

A Prospective Comparison of Prostate Cancer at Autopsy and as a Clinical Event: The Hawaii Japanese Experience¹

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Abstract

Prostate cancer was diagnosed in life among 274 of 8006 (3.6%) members of a cohort of Japanese men in Hawaii between 1965 and 1990. Only 55 (20%) of the 274 diagnosed cases died with prostate cancer, and they accounted for only 2% of the 2893 deaths that occurred among the men during this period. None of the 61 men whose tumor was found incidentally to a transurethral resection died as a result of this cancer, while it was the cause of death of 9 of 106 (8%) men with clinical cancer localized to the prostate. Forty-six of the 107 (43%) men with more extensive disease at the time of diagnosis died from prostate cancer. Step sectioning of the prostate identified prostate cancer in 80 of 293 (27%) autopsied Hawaii Japanese men who died after 50 years of age, reaching a frequency of 63% (10 of 16) among men over 80 years of age. The volume of 48 (60%) of these cancers was less than 150 mm³. These small tumors would probably not have been discovered in a screening program. Tumors larger than 1000 mm³ would probably be discovered using modern diagnostic procedures but were found in only 13 (4.4%) of the autopsied men. It is likely that a screening program to detect and treat such large, unsuspected tumors in this population would have had little impact upon the already low proportion of deaths due to prostate cancer among these Japanese men.

Introduction

There are wide international variations in the incidence rates of prostate cancer, with low rates prevailing in Oriental populations and high rates among U.S. whites and blacks (1). Clinically occult cancers are included in incidence counts. They are asymptomatic tumors discovered in screening procedures or found unexpectedly in prostatic tissue removed for the treatment of benign disease. This suggests that some of the variation in incidence can be explained by the different levels of diag-

nostic effort in different countries. Generally, however, the rank order of prostate cancer frequency by countries is similar, whether based on incidence data or death certificates (2).

Systematic autopsy studies of the prostate in men not known to have prostate cancer in life indicate that as many as one-third of older men in studied populations have occult prostatic cancers (3). This suggests that prostate cancer induction is a common event in many countries and that some of the international differences in incidences and mortality are the result of environmental factors that promote tumor growth in populations experiencing high rates of clinically apparent cancer.

Recent publications have discussed the use of screening procedures (4, 5) to identify unsuspected prostate cancers in order to initiate surgical or radiation therapy before the tumor has disseminated. Screening and early treatment of cancer would be beneficial if applied to tumors with a high probability of future morbidity and mortality but would be unrewarding if applied to tumors that remain in a latent occult form over many years and do not contribute to mortality. The latter possibility is especially relevant to prostate cancer, which affects older men at high risk of death from many other causes.

This report assesses the relative impact of prostate cancer on the health of a cohort of Japanese men living in Hawaii who experience incidence and mortality rates of this cancer that are midway between those of Japan and the rest of the United States (1, 6, 7). It is based upon a prospective study of a defined population that has been carefully followed for the development of heart disease, stroke, and cancer and it includes a systematic dissection of the prostate in a subset of autopsied men who have died without clinical evidence of prostate cancer prior to death. We believe that it is reasonable to relate the results of these autopsy studies to the incidence and behavior of prostate cancer in this population.

Materials and Methods

The subjects for this study were American men of Japanese ancestry, born from 1900 to 1919 and residing on the Hawaiian island of Oahu. They were identified by the Honolulu Heart Program in 1965 through use of the comprehensive 1942 Selective Service draft registration files (8). Of 11,148 identified men, 8,006 (71.8%) were interviewed and examined between 1965 and 1968. One hundred eighty men (1.6%) died before they could be examined, and 2962 (26.6%) did not participate in the program. Based on a 19-year follow-up survey of the study subjects since their examination, it was determined that only 1.3% of the men could not be located on Oahu.

Received 7/30/91.

¹ Supported by Grant R01-CA33644 from the National Cancer Institute, NIH, Bethesda, MD 20892.

