PROSTATIC CANCER

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INTRODUCTION

The management of prostate cancer in all its forms in man has undergone a substantial adjustment in our thinking within this decade. Reasons for this include the evolution of treatment, the application of new scientific concepts, and further progress in all fields of medicine. However, specifically, in terms of hormonal factors, the accuracy of diagnosis, the determination of the extent of disease, and the application of multimodal therapy, have resulted in initial changes in the approach to the management of cancer as we know it.

The authors contributing to this book are individuals involved with the day-to-day progress in all aspects of this field. At various times many of them have served effectively and worked with, or have been involved in, the National Prostatic Cancer Project, a program supported by the National Institutes of Health. Throughout all of our endeavors Dr Jack Saroff has assisted us, both in the preparation of this book and in many of the concepts that will be expressed. His recent and untimely death has deprived us not only of a good friend and colleague but of one who has made substantial contributions to the management of prostate cancer. Thus, by common consent, we dedicate this book to him.

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Director
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Buffalo, New York
February 6, 1978

CONTENTS

Epidemiology and Etiology

1

Warren Winkelstein, Jr.,
and Virginia L. Ernster

Cancer of the prostate is a disease of unknown etiology. Several reviews of the epidemiologic aspects of this neoplasm have been published.[1-4] It is primarily a disease of older men; mortality rates increase markedly with age after about the fiftieth year. This malignancy occurs with strikingly different frequencies in various regions of the world, across racial groups, and over different time periods. In the United States today, it accounts for 10% of cancer mortality in males and ranks second in overall cancer incidence among men.[5-6] In this chapter the etiologic hypotheses and inferences that can be derived from our knowledge of the epidemiology of prostatic cancer will be discussed.

Epidemiology, the study of disease distribution in human populations and the factors which affect it, has been useful in eliciting some of the associations of particular cancers, viz, smoking and lung cancer, ionizing radiation and leukemia, and occupational exposure to aniline dyes and bladder cancer. Whereas the laboratory investigator can usually specify exact experimental conditions, epidemiologists must study human populations in their environment, with all their biologic, behavioral, and environmental variables. Variation in disease is often based on such characteristics as age, marital status, sexual practices, occupational exposures, and diet, all of which "naturally" differ among populations. Any demographic or biologic characteristic, social practice, or environmental exposure found to increase the chances of developing a disease is known as a *risk factor*; conversely, any practice or exposure which lowers those chances is thought to be *protective.*

Etiology—the cause of a disease—does not derive solely from epidemiologic studies. Usually, however, hypotheses initiated in clinical or laboratory settings must be tested using epidemiologic methods. For example, the association of cigarette smoking and lung cancer, first suggested on the basis of clinical observations, was strengthened considerably through case-control studies. Evidence of the carcinogenicity of diethylstilbestrol (DES) in mice reported over two decades ago has been cited as a parallel study to that linking vaginal adenocarcinoma in young women to DES. In any instance, valid etiologic inferences must be consistent with the epidemiologic evidence, that is, they must fit the distribution of purported risk factors and disease in the population.

EPIDEMIOLOGY

The validity of inferences derived from epidemiologic studies depends on the accuracy with which the observations are made. This applies both to the independent variables postulated to affect the occurrence of the disease (ie, risk factors) as well as to the identification of cases of the disease under study. With respect to prostatic cancer, the latter issue is particularly troublesome.

For most cancers, disease is manifested by clinical signs and symptoms prior to death. Thus, epidemiologic studies can be designed for representative sampling. However, for prostatic carcinoma, a substantial but undetermined proportion of the disease is latent and only incidentally discovered at autopsy or when surgical intervention is undertaken for other reasons. Thus, samples of clinically diagnosed cases may not be completely representative of all men at risk of developing the disease. Moreover, the possibility that men with latent cancer will be included in control groups in epidemiologic studies is substantially greater for prostatic than for other cancers. This bias would, however, have the effect of diminishing true differences between cases and controls rather than artificially demonstrating differences which do not exist.

The problem created by the occurrence of latent prostatic cancer has an indeterminate effect on the interpretation of descriptive statistics such as mortality and incidence rates over time, and comparisons between groups with different medical care systems and case-recording mechanisms. At the present time, we know of no way out of this dilemma and would question comparative statistics drawn from countries that vary considerably in their medical-screening and case-reporting facilities. On the other hand, where the levels of medical diagnosis and care are high and where statistics are gathered according to standardized and rigorous procedures, we expect the latency bias to be minimized.

