001). These findings have led to genome-wide searches for prostate cancer susceptibility alleles in collections of prostate cancer families. In spite of extensive effort, a prostate cancer equivalent of *BRCA1* or *-2* has proved elusive. At least eight different loci have been reported to reach some level of significance in linkage studies, and over a dozen more loci have been implicated over the past six years by multiple groups worldwide working on this problem. Two candidate prostate cancer susceptibility genes have been identified by positional cloning efforts, *HPC2/ELAC2* and *RNase L* (Tavtigian et al., 2001; Carpten et al., 2002). These genes most likely account for a small proportion of either hereditary prostate cancer or prostate cancer in general, with their most important effects possibly being mediating by common, low penetrance alleles. The paucity of consistent signals in different genome-wide scans of prostate cancer families supports the conclusion that the genetics of this disease are quite complex, making the influences of major genes difficult to detect. This outcome is perhaps not surprising given the high prevalence of prostate cancer and its late onset, etiologic heterogeneity, and inability to define more genetically homogeneous subsets of disease. The formation of a large collaborative group to address these questions provides reason for optimism in this area (Xu, 2000).

In addition to major gene effects, extensive studies are underway to identify more common "low penetrance" alleles which may be important in determining or modifying prostate cancer risk. The identification of common sequence variants in the androgen action pathway has implicated both the androgen receptor and various androgen-metabolizing enzymes as important candidates in this respect (Ross et al., 1998). Additional studies investigating genetic variation in DNA repair, carcinogen metabolism, and inflammation pathways as risk factors for prostate cancer are underway. While on an individual basis such genetic variants are of limited use for risk assessment, consistent associations of candidate genes can implicate novel pathways as etiologic factors. Furthermore, it is possible that such variants, either alone or in combination with other risk factors, may be useful to stratify risk for prevention or early screening studies.

Gene expression studies—New diagnostic and prognostic markers

In addition to PSA and PSMA, recent expression studies have identified a large number of potentially important biomarkers, which are being investigated for their diagnostic, prognostic, and therapeutic potential. A sampling of these markers includes

hepsin, PSCA, AMACR, TARP, STEAP, PCGEM1, DD3, S100P, and PIM1 (See Table 1). AMACR, an enzyme involved in β oxidation of fatty acids, appears to be a powerful new marker for prostate cancer (Jiang et al., 2001). Antibodies to PSCA, a cell-surface antigen expressed in normal prostate and in prostate cancer tissues, have demonstrated antitumor activity in xenograft models of prostate cancer (Saffran et al., 2001). Finally, the ability to develop a molecular classification system to identify tumors with poor prognosis or otherwise stratify tumors for treatment options is a current area of intense interest (Singh et al., 2002).

Conclusion

The dilemma of prostate cancer presents the clinician and basic researcher with a number of challenges somewhat unique in human oncology. Its frequent occurrence, tendency for a long natural history, common multifocality and morphologic heterogeneity, and progression to hormone refractory state are all poorly understood aspects of this disease. However, the rapid pace of advances, both technologically and mechanistically, provides a platform for the systematic cataloging and characterization of the normal and cancerous prostate cell phenotype and underlying genotype. This in turn should set the stage for highly rational approaches to the development of new preventive, prognostic, and therapeutic strategies, which are urgently needed for this common malignancy.

References

Bastacky, S.I., Wojno, K.J., Walsh, P.C., Carmichael, M.J., and Epstein, J.I. (1995). Pathological features of hereditary prostate cancer. J. Urol. *153*, 987–992.

Berges, R.R., Vukanovic, J., Epstein, J.I., CarMichel, M., Cisek, L., Johnson, D.E., Veltri, R.W., Walsh, P.C., and Isaacs, J.T. (1995). Implication of cell kinetic changes during the progression of human prostatic cancer. Clin. Cancer Res. *1*, 473–480.

Boring, C.C., Squires, T.S., and Tong, T. (1992). Cancer statistics, 1992. CA Cancer J. Clin. *42*, 19–38.

Bostwick, D.G. (1989). Prostatic intraepithelial neoplasia (PIN). Urology *34*, 16–22.

Bunting, P.S. (2002). Screening for prostate cancer with prostate-specific antigen: beware the biases. Clin. Chim. Acta *315*, 71–97.

Carpten, J., Nupponen, N., Isaacs, S., Sood, R., Robbins, C., Xu, J., Faruque, M., Moses, T., Ewing, C., Gillanders, E., et al. (2002). Germline mutations in the ribonuclease L gene in families showing linkage with HPC1. Nat. Genet. *30*, 181–184.

Chan, J.M., Stampfer, M.J., Giovannucci, E., Gann, P.H., Ma, J., Wilkinson, P., Hennekens, C.H., and Pollak, M. (1998). Plasma insulin-like growth factor-I and prostate cancer risk: a prospective study. Science *279*, 563–566.

Chen, C.D., and Sawyers, C.L. (2002). NF-kappa B activates prostate-specific antigen expression and is upregulated in androgen-independent prostate cancer. Mol. Cell. Biol. *22*, 2862–2870.

Chesire, D.R., Ewing, C.M., Gage, W.R., and Isaacs, W.B. (2002). In vitro evidence for complex modes of nuclear beta-catenin signaling during prostate growth and tumorigenesis. Oncogene *21*, 2679–2694.

De Marzo, A.M., Putzi, M.J., and Nelson, W.G. (2001). New concepts in the pathology of prostatic epithelial carcinogenesis. Urology *57*, 103–114.