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Surveillance of hospital discharges and death notices have been conducted daily by the study staff to identify all newly diagnosed heart attacks, strokes, and cancers. Cancer has been a reportable disease in Hawaii since 1960, and new tumors are recorded by the Hawaii Tumor Registry. Consequently, contact with the Registry has also been made at regular intervals to ensure that no new cancers were missed. The study includes all prevalent and incident cancers, as well as deaths through August 1990. Tumors entered into the study over the entire period were derived from a variety of community and academic hospitals during a time frame characterized by increasingly sophisticated diagnostic methods.

Ultrasound and assays of prostate-specific antigen were not generally available during the first half of this prospective study. For this reason, the extent of prostate cancers diagnosed in life was mainly based on physical examination, bone scans, and X-ray examination. The following levels of clinical status at time of diagnosis were used: (a) occult tumors found incidental to TUR³ in no more than three of all totally embedded tissue chips; (b) clinical tumors, defined as those confined to the prostate and clinically suspected prior to biopsy or found incidentally in more than three TUR chips; (c) tumors extending beyond the prostate locally; (d) tumors metastatic to regional nodes; (e) tumors metastatic to distant sites.

The underlying cause of all deaths was determined by a panel of two or more study physicians after reviewing all available records. Diagnostic differences among panel members were resolved by consensus agreement after discussion of each case.

The presence of clinically unsuspected prostate cancer at autopsy was determined by making 3-mm step sections through the entire organ, selecting only those subjects with no premortem diagnosis of prostate cancer or surgical removal of the prostate during life. Whole mount sections were stained with hematoxylin and eosin. The outline of each section was traced on paper, and all cancers were outlined. The volume of each tumor was calculated according to the method shown in Fig. 1. This volume has been shown to be highly correlated with the Gleason grade of such tumors (9). A circle was drawn with a radius of 1 cm from the center of the urethra in order to assess the frequency of tumors in the periphery of the organ (i.e., tumors most likely to be missed in TUR). The men selected for this autopsy study were from the cohort (n = 216) of 8006 examined men or were Hawaii Japanese patients at the Kuakini Medical Center who were in the same age range but had not participated in the original examination (n = 77). Nonparticipation in the original examination resulted from one of the following causes: draft registration was in a locality other than Oahu (i.e., another Hawaii island or on the U.S. mainland), or the subject chose not to participate in the study.

The flow chart shown in Fig. 2 summarizes the prostate cancer experience of the men in this study.

Results

Table 1 shows that, through 1990, 274 prostate cancers have been diagnosed during life among the 8006 cohort men (3.4%). The cancers were localized to the prostate

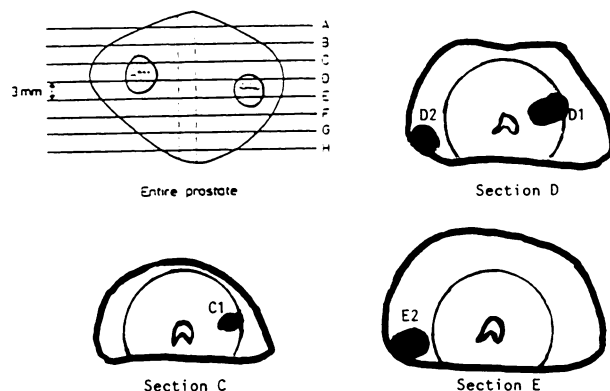


Fig. 1. Diagnostic example showing method of estimating tumor volume and probability of tumor being found incidentally by TUR. The circle with a radius of 1 cm from the center of the urethra shows the probable limits of tissue resection. The illustrated case shows two cancers, one within and one outside the limits of this procedure. The volume of cancer in this specimen is based on the sum of the volumes of each tumor. In this example: C1 = 4 mm × 4 mm × 3 mm = 48 mm³; D1 = 4 mm × 7 mm × 3 mm = 84 mm³; D2 = 4 mm × 6 mm × 3 mm = 72 mm³; E2 = 5 mm × 7 mm × 3 mm = 105 mm³. Total volume: 48 + 84 + 72 + 105 = 309 mm³.

in 167 of the 274 men (61%), and among these, 61 were found incidental to a TUR. Seven men had developed cancer prior to baseline examination. The mean age at diagnosis was 71.6 years. Prostate cancer was the cause of death in 55 (20%) of these men, while death was caused by some other disease in 59 cases (22%). Review of the clinical background of the 2893 cohort deaths during this period indicates that cancer accounted for 851 deaths (29%); and, among these, prostate cancer accounted for 55 deaths (2% of all deaths and 6% of cancer deaths). During the same time period, there were 422 deaths from coronary heart disease (15%), 239