Descriptive Statistics: Mortality and Incidence

Age-Specific Mortality and Incidence by Race The most useful indicators of the extent of disease occurrence in a population are mortality rates (ie, deaths per unit population per year) and incidence rates (ie, *new* cases per unit population per year). While prevalence (all existing cases per unit population at a *particular* point in time) is a practical measure for the purpose of planning for health and medical care services, it is not useful for developing etiologic hypotheses and inferences. The epidemiologist would even prefer not to use mortality rates because case fatality (ie, deaths per 100 cases during a particular time period) varies greatly among different cancers and, indeed, for the same cancer

at different places and at different times. Nevertheless, mortality statistics are often the only data available. For the United States, complete mortality statistics have been collected on a nationwide basis since the 1930s. An excellent representative estimate of cancer incidence is available from the Third National Cancer Survey (1969–1971), and an ongoing network of cancer registries now exists across the country (Surveillance, Epidemiology and End Results—SEER—program of the National Cancer Institute).

In Figure 1, age-specific prostatic cancer mortality and incidence rates for whites and blacks are shown for the United States in 1970. Prostatic cancer is relatively rare under the age of 50, after which time it rises more rapidly with age than any other cancer. Both mortality and incidence increase at an almost constant exponential rate, indicated by the nearly straight line of the curves shown in Figure 1. Although it is tempting to interpret the difference between incidence and mortality as a measure of severity or survivorship, the reader is cautioned that many other factors may be operative, including differential risks by age of dying of other causes as well as the fact that deaths at one age may not be referent to the same individuals who are incident cases at that age.

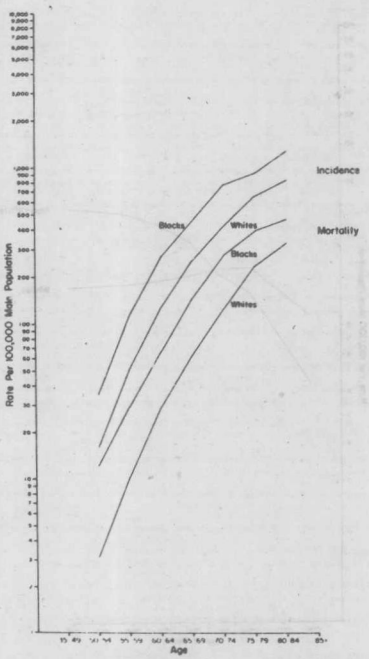

Figure 1. Age-specific prostatic cancer mortality and incidence rates per 100,000 males, whites and blacks, United States, 1970 (Cutler and Young, 1975[6]).

The most striking aspect of the epidemiology of prostatic cancer in the United States is the racial difference in occurrence. Age-adjusted rates among blacks are approximately 65% higher than among whites.[6] However, black rates have not always exceeded those of whites, a phenomenon discussed below.

Time Trends (Age-Adjusted) As shown in Figure 2, age-adjusted prostatic cancer death rates for all males in the United States have been relatively stable since 1940. In the decade 1930 to 1940 there was an increase of approximately 40%. This could well be explained by improvements in mortality reporting and changes in the international coding procedures according to which causes of death are ascribed. However, the overall mortality picture generally reflects the white experience. When nonwhites are considered separately, a somewhat different pattern emerges, with a steady increase in age-adjusted rates apparent from 1930 on. This has resulted in a shifting of the positions of the two racial groups relative to one another. Until 1945, at all ages combined, whites had higher death rates than nonwhites. However, as early as 1930, prostatic cancer mortality among young men was higher in nonwhites than whites. With time, successively older age groups followed this pattern. By 1965 nonwhite rates for all age groups through age 85 had exceeded comparable white rates.

