Review

Genetic Characteristics of Prostate Cancer

Michael Huncharek¹ and Joshua Muscat
Department of Radiation Oncology, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts 02114 [M. H.], and Division of Epidemiology, American Health Foundation, New York, New York 10017 [J. M.]

Abstract
Prostate cancer is the most commonly diagnosed malignancy in United States males. Unfortunately, numerous controversies surround clinical management for early stage disease and the utility of population screening. Much of this controversy stems from the lack of knowledge about the biology of prostate cancer, including the lack of clearly defined risk factors, absence of markers indicative of aggressive clinical behavior, as well as a lack of a clear understanding of its underlying genetic features. This paper reviews currently available evidence regarding the genetic characteristics of adenocarcinoma of the prostate, including the impact of family history on disease risk, the nature of structural genetic aberrations, and the possible role of oncogenes and tumor suppressor genes in its pathogenesis. A clearer understanding of these issues will hopefully lead to more effective and rational treatment policies in addition to the development of effective disease prevention strategies.

Introduction
Adenocarcinoma of the prostate is now the most common malignancy in adult males in the United States. In 1994, an estimated 200,000 new cases will be diagnosed resulting in approximately 38,000 deaths (1). Over the last 12 years the incidence of prostate cancer increased 50%. Likewise, deaths from this disease increased 40% over this same period (2). With an aging population and decreases in death rate from cardiovascular and other chronic diseases, the increase in incidence and mortality from prostate cancer is expected to continue to rise. Clearly, carcinoma of the prostate represents a major clinical and public health challenge.

Current clinical management of early stage prostate cancer remains controversial. With the development of a prostate specific marker, i.e., PSA, early detection of this malignancy is far more common than in the past. Unfortunately, although biochemical diagnosis is possible in many asymptomatic patients, the difficulty in distinguishing prostate cancers that will remain clinically silent from those destined for aggressive, metastatic behavior, remains problematic. Development of a marker capable of making this distinction would be of great value.

Yet another problem in the management of cancer of the prostate is the lack of effective treatment for advanced disease, i.e., those with metastases. Hormonal deprivation provides only temporary palliation, and few other avenues of treatment exist. At present, little is known regarding the mechanisms of acquired androgen independence hindering advances in developing more effective treatments for this group of patients.

Cancer is fundamentally a genetic disease with the normal genetic functions governing cell growth altered by a variety of mechanisms. Tumor development is thought to arise through a series of genetic alterations leading to abnormal cell growth. The colon cancer model, developed by Fearon and Vogelstein (3) serves as an important paradigm for this process. In addition, such mechanisms as “dysregulation of growth factor networks” may be involved in the development of prostate tumors (4). At present, relatively little is known regarding the genetic characteristic and molecular biology of prostate cancer (5). An increased understanding of the pathogenesis of this tumor has important implications for disease prevention, diagnosis, and effective treatment. This paper reviews current knowledge regarding the genetic characteristics of this tumor derived from epidemiological, clinical, and laboratory research. These data will also be discussed in the context of possible avenues for additional research.

Family History and the Risk of Prostate Cancer
A number of hypotheses have been put forth regarding the etiology of prostate cancer. These include possible roles for dietary fat intake, vitamin A, sexual activity, and body size, among others. With the possible exception of dietary fat intake, most of these hypotheses remain unsupported by existing data. Identification of high-risk groups has, therefore, not been possible. As with many cancers, the role of family history in the etiology of prostate cancer is unclear. Although a possible genetic etiology has been proposed, definitive evidence is lacking.