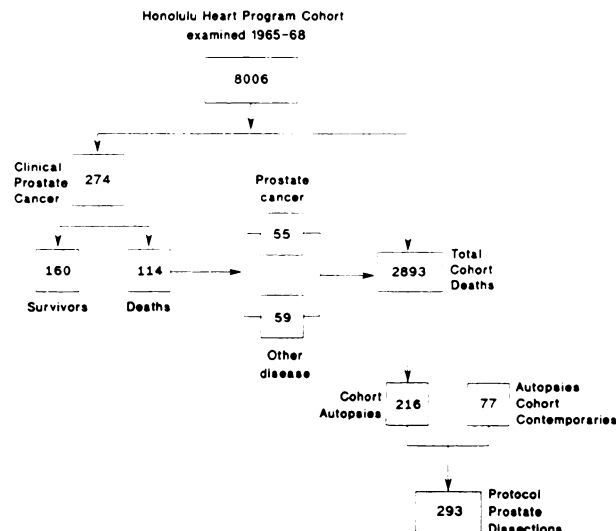


Fig. 2. Flow chart showing the distribution of prostate cancer cases, deaths, and autopsies in the study population.

³ The abbreviation used is: TUR, transurethral resection.

Table 1 Prostate cancer diagnosed in life

Extent at diagnosis	No.	Mean age at diagnosis	Mean years of survival after diagnosis (range)	Deaths		
				Total (%) ^a	Due to prostate cancer (%)	Due to other disease (%)
Incidental	61	70.2	8.2 (0.1-30.5)	17 (28)	0	17 (28)
Clinical, prostate only	106	72.7	7.8 (0.8-29.2)	31 (29)	9 (8)	22 (21)
Local extension	34	70.5	8.2 (0.3-27.9)	22 (65)	10 (29)	12 (35)
Regional nodes	21	70.2	6.6 (1.5-15.7)	7 (33)	5 (24)	2 (10)
Distant metastases	52	72.3	4.1 (0.2-13.5)	37 (71)	31 (60)	6 (12)
Total	274	71.6	7.1 (0.1-30.5)	114 (42)	55 (20)	59 (22)

^a Percentage of total number of diagnosed cases.

deaths due to cerebrovascular disease (9%), and 86 deaths from chronic lung disease (3%). Prostate cancer ranked fourth among cancer deaths, following lung (234 deaths), stomach (157 deaths), and colorectum (138 deaths).

Table 1 also shows that none of the 61 men whose diagnosis of prostate cancer was incidental to a TUR died of this cancer, as compared with 9 (8%) prostate cancer deaths among 106 men whose tumors were clinically suspected and confined to the prostate. Prostate cancer caused the death of 15 (27%) of the 55 men whose tumors extended beyond the prostate locally or had spread to regional nodes and 31 (60%) of the 52 men whose cancer already had distant metastases when first diagnosed. The mean duration of life from time of diagnosis of prostate cancer to August 1990, the termination date of the study, was 8.2 years for incidental tumors, 7.8 years for clinical tumors confined to the prostate, 7.6 years for tumors that had extended beyond the prostate locally or involved regional nodes, and 4.1 years for men who had distant metastases at the time of diagnosis.

Table 2 assesses the experience of the 106 men whose tumors were suspected clinically and confined to the prostate or were present in more than three of totally examined prostatic TUR chips. These men were divided into three groups: those treated for cure by radical resec-

tion; those treated by some form of irradiation; and those who did not receive curative treatment. The latter group included men who received no specific treatment, those who were given TUR for relief of obstruction, and those treated with orchiectomy. Prostate cancer was the cause of death in three instances in each of these three treatment groups. Men who received only symptomatic treatment died because of prostate cancer in 3 of 19 (16%) instances, while 6 of 12 (50%) deaths among men treated for cure were caused by prostate cancer.