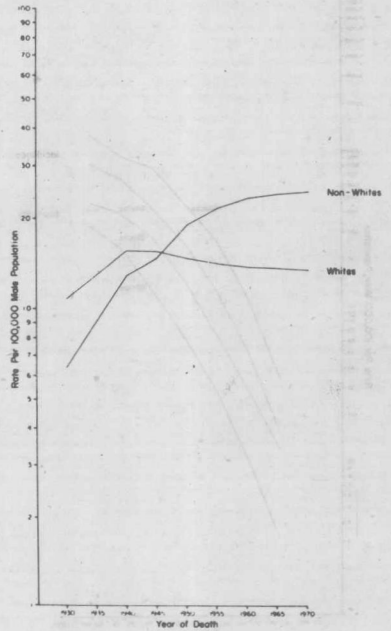

Figure 2. Age-adjusted mortality rates for prostatic cancer per 100,000 males, 1930–1970, by race (United States Public Health Service, *Vital Statistics of the United States.* (Mortality Series 1935–1970.)

Additional insight into time trends can sometimes be provided by an analysis of age-specific rates calculated for birth cohorts. Thus one views the mortality experience at each age of a given generation as opposed to a cross-sectional analysis which examines the experience of several generations simultaneously. When this was done for prostatic cancer, it appeared that the nonwhite birth cohorts of 1896 to 1900 experienced relatively higher rates at almost all ages as compared with both earlier and later cohorts (see Table 1).[7] In fact Table 1 suggests a general decline in mortality at each age for which data are available for birth cohorts following 1896 to 1900. Of course, prostatic cancer occurs more frequently in the older age groups, and data are not yet available for the complete lifespan of the 1896 to 1900 cohort or for subsequent cohorts. Thus it will be of interest to monitor such rates in the future. If trends observed in younger men persist, one can anticipate that mortality from prostatic cancer in blacks will stabilize and possibly even begin to decline in the not too distant future.

Table 1. Prostatic Cancer Mortality Rates Per 100,000 By Cohort for U.S. Nonwhite Males Born 1861–1920 (sources same as Figure 2)

	Birth Cohorts											
Age	1861–1865	1866–1870	1871–1875	1876–1880	1881–1885	1886–1890	1891–1895	1896–1900	1901–1905	1906–1910	1910–1915	1916–1920
40–44						1.10	2.02	1.65	2.15	1.61	1.26	2.68
45–49					3.48	4.76	6.55	7.23	4.71	4.66	2.73	2.43
50–54				5.41	11.35	15.95	15.65	23.35	16.34	15.82	13.39	12.03
55–59			18.78	22.40	32.08	41.41	39.05	44.44	30.85	32.43	29.90	
60–64		23.98	45.90	50.19	60.42	77.72	84.21	81.35	77.39	68.21		
65–69	35.12	60.24	72.26	74.05	97.25	141.06	147.39	177.09	149.00			
70–74	66.50	90.10	125.96	143.03	168.49	224.73	235.89	276.70				
75–79	151.36	129.82	219.20	234.44	299.59	304.24	399.90					
80–84	155.56	299.06	380.56	371.54	359.15	471.30						

A similar cohort analysis of mortality for whites in the United States revealed no such generational pattern, a finding consistent with the fact that cross-sectional rates for whites have shown very little change in the past five decades.

Geographic Variation: International and National The study of geographic differences in disease occurrence provides an opportunity to identify genetic or environmental factors which may be of etiologic importance. Such comparisons, however, suffer due to variations in diagnosis, differences in case fatality rates, and inaccuracy and incompleteness of records. While an exhaustive compendium of international incidence statistics has been compiled it is our feeling that incidence data for most countries have not yet reached the point where they can be used for comparative purposes.[8] Recognizing that international mortality data require cautious interpretation, we have nonetheless reached the following

conclusions based on an examination of the most frequently consulted sources of international mortality statistics.[9,10]

For those nations for which statistics are available, it appears that the developed nations of Western Europe, North America, and Australia/New Zealand generally have the highest age-adjusted rates. The range of differences between them is quite small and could easily be accounted for by random variation. A second group of countries with intermediate rates can be identified in eastern and southern Europe. Included in this group are several countries in Latin America. Again, variation between these countries is not remarkable. Finally, there is a third group characterized by extremely low rates, comprised of countries in eastern Asia. Japan is perhaps the most interesting and important of these, since its vital statistics system is thought to be of a particularly high caliber. Furthermore, the presence of substantial numbers of Japanese migrants to the United States, where overall mortality rates are relatively high, provides an opportunity to study the issue of genetic vs environmental etiology. Unfortunately, mortality statistics are unavailable for most countries of the world, including many nations in Africa, South and Central Asia, the Near East, and much of Latin America.

