SUMMARY

This volume offers one of the most comprehensive population-based evaluations ever published on demographic and clinical features of prostate cancer cases. The results provide insights into the likely directions for prostate cancer research over the next decade, related to etiology and prevention, early detection and therapy.

Prostate cancer is the most frequently diagnosed cancer in the United States, yet our understanding of risk factors and the causes of prostate cancer continues to lag far behind that of other major cancers. The strong racial-ethnic variation in incidence and mortality offers one of the most interesting leads to the etiology of this disease. Although the dramatic trends in prostate cancer incidence rates observed by SEER between 1987 and 1995 due to the increased utilization of PSA testing have made international comparisons of prostate cancer incidence more difficult, blacks, as they have for decades, continue to have the highest prostate cancer rates in the world. Non-Hispanic whites in the United States also have relatively high rates in comparison to other populations around the world, even though their age-adjusted incidence rate in recent years remains approximately 40% less than that of blacks. Hispanic whites have substantially lower rates than non-Hispanic whites and Asian-Americans and Native Americans have even lower incidence rates. Nonetheless, Asian-Americans have prostate cancer rates which are increased over those of Asians in their native lands. This extraordinary racial-ethnic variation in incidence is most likely due to a combination of genetic and environmental influences and etiologic research is currently focused on identifying the precise genetic and environmental factors predisposing to prostate cancer development.

Although many environmental factors are being explored as prostate cancer risk factors, one focus of environmental research in the near future will be on diet. Dietary fat consumption is now reasonably well established as a contributor to prostate cancer development. However, little is known about the details of this relationship in terms of which subcomponents of fat are most associated with risk, during what periods of life high fat consumption conveys the greatest risk, or through what biological mechanisms fat operates to influence prostate carcinogenesis.

Other dietary hypotheses are being pursued with equal vigor. Dietary fiber, such as that found in certain grains and fruits, is of current interest. Certain male hormones which influence prostate growth are secreted from the liver into the small intestine and then reabsorbed. Fiber binds these hormones, leading to excretion rather than reabsorption and thereby reducing exposure to the prostate.

Micronutrients, especially certain vitamins and minerals, have long been of interest as cancer chemopreventive agents. Prominent among these have been vitamins which serve as antioxidants. These agents inactivate chemical moieties known as free radicals that can damage DNA, inducing mutations or other genetic changes, which

are critical to the carcinogenic process. Lycopene is one of a family of carotenoid antioxidant micronutrients which is being studied as a possible cancer prevention agent. Lycopene is found primarily in tomato or tomato products and is one of the more potent carotenoid antioxidants. For unknown reasons, it is concentrated by the prostate. Prospective epidemiologic studies have provided highly suggestive evidence that lycopene reduces prostate cancer risk. A recent clinical trial of skin cancer chemoprevention unexpectedly found a reduced risk of prostate cancer with selenium supplementation, which will likely become a target of future investigations.

Finally, phytoestrogens, i.e., plant estrogens such as isoflavonoids found in soy products, have been suggested as possible preventive nutrients for prostate cancer, because they can weakly bind androgen hormone receptors in the prostate and interfere with prostate growth. As Asian populations are traditionally heavy consumers of phytoestrogen-rich foods, this hypothesis may help explain the low prostate cancer rates in these populations.

Genetic studies related to prostate cancer etiology likely will focus in the near future around two major themes. Prostate cancer is a familial disease; first degree relatives of men with prostate cancer have a two- to three-fold excess risk of developing the disease. When thinking about prostate cancer occurring in families, it is important to distinguish the terms hereditary and familial. Hereditary prostate cancer is more specific and describes a distribution of cancer cases within a family that is consistent with inheritance of a single gene. This type of genetic susceptibility is characterized by an early age at onset and multiple affected men within the family. Several of these types of susceptibility genes have already been identified and cloned for other cancers such as breast cancer, and there is strong evidence that multiple such genes also exist for prostate cancer. The putative locus of one such gene was recently narrowed to a small area of chromosome 1q. A major focus of genetic studies of prostate cancer in the near future will be the identification, cloning and characterization of this and other such susceptibility genes. However, these genes, while important, are not responsible for the majority of prostate cancer (although nearly half of prostate cancers diagnosed among men under age 55 may be due to these genes, current estimates suggest that approximately 9% of all prostate cancers are due to these genes). Prostate cancer that occurs more commonly in relatives of an affected individual than in the general population is given the more general term familial. Much familial and non-familial prostate cancer is likely to be multifactorial, involving more than one gene in combination with environmental exposures, as well as probably complex interactions between genes and environmental factors. A series of candidate genes that will likely contribute to prostate cancer risk in more subtle ways than the single inherited genetic traits that are necessary and sufficient to cause cancer have already been proposed. Lifelong exposure to the effects of these genes is needed to increase prostate cancer risk. Individually these genes lead to low relative increments in cancer risk but, in combination, are likely to be responsible for a large percentage of prostate cancer cases. Among the genes in this category already proposed to influence prostate cancer risk are a series of genes whose products influence androgen secretion and metabolism, the vitamin D receptor gene as vitamin D influences proliferation and differentiation of prostate cells, genes involved in metabolism and transport of fatty acids, and genes involved in the metabolic activation or detoxification of environmental