Systematic autopsy studies were performed on 293 men (216 or 74% from this cohort, and 77 or 26% who were in the same age range but not in the examined cohort). Prostate cancer was slightly more frequent among the 216 subjects who had participated in the baseline examination than in the 77 who had not, 29.2% versus 22.1%, respectively ($P = 0.3$). The mean age at autopsy was 67.9 years. Table 3 indicates that the frequency of this cancer at autopsy rose with increasing age, from 19% in men below 59 years of age to 63% in men over 80 years of age. The mean age of men with occult cancer was 70.2 years. Table 4 indicates that the volume of 48 of the tumors (60%) was less than 150 mm³ and that the volume of the tumors appeared to increase with increasing age at time of death. The tumors were multicentric in 30 cases (37.5%), and multicentricity did not appear to be related to age.

The prostate cancers discovered at autopsy were more than 1 cm from the urethra in 46 cases (57.5%) and at or less than 1 cm in 34 cases (42.5%). The mean volume of tumors at the periphery of the organ was 168 mm³ (8-900 mm³), compared to more central tumors, which had an average volume of 3815 mm³ (84-27,700 mm³).

Discussion

Hawaii Japanese men experience age-adjusted annual prostate cancer mortality rates per 100,000 that are much lower than those of Hawaii whites, 9.2 versus 24.4, respectively (7). Their age-adjusted annual incidence rates are also lower than those of Hawaii whites, 54.1 versus 86.7 (7).

The ratio of mortality to incidence rates of prostate cancer is not related to the frequency of the tumor from one nation to another but tends to be low in countries

Table 2 Clinical cancer confined to prostate: treatment and survival

	No treatment for cure	Radical resection	X-ray or other radiation
No.	43	35	28
Average age at diagnosis and initial treatment	75.6	69.6	72.2
Mean post treatment survival, years (range)	5.9 (0.8-29.2)	9.0 (1.7-28)	5.7 (2.3-12.3)
Number of deaths (%) ^a	19 (44)	6 (17)	6 (21)
Death due to prostate cancer (%)	3 (7)	3 (9)	3 (11)
Death due to other causes (%)	16 (37)	3 (9)	3 (11)

^a Percentage of total number of cases diagnosed.

Table 3 Frequency of cancer in step sectioned prostate glands, autopsied Hawaii Japanese men, 1970-1990

Age at death (years)	Total	Prostate cancer (%)
≤59	48	9 (19)
60-69	131	29 (22)
70-79	98	32 (33)
80+	16	10 (63)
Total	293	80 (27)
Mean age, years (range)	67.9 (50.1-88.8)	70.2 (54.6-88.8)

that can afford to apply sophisticated medical diagnostic procedures to older men and high in countries whose economic priorities do not favor the screening of older men for occult disease (10). Thus, the ratio is 0.31 for Los Angeles U.S. whites, 0.33 for Canadians, and 0.32 for Japanese in Japan. In contrast, the ratio is 0.9 in Warsaw, Poland, and 0.78 in Szabolcs, Hungary. The ratio of mortality to incidence among the Japanese men of this cohort was 0.20, as compared with 0.42 for Japanese in the Hawaii state registry (7). This suggests that our subjects had more intensive health surveillance than other Hawaii Japanese men. In spite of this, our autopsy findings suggest that many prostate cancers in this population have escaped detection. It was found at autopsy in 80 of 293 men (27.3%) who had no prior history of prostate cancer, while it was diagnosed in life in 274 of 8006 men (3.4%).

It is noteworthy that none of the 17 deaths among the 61 incidental cases of prostate cancer (Table 1) was due to the prostate cancer and that only 9 (8%) of 106 men with a tumor localized to the prostate died as a result of this cancer. It is probable that some clinically diagnosed cases in this study were understaged at the time of diagnosis. Diagnostic procedures have become increasingly refined over the life of the study, and some patients in the earlier years may well have been assumed to have had localized disease when, in fact, their tumors had already metastasized. Other subjects were too ill from other diseases to warrant extensive work-up.