The Mormon population of Utah has served as an important epidemiological cohort for the study of familial factors in various cancers. This is due to the availability of extensive genealogical records providing a unique resource for such work. An early study by Meikle and Stanish (5) in Utah Mormons examined familial aspects of prostate cancer. This analysis showed that brothers of probands with prostate cancer diagnosed before age 62 years had a 4 times higher relative risk for developing this malignancy. An additional report among the same population published in 1982 examined familial site-specific clustering of cancer with an emphasis on the genetic epidemiology of prostate cancer (6). Almost 3000 cases of adenocarcinoma of the prostate were studied. A case-control analysis showed that brothers of patients diagnosed with prostate cancer at age 64 years or earlier were almost 6 times more likely to develop this tumor than controls. Elevated risk was also noted among brothers of patients diagnosed later in life, i.e., between ages 65 and 80 years (2–3 times that seen among controls). Overall, cancers of the prostate, lip as well as melanoma appeared the most “familial” of all cancer sites.
Investigators from the Brady Urological Institute at Johns Hopkins performed a case-control study to estimate the relative risk of developing prostate cancer for men with a positive family history (7). Six hundred-forty spouse controls were used in this analysis. Fifteen % of cases had a father or brother with prostate cancer as compared with only 8% of controls ($P < 0.001$). Men with a father or brother affected were twice as likely to develop prostate cancer in contrast to those with no affected relatives. An additional finding was a trend of increasing risk with increasing number of affected family members, i.e., men with 2 or 3 first-degree relatives with prostate cancer had a 5- and 11-fold increased risk of developing this malignancy, respectively (7). An additional study from Quebec, Canada, found a similar increase in risk of developing prostate cancer among men with first-degree relatives also affected with this tumor (8). In a case-control analysis, patients with one to four affected first-degree relatives were 8 times more likely to develop prostate cancer as compared with population based controls (odds ratio; 8.7; 95% confidence interval, 2.00–38.17). The authors speculated that, in addition to genetic factors, environmental influences, e.g., nutrition and lifestyle, may also be important.

With the existing evidence of familial clustering of prostate cancer, Carter et al. (9) undertook a study to define the nature of this “familial aggregation” and to determine if Medelian inheritance could explain prostate cancer clustering. This study examined 691 families identified via a single prostate cancer proband. Families of probands with early onset disease were used because if simple Medelian inheritance is operative in prostate cancer, it is most likely to be seen in such families. Both early age at onset of disease in the proband and multiple affected family members were both important determinants of risk of prostate cancer in these families. Relatives of cases had a higher age-specific cumulative risk of disease compared to relatives of older cases (9). No interaction was noted between these two variables suggesting that they are entirely independent. A segregation analysis was also performed to assess whether the observed familial clustering was consistent with Medelian inheritance. As the authors state, “A model of autosomal dominant inheritance of a rare allele that predisposes carriers to be affected at earlier ages and in higher proportions than noncarriers gave the best fit to these families” (9). They concluded that this inherited form of prostate cancer accounts for a significant proportion of early onset disease, and in higher proportions than noncarriers gave the best fit to these families” (9). They concluded that this inherited form of prostate cancer diagnosed by age 85 years. This report was the first to describe an autosomal dominant mode of inheritance of this tumor.

The development of a serum marker for prostate cancer (PSA) has revolutionized the detection and management of this malignancy. Nonetheless, at present, the use of PSA in conjunction with a digital rectal exam and transrectal ultrasound for screening men at normal risk for prostate cancer remains controversial (10). The growing evidence for familial clustering of prostate cancer raises the question whether a high-risk population suitable for intensive screening can be identified based on family history. A recent study by McWhorter et al. (11) provides some preliminary information on this question. By using the Utah Cancer Registry, 17 sets of two brothers with prostate cancer were identified. A total of 34 first-degree relatives of these probands were identified (ages 55–80 years). Each underwent a screening examination that included a serum PSA, a digital rectal examination, a transrectal ultrasound, and core needle biopsies of the prostate. Eight of 34 (24%) first-degree relatives were found to have previously unsuspected prostate cancer, whereas only one case was expected ($P < 0.01$). Three subjects had abnormal PSAs and four had abnormal digital rectal examinations. Seven patients subsequently underwent total prostatectomy and lymph node dissection. Three had pathological stage B disease and four had stage C; none had positive lymph nodes.

Despite the findings outlined above, it is unclear at present if such screening would result in decreased mortality from this disease. It is, therefore, questionable whether family history alone is capable of defining a high-risk group suitable for intensive screening.

**Genetic Aberrations**

**Ploidy and S-Phase Fraction.** Histological grade and clinical stage are both recognized as important prognostic variables in prostate cancer. Nonetheless, both parameters are subjective and their predictive value remains somewhat limited. That is, although tumors of low histological grade tend to follow a more benign course than do high-grade tumors, the majority of localized prostate tumors are of intermediate grade. This large segment of prostate cancers is characterized by a highly variable natural history. More objective prognostic criteria would, therefore, potentially eliminate some of this uncertainty.