Within the United States published data concerning geographic variations of prostatic cancer mortality are inconsistent. When age-adjusted mortality rates for white males by state for the pericensal period 1959 to 1961 were examined, it appeared that rates in the three northern New England states and most of the northern tier states west of the Mississippi to the Pacific Coast were from 1½ to 2 times higher when compared with most of the southern tier states east of Arizona and Utah.[11] A rather different pattern is evident in the recently published *Atlas of Cancer Mortality,* which provides age-adjusted mortality rates for white males by county for the 20-year period 1950–1969.[12] Maps in the *Atlas* show that a number of counties in the upper midwest states of Minnesota and Iowa had an apparent excess of prostatic cancer mortality, and scattered high-rate counties were found in the Rocky Mountain plateau area, Texas, the southeastern states, and in the upper mid-Atlantic and central New England areas.[12]

Incidence data are not available for most of the United States, but an examination of the nine areas included in the Third National Cancer Survey shows no clear-cut regional patterns despite a range of rates from a low of 37 per 100,000 males in Pittsburgh to a high of 54 per 100,000 in Minneapolis-St. Paul.[6]

From the foregoing it appears that no obvious regional pattern for prostatic cancer exists in the United States. It may well be that individual counties identified in the recent *Atlas* will be found to have particular environmental characteristics which lead to increased risk of the disease, but this has not as yet been investigated.

Analytic Epidemiology: Environmental Factors

Nature (Genetic vs Nurture): Migrant Studies The marked racial and international differences in prostatic cancer statistics might be explained on either a genetic or an environmental basis. Migrant studies are particularly useful for making this distinction if the assumption can be made that migrants are genetically representative of the native populations from which they come. If genetic mechanisms are responsible for disease occurrence, then one would expect rates in the host country to be quite similar to those in the country of origin. Alternately, if environmental factors are dominant, one would expect migrants to assume rates experienced in the host country.

The extensive migrant populations in the United States have been studied for many cancers. With respect to prostatic cancer, the migration experience of the Japanese is particularly relevant. Most of the Japanese migration to the United States came from a limited geographic area around Hiroshima, suggesting a homogeneous genetic makeup among the migrants. Within the United States migrants settled in two distinct areas, namely, Hawaii and California. In Table 2, recent mortality rates are shown for Japanese in Japan, Hawaii, and California. These data reveal a clear difference between the low rates in Japan and the much higher rates in Hawaii and California.

Table 2. Average Annual Prostatic Cancer Mortality by Age for Japanese in Japan, Hawaii, and California

	Japan (1970)*		Hawaii (1968–1972)†		Calif. (1969–1973)‡	
Age	Population	Deaths/ 100,000	Population	Deaths/ 100,000	Population	Deaths/ 100,000
55–64	3,798,000	3.2	9,638	4.2	817	—
65–74	2,361,000	14.7	5,203	24.8	550	36.4
75+	862,000	43.8	2,826	184.0	409	195.6

* World Health Organization 1973.
† L. Kolonel (unpublished data).
‡ Bragg and Austin (unpublished data).

Since large-scale migration has not occurred for many years, one may infer that rates among Japanese-Americans will increasingly reflect the influence of members of the second and subsequent generations. In 1970 the age-adjusted incidence rate for prostatic cancer among Japanese in the five San Francisco Bay Area counties participating in the Third National Cancer Survey was 6.3 (S.E. ± 3.1) per 100,000, and by 1975 this figure had already climbed to 49.6 (S.E. ± 23) per 100,000 according to K. Bragg and D. F. Austin (personal communication, 15 July 1977). Of course, these rates are based on very small numbers and must be interpreted cautiously. Nevertheless, all of these observations taken

together suggest that environmental factors predominate in determining risk of prostate cancer.

Further support for the environmental hypothesis comes from the observation that the prevalence of latent prostatic carcinoma is the same in autopsy series among Japanese in Japan and in Hawaii.[13] This suggests that an environmental factor(s) precipitates the change from latent to clinical disease.