The autopsy study understates the actual frequency of prostate cancer in the cohort because men with pre-mortem diagnoses of this tumor were not included in the analysis. We recognize that autopsy subjects are not representative of all deaths among Hawaii Japanese. Deaths due to heart disease are underrepresented and cancer deaths are overrepresented among autopsied subjects in our population (11). This may not have affected our results, because a study of clinically unsuspected prostate cancer in Japanese autopsy subjects showed a uniform distribution of these tumors among all disease categories (12). The slightly increased frequency of occult cancer among cohort men as compared with men who had not participated in the baseline examination is consistent with a previous study of clinical prostate cancer that showed a small but statistically nonsignificant ($P = 0.11$) advantage in prostate cancer-free survival among nonparticipants (13). When all of these factors are taken into consideration, we believe that the prostate cancer experience of the study population is representative of the Hawaii Japanese population.

Table 4 Mean and range of age at death for autopsied men, by status of prostate cancer, tumor volume, and number of tumors

Prostate cancer cases by	n	Age at death (years)	
		Mean (SE)	Range
Tumor volume (mm ³)			
<150	48	68.7 (0.87)	55.5-83.4
150-999	19	71.9 (2.19)	57.2-88.8
≥1000	13	73.3 (2.32)*	54.6-84.0
No. of tumors			
1	50	69.9 (1.04)	55.5-84.0
2	17	71.2 (2.05)	59.0-88.8
3	13	71.2 (2.30)	61.4-80.6

* P for trend = 0.025, based on mean age at death.

It is reasonable to assume that greater clinical effort would have increased the number of prostate cancer cases diagnosed before death in the study participants. Tumors with volumes greater than 1000 mm³ would probably have been identified by some combination of digital palpation, ultrasound examination, or prostate-specific antigen assay. Such large tumors, however, constituted only 16% of the unsuspected prostate cancers (13 of 80), and they were found in only 4.4% (13 of 293) of the autopsied men in this study. If a screening program had been conducted on the cohort on a regular basis, 342 additional men with larger cancers (4.4% of the 7732 cohort men without clinical prostate cancer) may have been identified.

Men with tumors smaller than 150 mm³ constituted 60% of the men with unsuspected cancers (48 of 80) and 16% of the autopsy men. It is unlikely that existing diagnostic procedures would have discovered these small cancers. There is a significant age gradient in the size of prostate cancer, and the largest tumors carry the highest probability of metastasis (14). The largest cancers are found in the oldest men, who are most likely to be affected by diseases of the elderly (e.g., stroke, heart disease, obstructive lung disease, other cancer). These complicating diseases will reduce the number of men eligible for curative treatment or erase its benefits by causing death in the early posttreatment years. The cost of wider application of diagnostic screening procedures in order to identify men for radical treatment of early prostate cancer can be justified if it can benefit a substantial number of screened men without lowering their quality of life or imposing too high a risk of operative mortality. Chodak and Schaenberg (5) indicate that the operative mortality from radical resection of the prostate is 1%, to which should be added failure of curative surgical or radiation treatment to prevent recurrence and subsequent death due to prostate cancer.

Studies in the United States (15) and Sweden (16-18) show no significant survival differences between treated and untreated men with early prostate cancer. The experience of the men in this cohort is consistent with these findings. The mean age of cohort men who were selected for radical surgery was lower than the age of men given X-ray therapy (69.6 years versus 72.2 years), and the age difference was even greater when surgical cases were compared to men treated symptomatically (69.9 years versus 75.6 years). It is likely that this difference in age is related to the better health status of men selected for surgery. The results in Table 1 show that

only 9 of the 106 localized cases had died due to prostate cancer so far, compared with 21% due to other causes.

The choices and results of different types of treatment of localized prostate cancer are heavily influenced by age and the presence of intercurrent disease (Table 2). Death due to causes other than prostate cancer occurred in 16 of 43 (37%) men with early cancer treated symptomatically and in 6 of 63 (10%) of men treated for cure (Table 2). It is unlikely that intensive screening would have greatly diminished the already low proportion of deaths due to prostate cancer in this cohort of Hawaii Japanese men (2% of all deaths). We recognize, however, that only a randomized study of early prostate cancer can determine whether radical surgery might confer a survival advantage upon treated men as compared to untreated men.

These results call for additional prospective studies in other ethnic groups. These should assess the potential results of screening and radical treatment for asymptomatic prostate cancer within the framework of the total health experience of each population. In the meantime, the risks and benefits of radical surgery should be explained to patients as objectively as possible.

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Cancer Epidemiol Biomarkers Prev 1992;1:189-193.

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