Analysis of DNA content (i.e., ploidy) has been suggested as an additional prognostic indicator in prostate cancer. This is based on prior experience with a variety of other solid neoplasms (12). In an early study, Tribukait (13) showed that in prostate tumors, DNA ploidy correlates with degree of cellular anaplasia. These same investigators also attempted to estimate the relationship between ploidy and survival in a group of untreated patients with prostate cancer. One hundred fifty-seven patients were followed and remained untreated until the development of symptoms of disease progression. All patients had stage B and C disease without clinical evidence of metastases. DNA flow cytometry was done on fine needle aspiration biopsy material at the time of diagnosis. The majority of patients had moderately differentiated tumors. Minimum follow-up for the entire group was 4 years.

The survival experience of these patients was as follows. Within 4 years of diagnosis, only 5% of patients with diploid tumors died, whereas 30% of those with tetraploid tumors did so. Sixty % with a “single nonetraploid aneuploid cell line” died within 4 years of diagnosis. Also of interest, the time to local progression was shorter for patients with nondiploid tumors. Ploidy also was related to development of distant metastases. Three % of subjects with diploid tumors developed metastases during the study period versus 12% with aneuploid neoplasms.

Frankfurt et al. examined the relationship between DNA ploidy, tumor grade, and stage (14). A total of 45 prostatectomy specimens and 11 biopsy specimens were analyzed by using flow cytometry. Forty-four % of specimens were aneuploid, and there was a clear association between pathological stage and ploidy, i.e., frequency of ploidy increased with advancing stage. All stage B tumors were diploid, whereas over 72% of patients with distant metastases (stage D2) were aneuploid. Of the poorly differentiated tumors, 71% were aneuploid, whereas only 36% of tumors with a Gleason score of 5 or 6 were aneuploid. Of note, in nearly two-thirds of patients with aneuploid tumors, pelvic nodal or distant metastases were found. Only 18% of diploid tumors showed such spread. The authors speculated that ploidy, in conjunction with a degree of histological differentiation, may improve prognostic evaluation of these tumors.

Several recent studies have examined this latter topic. Stephenson et al. (15) examined patients with metastatic prostate cancer, i.e., stage D1. Tumor samples from a total of 82 patients were analyzed by using flow cytometry; 49 tumors were aneuploid and 33 were diploid. After controlling for
possible confounding factors, e.g., age, grade, etc., a significant survival difference was noted. That is, median survival among patients with aneuploid tumors was 5.0 versus 8.8 years for patients with diploid tumors. Flow cytometric DNA measurements of nodal metastases was, therefore, felt to represent a strong predictor of survival in this patient group. 

Visakorpi et al. (16) from Finland, examined both DNA ploidy and S-phase fraction (16). Seventy-eight untreated cases of histologically confirmed prostate cancers were studied by flow cytometry by using paraffin-embedded tissue. All T stages were represented with 26 patients presenting with metastatic disease. Both DNA aneuploidy and SPF above the median of 4.2% were associated with high histological grade and presence of distant metastases. These parameters were also predictive of shorter 10-year, progression-free survival and overall survival (P = 0.004 and P = 0.0001, respectively). No patient with an SPF above the median survived 10 years, whereas 45% with an SPF below the median did so. Also of interest, SPF appeared related to response to hormonal therapy in patients with metastatic tumor. That is, of seven tumors with SPF above 12%, none responded to hormonal manipulation, whereas 52% of those with lower SPFs did so. DNA ploidy, tumor grade, T-stage, or M-stage did not correlate with endocrine responsiveness.

The clinical importance of DNA ploidy as an adjunct to conventional clinicopathological data remains unclear. Several early studies found that ploidy offered limited prognostic information in clinically localized disease (17) while others (as cited above) have noted evidence to the contrary. Although most primary tumors are diploid, there appears to be a correlation between high-grade histologic and aneuploidy. Metastatic tumors are also often aneuploid. Therefore, increasing evidence suggests that this parameter may be informative regarding the biological behavior of prostate tumors. Further work will be required among patients carefully matched for stage, grade, and other important parameters to define a clear role for routine assessment of DNA content and SPF.

Cytogenetics. Cytogenetic analyses of human tumors have yielded important information of both clinical and epidemiological interest. The majority of such analyses concern hematological malignancies and malignant lymphomas. Epithelial tumors represent a minority of tumors studied with very limited data available on adenocarcinoma of the prostate. Tissue heterogeneity represents an important complicating factor of such analyses. As pointed out by Micale et al. (18), "The prostate is often characterized by morphologically distinct areas of tumor that may differ genotypically. Foci within a prostate tumor show varying degrees of differentiation and may contain cells which differ karyotypically." The presence of normal epithelium and stroma within the tumor further complicates these studies because the origin of the cells being analyzed may not always be certain.