carcinogens. All of these proposed candidate genes are polymorphic, i.e., there exist small sequence variations in the structure of these genes among individuals and populations. Moreover, for some genes these polymorphisms have been shown to influence the gene product (i.e., they are functional polymorphisms) and, for some, there are substantial variations in the frequency of the polymorphic alleles among the racial-ethnic groups showing the greatest variation in prostate cancer incidence.

As discussed at length in the sections above, the rapid increase in incidence of prostate cancer during the late 1980's and early 1990's is thought to be due largely, if not entirely, to increased utilization of prostate specific antigen (PSA) testing. PSA is a prostate-specific protease that is produced by prostatic epithelial cells and is being extensively evaluated in serum as a screening method for detecting occult prostate cancer (i.e., asymptomatic prostate cancer confined to the prostate in otherwise healthy individuals). The increased incidence of prostate cancer that has occurred in the past decade has not been confined only to an increase in localized disease, however, as one might anticipate if PSA screening was solely responsible. In fact, there has been an increase in regional disease (i.e., disease that has extended through the prostatic capsule and beyond). However, this increase in regional disease is likely an indirect consequence of PSA screening. A common therapy for men with PSA-detected cancer is radical prostatectomy. Staging is often upgraded as a result of the detailed histologic examination of the prostate which occurs following surgical removal.

Strong evidence is presented in this monograph that PSA detected prostate cancer is largely moderate grade (Gleason score 5-7). As moderate grade prostate cancer detected clinically carries with it substantial mortality from prostate cancer, PSA appears to be detecting largely clinically meaningful disease. These encouraging data regarding the possible value of PSA screening further magnify the importance of the ongoing national trial to determine the efficacy of PSA in reducing prostate cancer mortality (the ultimate measure of the efficacy of any cancer screening tool). In the meantime, PSA has already become widely utilized in clinical practice, in large part because it is a non-invasive and relatively inexpensive test. The sensitivity of PSA testing for prostate cancer (i.e., the proportion of men with prostate cancer who test positive) in one large study was 67% although others have reported higher values. One study reported the specificity (i.e., the proportion of men without prostate cancer who are negative by screening) of PSA screening to be as high as 97%, but most other studies have reported much lower values. Future research in early detection strategies for prostate cancer, in addition to determining whether PSA screening is efficacious in reducing prostate cancer mortality, is likely to focus on strategies which maximize both sensitivity and specificity of PSA screening. Using PSA biochemical subfractions, incorporating age- and race-specific cutpoints of positivity, and adjusting serum PSA concentrations by prostatic volume (PSA density) are among the methods which will be undergoing further evaluation. As prostate cancer outcome is highly dependent on detection prior to distant spread, identification of a suitable screening test for prostate cancer is a critical public health issue.

It is clear from this report that prostate cancer mortality has declined slightly in recent years, with apparent gains in increasing short- and long-term survival from prostate cancer diagnosed at a localized

or regional stage. Noteworthy is the continued absence of improvement in survival from distant stage prostate cancer. The situation in black men is particularly urgent, as survival is worse among black men at every stage at diagnosis and the survival gap with whites continues to widen. Radical prostatectomy or external beam radiation therapy are both widely used as definitive therapy for localized prostate cancer, although some cancer specialists question whether any treatment is required for very early prostate cancer, especially among the elderly. Hormonal therapy (by androgen blockade or by other methods of reducing androgen exposure to prostate cancer cells) has been the mainstay of initial treatment for advanced prostate cancer for over 50 years. Despite early responsiveness to hormonal manipulation, prostate cancer eventually becomes androgen refractory, through genetic changes that are just now being understood. Translational research, aimed at understanding the basic biology and molecular genetics of prostate cancer so that targeted therapies can be developed and implemented, holds the key to more effective therapeutic management of advanced prostate cancer in the future.