Denmeade, S.R., Nagy, A., Gao, J., Lilja, H., Schally, A.V., and Isaacs, J.T. (1998). Enzymatic activation of a doxorubicin-peptide prodrug by prostate-specific antigen. Cancer Res. *58*, 2537–2540.

Fang, J., Metter, E.J., Landis, P., Chan, D.W., Morrell, C.H., and Carter, H.B. (2001). Low levels of prostate-specific antigen predict long-term risk of prostate cancer: results from the Baltimore Longitudinal Study of Aging. Urology *58*, 411–416.

Feldman, B.J., and Feldman, D. (2001). The development of androgen-independent prostate cancer. Nat. Rev. Cancer *1*, 34–45.

Gong, M.C., Chang, S.S., Sadelain, M., Bander, N.H., and Heston, W.D. (1999). Prostate-specific membrane antigen (PSMA)-specific monoclonal antibodies in the treatment of prostate and other cancers. Cancer Metastasis Rev. *18*, 483–490.

Hsing, A.W., and Devesa, S.S. (2001). Trends and patterns of prostate cancer: what do they suggest? Epidemiol. Rev. *23*, 3–13.

Isaacs, W., and Kainu, T. (2001). Oncogenes and tumor suppressor genes in prostate cancer. Epidemiol. Rev. *23*, 36–41.

Jiang, Z., Woda, B.A., Rock, K.L., Xu, Y., Savas, L., Khan, A., Pihan, G., Cai, F., Babcook, J.S., Rathanaswami, P., et al. (2001). P504S: a new molecular marker for the detection of prostate carcinoma. Am. J. Surg. Pathol. *25*, 1397–1404.

McNeal, J.E. (1978). Origin and evolution of benign prostatic enlargement. Invest Urol. *15*, 340–345.

Narla, G., Heath, K.E., Reeves, H.L., Li, D., Giono, L.E., Kimmelman, A.C., Glucksman, M.J., Narla, J., Eng, F.J., Chan, A.M., et al. (2001). KLF6, a candidate tumor suppressor gene mutated in prostate cancer. Science *294*, 2563–2566.

Nelson, W.G., De Marzo, A.M., Deweese, T.L., Lin, X., Brooks, J.D., Putzi, M.J., Nelson, C.P., Groopman, J.D., and Kensler, T.W. (2001). Preneoplastic prostate lesions: an opportunity for prostate cancer prevention. Ann. N Y Acad. Sci. *952*, 135–144.

Neshat, M.S., Mellinghoff, I.K., Tran, C., Stiles, B., Thomas, G., Petersen, R., Frost, P., Gibbons, J.J., Wu, H., and Sawyers, C.L. (2001). Enhanced sensitivity of PTEN-deficient tumors to inhibition of FRAP/mTOR. Proc. Natl. Acad. Sci. USA *98*, 10314–10319.

Pound, C.R., Partin, A.W., Eisenberger, M.A., Chan, D.W., Pearson, J.D., and Walsh, P.C. (1999). Natural history of progression after PSA elevation following radical prostatectomy. JAMA *281*, 1591–1597.

Rodriguez, R., Schuur, E.R., Lim, H.Y., Henderson, G.A., Simons, J.W., and Henderson, D.R. (1997). Prostate attenuated replication competent adenovirus (ARCA) CN706: a selective cytotoxic for prostate-specific antigen-positive prostate cancer cells. Cancer Res. *57*, 2559–2563.

Ross, R.K., Pike, M.C., Coetzee, G.A., Reichardt, J.K., Yu, M.C., Feigelson, H., Stanczyk, F.Z., Kolonel, L.N., and Henderson, B.E. (1998). Androgen metabolism and prostate cancer: establishing a model of genetic susceptibility. Cancer Res. *58*, 4497–4504.

Saffran, D.C., Raitano, A.B., Hubert, R.S., Witte, O.N., Reiter, R.E., and Jakobovits, A. (2001). Anti-PSCA mAbs inhibit tumor growth and metastasis formation and prolong the survival of mice bearing human prostate cancer xenografts. Proc. Natl. Acad. Sci. USA *98*, 2658–2663.

Singh, D., Febbo, P.G., Ross, K., Jackson, D.G., Manola, J., Ladd, C., Tamayo, P., Renshaw, A.A., D'Amico, A.V., Richie, J.P., et al. (2002). Gene expression correlates of clinical prostate cancer behavior. Cancer Cell *1*, 203–209.

Stanford, J.L., and Ostrander, E.A. (2001). Familial prostate cancer. Epidemiol. Rev. *23*, 19–23.

Stanford, J.L., Stephenson, R.A., Coyle, L.M., Cerhan, J., Correa, R., Eley, J.W., Gilliland, F., Hankey, B., Kolonel, L.N., Kosary, C., et al. (1999). Prostate Cancer Trends 1973–1995, SEER Program, National Cancer Institute NIH Pub No 99–4543 (Bethesda, MD)

Tavtigian, S.V., Simard, J., Teng, D.H., Abtin, V., Baumgard, M., Beck, A., Camp, N.J., Carillo, A.R., Chen, Y., Dayananth, P., et al. (2001). A candidate prostate cancer susceptibility gene at chromosome 17p. Nat. Genet. *27*, 172–180.

Truica, C.I., Byers, S., and Gelmann, E.P. (2000). Beta-catenin affects androgen receptor transcriptional activity and ligand specificity. Cancer Res. *60*, 4709–4713.

Xu, J. (2000). Combined analysis of hereditary prostate cancer linkage to 1q24–25: results from 772 hereditary prostate cancer families from the International Consortium for Prostate Cancer Genetics. Am. J. Hum. Genet. *66*, 945–957.