Karyotypic information complements data generated from studies of DNA content and also serves to further elucidate the specific "genetic cascade" of events that may be involved in prostate tumor development. In addition, tumor karyotype may be related to prognosis as seen in some leukemias and non-Hodgkin's lymphoma (19, 20).

Brothman et al. (21) evaluated 30 cultured primary prostate tumors obtained from patients undergoing radical prostatectomy. Most patients had early stage disease with only one sample being from a patient with a stage C tumor. Also only one patient received prior radiation or chemotherapy. Twenty-one samples showed normal male karyotypes, i.e., 46XY. Nine of 30 (30%) showed some clonal aberration. Five of these were hyperdiploid, whereas one sample showed double-minute chromosomes. Three tumors exhibiting structural abnormalities included one with loss of the Y chromosome, partial trisomy of chromosome 4, and one with a translocation between the long arms of chromosomes 5 and 7 (21). A correlation was noted between poorly differentiated histology and cytogenetic changes. That is, the majority of specimens with cytogenetic aberrations were from samples of poorly differentiated tumor, i.e., 56% of poorly differentiated specimens had chromosomal aberrations versus 16% with more favorable histologies. No consistent abnormality among the 30 specimens examined was noted.

The authors reviewed the data on karyotypic abnormalities in prostate cancer accumulated up to 1989. These were data based on the analysis of only 11 primary prostatic tumors. Loss of chromosomes 1, 2, 5, and Y, as well as gain of chromosomes 7, 14, 20, and 22 were described. In addition, rearrangements involving 2p, 7q, and 10q were observed commonly.

A somewhat later study from Sweden analyzed 57 primary prostatic adenocarcinomas (22). Cytogenetic analysis after short-term culture was performed by using material obtained by radical prostatectomy. Patients represented the full range of pathological stages with most having locally advanced disease, i.e., extracapsular extension of tumor (74%). Twenty-two patients had known metastatic disease. Histologically, 5 samples were well-differentiated tumors, 30 were moderately differentiated, and 22 were poorly differentiated. Twenty-four of 57 (42%) had normal karyotypes. Of the remaining samples, 18 showed structural nonclonal aberrations. All other specimens had clonal karyotypic abnormalities.

The most common clonal numerical aberration was loss of the Y chromosome, which was found in six tumors. Structural chromosomal rearrangements, often with associated numerical changes were noted in 12 tumors. The most frequently involved chromosomes were 1, 7, and 10. The aberrations seen in chromosome 1 were different in each case with no obvious breakpoint clustering. In contrast, breakpoints in chromosomes 7 and 10 were clustered at bands 7q22 and 10q24. Loss of chromosomal material on chromosome 8 (8p) was noted in four tumors, i.e., unbalanced translocations and monosomies (22). It is interesting to note that loss of 8p loci was associated with high tumor grade.

Several recent papers have highlighted the technical limitations of conventional karyotypic analysis in solid tumors (23, 24). Conventional techniques examining metaphase preparations from prostatic tumors show structural or numerical abnormalities in only a minority of cases. FISH is a relatively new technique developed to enumerate specific chromosomes within metaphase and interphase nuclei (23). Chromosome-specific DNA probes are used and have demonstrated superior sensitivity in detecting aneuploid prostate tumors (23).

Brown et al. (23) used FISH techniques by using 12 chromosome probes to analyze 40 randomly selected radical prostatectomy specimens for chromosomal abnormalities. Probes for chromosomes 4, 6, 7, 8, 9, 10, 11, 12, 17, 18, X, and Y were used, and 16 of 40 (40%) samples contained chromosomal aneuploidies. Chromosome 8 was aneuploid in nine cases (23%), whereas gain of chromosome 7 was observed in eight tumors (20%). Chromosome 17 was aneuploid in four tumors, and "chromosomes 10, 11, 12, 18, and Y were each aneuploid twice" (23). One tumor showed loss of chromosome 9.