An examination of mortality rates among migrants to the United States from European countries generally reveals no such definitive change in the direction of host-country rates as revealed for Japanese. No doubt this is due in part to the fact already indicated that rates in those countries from which the bulk of European migration occurred are much closer to those in the United States as a whole, probably reflecting greater similarities in life style.

Environmental Factors In this section, urban/rural comparisons of prostatic cancer rates, and possible associations of the disease with measures of air pollution, occupation, and smoking behavior, will be discussed.

When 1950 age-adjusted incidence rates were compared for urban and rural areas of New York, Connecticut, and Iowa, areas which had good registries at the time, a small excess of about 10% was observed in urban areas.[1] However, when age-adjusted mortality rates between urban and rural counties of the entire United States for the period 1950 to 1969 were examined, no difference was observed.[14] Elsewhere, a case-control study of prostatic cancer patients and other hospitalized men found a higher proportion of cases to be residents of small towns.[15] Given these rather contradictory results, it is not possible to conclude that there is any appreciable difference between urban and rural areas in the occurrence of prostatic cancer.

The lack of an association between prostatic cancer and urbanization seems inconsistent with findings elsewhere of an association between suspended-particulate air pollution and mortality from this disease as observed in two community-wide studies of air pollution effects in the United States.[16,17] Both of these studies controlled for differences in social class. However, the possibility that the association might be explained by other unaccounted-for covariables cannot be assessed.

Based on previous suggestions in the literature, the authors of one of the air pollution studies hypothesized a possible carcinogenic effect from airborn cadmium particles.[16] Animal studies had shown cadmium to be a carcinogen capable of inducing testicular tumors in rats.[18] An excess of prostatic cancer mortality had also been reported based on uncontrolled observations among cadmium workers.[19,20] Later, a careful retrospective case-control study, using a lifetime cadmium exposure index based on dietary, smoking, and occupational histories, found no significant differences.[21] Another retrospective case-control study examined general

occupational differences between cases and controls and also found no differences, although the study groups were drawn from a very homogeneous socioeconomic population.[22] Our own comparisons of occupations for deaths due to prostatic cancer and matched controls revealed that cases were more likely to have belonged to certain occupational groups, including compositors/typesetters, painters, and shipfitters.[23] Elsewhere, a cohort study of workers in a cadmium smelter demonstrated an excess of observed over expected prostatic cancer deaths in those men whose cadmium exposure had begun at least 20 years prior to death.[24] Finally, in a cohort of 6,000 rubber workers, excess deaths from prostatic cancer were observed in several job categories, one of which involved cadmium exposure.[25] These studies can hardly be considered definitive of occupational hazards for prostatic cancer, and more work along these lines is to be encouraged.

The prostate is among the major cancer sites for which an association with smoking has not been demonstrated despite a number of studies addressed to this question.[26] This lack of an association was most recently confirmed in an examination of smoking history among cancer patients included in the Third National Cancer Survey.[27]

Behavioral Factors In attempting to explain the marked racial differential in prostatic cancer occurrence, one must consider the possibility that it might be accounted for by factors associated with socioeconomic status (SES). It is possible that some social factors independent of racial differences might be associated with the etiology of prostatic cancer. Numerous studies have examined this question; most of them predated the dramatic black/white reversal in prostatic cancer rates, and few had similar results. Moreover, the studies that did include racial groups other than whites pooled "nonwhite" races together and also predated the dramatic black/white reversal in prostatic cancer rates. These studies have been reviewed recently and analyzed further, using both mortality and incidence data separately for whites and blacks from Alameda County, California, for the five-year pericensal period 1968 to 1972.[28] No SES gradient in prostatic cancer rates was observed for either whites or blacks, and black excess risk for the disease held up within age-specific comparisons for every socioeconomic level studied. As indicated earlier, the black/white difference in prostatic cancer is of recent origin, so that failure to explain it on the basis of SES should not necessarily be interpreted as supporting a genetic hypothesis.

Religion has proved to be a useful characteristic to measure in many epidemiologic studies since it is frequently a good indicator of sexual practices, fertility, dietary habits, smoking, alcohol use, and circumcision. Religion has been a study variable in several prostatic cancer studies. Investigations in New York City have indicated that Jews have a slightly lower risk for the disease.[29-31] It was thought that circumcision might be protective. However, a later study failed to demonstrate a difference in