

## Are some men more susceptible to prostate cancer than others and why? What are the treatments and their effectiveness? What are the possibilities for improvements in therapy?

D.J. Parekh and I.M. Thompson

### Are some men more susceptible to prostate cancer than others and why?

Prostate cancer is the most common malignant neoplasm in U.S. men. The estimated lifetime risk of disease is around 17% with a lifetime risk of death of around 3%. Prostate cancer is multifactorial in origin with genetic and environmental influences playing an important role in the origin and evolution of prostate cancer. The most common risk factors associated with prostate cancer development are increasing age, positive family history of prostate cancer, and African American ethnicity. Several loci of genetic susceptibility have been identified to be associated with prostate cancer risk as are associations with mediators of infection and inflammation. Other factors believed to be associated with prostate cancer risk are androgen exposure, estrogen, hormonal factors such as insulin like growth factors and obesity.

### What are the treatments and their effectiveness?

Patients with localized prostate cancer are usually treated with a curative intent. The most common modalities of treatment are:

1. *Active Surveillance*: This is a suitable approach for patients with less aggressive cancer who are potentially spared of the treatment related morbidity with a trade off of missing the window of curability. Patients on this approach are followed by serial serum prostate-specific antigen (PSA) examinations, serial digital rectal examination (DRE), endorectal coil MRI if available and repeat prostate biopsy at 18-24 month intervals with a low threshold to switch to active treatment if there is an upgrading of cancer or due to patient related anxiety. Long-term data about the effectiveness of this treatment is unavailable.
2. *Surgery*: Radical Prostatectomy by an open incision or in a minimally invasive fashion with laparoscopic surgery or with the help of a surgical robot are the most commonly surgical management approaches for localized prostate cancer. In the only randomized clinical trial comparing one treatment versus another, randomizing subjects to either surgery or

observation, surgery resulted in decreased rates of metastatic disease and cancer related mortality. Though surgery results in superior cancer control, it may lead to morbidity in the form of urinary incontinence and erectile dysfunction.

3. *Radiation therapy*: Radiation therapy is an effective modality for localized and locally advanced prostate cancer. It is administered in the form of radioactive “seeds” that are implanted in the prostate under ultrasound guidance (Brachytherapy) or in the form of External Beam Radiation. To date, no prospective randomized trials have compared the efficacy of radiation therapy to surgery or to surveillance to determine the superiority of any one modality. Besides urinary incontinence and erectile dysfunction, radiation may cause bowel and urinary bladder-related morbidity.
4. *Ablative therapies*: Recently, ablative therapies in the form of Cryotherapy and High Intensity Focused Ultrasound (HIFU) have been performed for localized prostate cancer as well as in salvage settings after failures of radiation therapy. Long term results for these modalities are unavailable.

### Issues with prostate cancer prevention

The goal of primary chemoprevention is to decrease the incidence of a specific cancer, ideally reducing not just the risk of cancer and treatment-related side effects, but mortality as well. Prostate cancer is an attractive and appropriate target for primary prevention because of its incidence, prevalence, and disease-related mortality. The most significant event in chemoprevention of prostate cancer occurred with the publication of the results of the Prostate Cancer Prevention Trial (PCPT). This landmark study, opened in 1993, was the first large-scale population-based test of a chemopreventive strategy in men at risk for prostate cancer. In the PCPT, 18,882 men 55 years of age and older with normal findings on digital rectal examination (DRE) and a PSA level of 3.0 ng/mL or less were randomly assigned to treatment with finasteride (5 mg/day) or placebo for 7 years. Prostate biopsy was recommended if the annual PSA level, adjusted for the effect of finasteride, exceeded 4.0 ng/mL or if the DRE findings were abnormal. The primary endpoint was the prevalence of prostate cancer during the 7 years of the study, as diagnosed by either for-cause biopsies (abnormal DRE findings or PSA level) or end-of-study biopsy. The Prostate Cancer Prevention Trial demonstrated that finasteride reduces the period prevalence of prostate cancer by 24.8%, with a slightly higher risk of high-grade disease. Recent studies have confirmed that the cancers prevented by finasteride are clinically significant and that finasteride does not result in

increased incidence of high-grade cancer. These *post hoc* studies demonstrated that the higher rate of high-grade cancers was due to detection bias in the finasteride group due to improved sensitivity of PSA, rectal examination, and prostate biopsy. Other 5 $\alpha$ -reductase inhibitors such as dutasteride as well as the antioxidants selenium and vitamin E, and other agents are currently being studied in randomized trials.

### **What are the possibilities for improvements in therapy?**

Despite several current therapeutic options, treatment related morbidity remains a significant concern for patients with prostate cancer. Several possibilities may improve upon the current options for prostate cancer. The most significant improvement would be differentiating clinically indolent from aggressive cancers. Development of biomarkers, accurate imaging modalities as well as better biopsy strategies may result in improvement of the prediction of the biologic course of prostate cancer. Patients with insignificant cancers will likely receive active surveillance or focal therapy while those with more aggressive cancers will continue to receive surgery or radiation therapy.

### **Suggested reading**

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