The authors further point out that high-grade tumors were more likely to be aneuploid by FISH, and tumors with chromosome 8 aneuploidies were of higher stage. Both findings were statistically significant. Prognostic significance of these find-
ings were not explored but was suggested as a further avenue for research. Of note, Alcaraz et al. (24) examined the prognostic significance of aneusomy of chromosome 7 by using FISH techniques. These authors examined 25 tumor specimens from patients dying from prostate cancer within 3 years of diagnosis and compared them to 25 control samples from patients surviving more than 5 years from time of diagnosis of prostate cancer. Cases and controls were matched for age, tumor grade, and pathological stage. One-hundred % of tumors from the poor prognosis patients were aneuploid versus 44% of the control group (P < 0.0001). Also of interest, statistical analysis revealed that only chromosome 7 aneusomy had a significantly higher incidence in the poor prognosis group compared with other chromosomes. Almost all (96%) poor prognosis tumors showed aneusomy of chromosome 7, suggesting that this aberration is a nonrandom alteration associated with aggressive biological behavior. As the authors point out, chromosome 7 aneuploidies have also been correlated with aggressive behavior in melanoma and bladder carcinoma (24).

The prognostic implications of karyotypic abnormalities is unclear. In Lundgren’s series (22) of 57 patients with prostate cancer cited earlier, an analysis of survival in relation to chromosomal aberrations was performed. Median follow-up from diagnosis was 2.6 years. Patients with clonal karyotypic abnormalities had shorter survival times (1.3 years) than those with normal karyotypes (>3.0 years; P < 0.05). In a multivariate analysis analyzing all other recognized prognostic factors for prostate cancer, the influence of karyotypic abnormalities on survival was not significant (22).

Oncogenes and Tumor Suppressor Genes

Oncogenes. Two classes of genes implicated in carcinogenesis are the “dominant oncogenes” and tumor suppressor genes, e.g., p53. The former, when mutated, become functionally dominant f)S3. The latter, when mutated, become functionally recessive.

The ras family of oncogenes is among the most common activated oncogenes in human cancer (27). This family consists of three members (H-ras, K-ras, and N-ras). These genes code for a protein that is located on the inner surface of the plasma membrane and has guanosine triphosphatase activity. In general, it is felt that ras mutations alone are not sufficient to induce human cancers but may be involved in a cascade of events involving other oncogenes and tumor suppressor genes in the carcinogenic process (28).

Early work from the late 1980s indicated that ras oncogenes were rarely activated in prostate cancer (29). Subsequent studies using PCR techniques showed similar infrequent mutations in these genes (30). In a 1992 analysis by Moul et al. (31), a total of 24 archival paraffin-embedded tumor samples from patients undergoing radical prostatectomy were examined by using PCR techniques (codons 12, 13, and 61). Twenty-one samples were stage C tumors, whereas the remainder were stage B. No ras mutations were found in this cohort of localized prostate carcinoma; a result in agreement with the available literature.

Although there is some suggestion that ethnic and/or racial differences may exist in relation to ras mutation frequency (32, 33) it appears that such mutations are rare among United States males with clinically localized disease. Additional work among a variety of populations will be necessary to provide definitive information regarding this subject.

The myc family of genes have also been studied in prostate cancer. These genes code for nuclear DNA-binding phosphoproteins involved in transcriptional regulation. Investigators at Columbia University examined both benign prostate tissue, as well as adenocarcinoma of the prostate obtained by prostatectomy (34). Six of nine tumor specimens showed elevated levels of c-myc transcripts, whereas none of the samples of benign hypertrophy did so. Tumor specimens with high c-myc expression were histologically high grade. The authors speculated that c-myc expression may be related to biological aggressiveness. Other work showed similar results, i.e., elevated c-myc expression in tumor samples as compared with benign hypertrophy (35). As Peehl (36) points out, although a clear role for the myc oncogene in prostate cancer has not been demonstrated c-myc amplification, rearrangement and overexpression is a feature of the LNCaP prostate cell line. This cell line was derived from a metastatic prostate tumor to a lymph node. It should also be noted that LNCaP is hormonally responsive, although in a study by Nag and Smith (37), androgen exposure did not appear to affect the level of c-myc RNA transcripts in studies using this cell line.

The sis oncogene codes for the B chain of platelet-derived growth factor, and its expression has been noted in a number of prostate cancer cell lines (38). Platelet-derived growth factor-like proteins were found expressed by both DU-145 and PC-3 cell lines, although PDGF receptors were not detected in either cell line (38). In a 1985 study, investigators found significantly elevated levels of sis-related proteins in the urine of patients with prostate cancer by using antibodies specific for this oncogene product. Elevated levels were also found in urine from patients with a variety of other neoplasms, e.g., breast and bladder. Further characterization of these findings is not available. Therefore, the role that sis may play in adenocarcinoma of the prostate is unclear.

The recent literature contains several additional reports detailing the potential involvement of additional oncogenes in this neoplasm. The bcl-2 oncogene was initially characterized in lymphoid neoplasms and is thought to function by “overriding programmed cell death mechanisms” (39). A study by McDonnell et al. (39) using immunohistochemical techniques demonstrated that bcl-2 was undetectable in 13 of 19 androgen-dependent prostate tumors. In contrast, 77% of androgen-independent neoplasms stained positively (39). Furthermore, by using a rat experimental system, these investigators showed that bcl-2 expression could be enhanced by androgen ablation. Such increased expression could possibly result in an “apoptosis-resistant phenotype” developing in the tumor cell population (39).

The HER-2/new gene has been implicated in the pathogenesis of breast and ovarian cancer (40, 41). Amplification of this oncogene is also correlated with a shorter interval to relapse and overall survival in breast cancer (40). One recent study indicated that overexpression of HER-2/new is correlated in prostate tumors with higher grade, higher stage of disease, and high S-phase and aneuploidy on flow cytometric analysis (42).

The HER-2/new oncogene encodes a phosphoglycoprotein related to the epidermal growth factor receptor (43). Some adenocarcinomas of the breast show overexpression of the epidermal growth factor receptor and neu, with overexpression associated with poor prognosis (44). Several reports indicate relatively low levels of expression of the EGFR receptor in
prostate cancer (45–46), although overexpression of the gene product has been observed in prostatic tumors (47).

Investigators from the University of Alabama have recently examined expression of this gene product in prostatic intraepithelial neoplasia and prostatic adenocarcinoma (48). Immunostaining in benign prostatic tissue showed staining for both pl60erb-3 and pl85erb-2 in the basal cells. The function of these cells is not known, although they are felt to possibly function as stem cells giving rise to secretory epithelial cells. A different staining pattern was found in intraepithelial neoplasia, i.e., staining for both of these products was observed within the luminal cells. Cytoplasmic staining was also seen in most dysplastic cells (48). As the authors state, “These findings demonstrate differences in the extent of expression as well as the subcellular distribution of pl60erb-3 and pl85erb-2 in dysplastic epithelium compared with benign epithelium” (48). Localized adenocarcinoma showed strong to moderate staining in 27 of 29 samples, whereas metastatic tumors showed a similar high proportion with positive immunostaining for these gene products. Increasingly, it is felt that adenocarcinoma of the prostate may arise from prostatic intraepithelial neoplasia. The finding of pl60erb-3 and pl85erb-2 in this lesion suggests that the function of such genes leads to abnormal proliferation, setting the stage for the cascade of genetic events responsible for tumorigenesis.

**Tumor Suppressor Genes.** Discovery of tumor suppressor genes was the outgrowth of investigations showing that neo-plastic transformation could involve gene products that negatively regulate cell proliferation. Inactinization via deletion or mutation of such genes leads to abnormal proliferation, setting the stage for the cascade of genetic events responsible for tumorigenesis.

The Rb gene is a tumor suppressor gene associated with the development of retinoblastoma in the immature retina. This occurs with mutation of both alleles either via inherited mutation or two somatic mutations. Rb mutations are also found in a variety of other neoplasms, such as a subset of osteosarcomas, soft tissue sarcomas, as well as breast and lung tumors (49). This suggests that the Rb gene may have an important regulatory function in a wide variety of tissues.

Bookstein et al. (50) recently examined Rb in the prostate cancer cell line DU-145. This cell line, in contrast to two others also studied (PC-3 and LNCaP), showed a mutation in exon 21. This results in a shortened Rb protein, i.e., amino acid loss, which was functionally inactive in tumor suppression. Replacement of Rb protein suppressed the tumorigenic properties of DU-145 cells, which suggests that inactivation of this gene plays an important role in the development of some prostate cancers. Further work by this same group documented an Rb mutation in prostate tissue obtained via prostatectomy or autopsy. This deletion was a 103-bp deletion within the promoter region of one Rb allele. A second mutation in this tumor resulted in loss of the second normal Rb allele (49). Investigators from Johns Hopkins University used PCR techniques to examine allelic loss of the Rb gene in prostate tumors (5). Eleven of 41 tumors examined (27%) demonstrated allelic loss of one copy of the Rb gene, suggesting an important role for this tumor suppressor gene in a subset of prostate carcinomas.

Unfortunately, only limited data are available regarding Rb in prostate carcinoma. It is unclear what proportion of prostate tumors harbor Rb mutations and what biological characteristics are associated with such abnormalities. Additional work is needed to clarify these issues.

The p53 tumor suppressor gene located on chromosome 17 is commonly mutated in a large variety of human cancers (51). Roughly one-half of all human tumors harbor p53 mutations making this suppressor gene one of the most intensely studied. Mutations occurring in the coding region of p53 associated with tumorigenesis occur largely in a region of the gene showing the greatest cross-species homology, i.e., between codons 117 and 286. (52). Within this region, four "hot spots" exist in which mutations appear to cluster: codons 132–143, 174–179, 236–248, and 272–281 (53). Most mutations affecting p53 are missense point mutations in these regions leading to a stabilized protein product that can be detected immunohistochemically.

The frequency of p53 mutations in prostate tumor tissue has been studied utilizing both mAb techniques and PCR amplification and DNA sequencing. Issacs et al. (54) studied five prostate cancer cell lines for p53 mutation (PC-82, TSU-PrI, LNCAp, PC-3, and DU-145; Ref. 54). The latter four were derived from metastatic tumor deposits, whereas PC-82 was derived from a primary tumor. DNA sequencing showed p53 mutations in TSU (codon 126), PC-3 (codon 138), and DU-145 (codons 223 and 274). One of two primary prostate tumors studied was also found to have a p53 mutation at codon 197. The authors transfected wild-type p53 into two cell lines with p53 mutations, which resulted in reduced colony formation. This suggests that p53 may play an important role in suppressing prostate tumorigenesis.

Development of immunohistochemical methods for identifying abnormal p53 gene product allows for retrospective analysis of archival, paraffin-embedded tumor tissue. Studies of prostate carcinomas using this technique indicated that only a relatively small proportion (10–20%) of tumors harbors the p53 mutation. Visakorpi et al. (55) found strong staining for p53 in 6% of 137 prostate specimens examined. Bookstein et al. (56) found 12.7% of 140 specimens positive by immunostaining. In this latter study, p53 accumulation appeared related to the stage of disease. Twenty-three percent of stage I–II tumors were immunohistochemically positive versus 4% of stage I–II neoplasms (56).

Noaone et al. (57) recently used p53 immunostaining to examine prostate tumor tissue from 92 patients. Thirty-two patients had tumors confined to the prostate with the remainder obtained from subjects with metastatic disease. All tumors with p53 mutations were stage D (metastatic) and of poorly differentiated histology (Glason 8–10 versus 5–7; P < 0.003). Nuclear accumulation of p53 was also correlated with androgen sensitivity, i.e., androgen-independent versus androgen-dependent (P < 0.0001). These data suggest that p53 mutation may be a late event in the development of prostate cancer and that such mutations may signify transition to androgen-independent growth. Chi et al. (58) recently characterized the nature of p53 mutations in a series of 44 prostate tissue specimens. Nucleotide bp transitions of A→G or T→C were the most frequent.

It is clear that if p53 could serve as a marker of clinical aggressiveness (e.g., its association with traditional indicators of poor prognosis, such as poorly differentiated histology and androgen independence) such a finding would have important applications in the prognosis and management of this tumor. Unfortunately, others have shown that p53 abnormalities are also a feature of a subset of early stage disease (i.e., stage A1; Ref. 59). The suggestion that p53 mutation is a late event in prostate carcinogenesis is, therefore, called into question, and it remains to be seen if such mutations are truly indicative of aggressive clinical behavior.

A number of studies published within the last 2 years present data on LOH in human prostate carcinoma (60, 61). Frequently involved chromosomes include chromosomes 8, 10,
16, and 18. Bergerheim et al. (60) performed deletion mapping of chromosomes 8, 10, and 16 in 18 human prostatic carcinomas. The highest frequency of allelic deletions was found on 8p (65%). The minimally deleted region was a distal deletion of the 8p arm “always including the NEFL locus” (60). Loss of 8p loci was further confirmed in a recent report from MacGrogan et al. (61). In a study of 63 primary prostate tumors, 46% showed gross loss of at least 1 of the 28 loci examined providing additional support for a possible tumor suppressor gene on 8p that is important in prostate cancer.

In Bergerheim’s study (60), allelic deletions on 16q were found in 56% of cases. Chromosome 10 showed a complex deletion pattern that suggested monosomy in 2 cases, translocation of part of the q arm in two cases, terminal deletion on the p arm in two cases, and terminal deletion of the q arm in two cases. It is interesting to note that 10q deletions have been the most common karyotypic abnormality noted in primary cultures of prostatic adenocarcinoma (62).

A study by Massenkeil et al. (63) from Zurich, Switzerland, found a somewhat less frequent occurrence of LOH in these chromosomes in an analysis of 39 prostatic carcinomas. Specimens were obtained via radical prostatectomy, transurethral resection, or at autopsy (four patients). Tumors were stage T2a or higher, and approximately one-half were high grade. One of 5 tumors showed LOH on 8p, whereas 3 of 21 tumors showed LOH on 16q. LOH on 18q was found in 2 of 17 tumors sampled. No allelic deletions were found on chromosome 10q.

Investigators from the M. D. Anderson Cancer Center (University of Texas) reported recently about a study examining LOH on chromosome 7 in human primary prostate carcinomas (64). On the basis of data showing LOH on chromosome 7 in a variety of neoplasms, including prostate and breast cancer, the authors analyzed tumors from 16 patients undergoing pelvic lymphadenectomy with or without radical prostatectomy. Twelve of 16 samples showed LOH at one or more loci on 7q. This high incidence suggests a possible tumor suppressor gene at 7q31.1–31.2, which is important in the development of prostate tumors.

Conclusions and Future Prospects

Adenocarcinoma of the prostate is now the most common malignancy among men in the United States. Despite available methods for diagnosis and treatment, a multitude of controversies surround its management. Development of PSA revolutionized prostate cancer diagnosis, with clinically unapparent disease now detectable by a simple blood test. PSA has also proven useful in monitoring therapy. Nonetheless, screening the general population for prostate cancer by using this method is controversial. At present, although early disease can often be detected, it is still not possible to reliably distinguish those tumors that will remain indolent and clinically insignificant from those destined for more aggressive biological behavior ultimately resulting in the death of the host. Definitive proof that screening, using current techniques, results in a decrease in mortality from prostate cancer is also unavailable.

Clinical management must be presented with a clear understanding of the morbidity associated with such treatment. Total incontinence, stress incontinence, impotence, and persistent irritation of bowel and bladder are a few of the side effects associated with surgical and/or external beam radiation therapy for prostate cancer. Without clear and unequivocal prognostic indicators, treatment-induced morbidity among patients essentially “overtreated” for their disease may outweigh potential marginal survival benefits.

A fundamental understanding of the biology of prostate cancer may lead to much improved strategies for therapeutic intervention. Molecular markers capable of distinguishing aggressive tumors from those which will remain indolent would be invaluable to the clinician caring for such patients. Slowly, information regarding the genetic characteristics of prostate cancer is emerging. At the population level, it appears that men with a history of a first-degree relative with prostate cancer are at increased risk of developing this tumor.

This increased risk may range from 2- to 10-fold depending on the number of affected first-degree relatives (7). An inherited form of prostate cancer may exist which is transmitted in an autosomal dominant fashion accounting for approximately 9% of all prostate tumors (9).

Multiple oncogenes have been examined in an attempt to find specific genes important in carcinogenic transformation of prostate tissue (65). At present no specific oncogene or group of oncogenes has been shown to play a clearly defined role in the development of prostate cancer. Additional work is needed in an attempt to determine if a “cascade” of genetic events occurs in prostate tumors, as seen in other neoplasms, e.g., colon adenocarcinoma.

Chromosomal studies show loss of genetic material at several locations, e.g., 8p and 10q. This suggests that tumor suppressor genes (as yet unidentified) may be located at these sites which have a role in the neoplastic process. Mutation of the p53 tumor suppressor gene appears infrequently in prostate cancer in contrast to may other tumor types. Available evidence suggests that such mutations are a late event in the transformation of prostate tissue. This finding awaits confirmation.

References


Genetic characteristics of prostate cancer.

M Huncharek and J Muscat


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