

The American Cancer Society National Prostate Cancer Detection Project and National Patterns of Prostate Cancer Detection and Treatment

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The American Cancer Society National Prostate Cancer Detection Project (ACS-NPCDP) was established in 1987 to demonstrate the feasibility of early detection as a cancer control strategy for prostate cancer. Before this project was developed, prostate-specific antigen (PSA) and transrectal ultrasound were emerging technologies that had been investigated

only in men already diagnosed with the disease. These new methods, of unknown potential for early detection, were combined with the previously studied digital rectal examination in a coordinated, multimodality intervention strategy.

To demonstrate the range of settings in which advancing early detection of prostate cancer might be possible, the ACS-NPCDP involved a multidisciplinary group of investigators from different medical facilities, including community hospitals, university medical centers, cancer centers, and private medical practices. An annual examination protocol was established to replicate periodic testing, and healthy men at risk of prostate cancer were recruited to participate for 5 years.

Although the ACS-NPCDP was established as a demonstration project, the project design incorporated several detection efficacy variables, such as sensitivity, specificity, and predictive value. Analyses of these outcomes were reported in several publications as the project progressed.¹⁻⁴ This report reviews the status and summary outcomes of the ACS-NPCDP. In addition, the patterns of detection and outcome in the ACS-NPCDP are compared with contemporaneous patterns of prostate cancer in the United States documented in the National Cancer Database (NCDB).

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Background

Ten clinical centers recruited 2,999 healthy men age 55 to 70 years who had no history of prostate cancer, were not already under evaluation for possible

prostate cancer, and provided informed consent before their participation. The participants were recruited from community populations by means of public service announcements and similar promotions. Details of the protocol have been described.^{1,4} Blood was drawn for PSA assessment before digital rectal examination or transrectal ultrasound was done. Real-time ultrasonography was performed in axial and sagittal projections. A suspicious outcome of digital rectal examination was defined by the presence of significant induration, nodularity, or asymmetry.

If a suspicious area was defined by transrectal ultrasound or digital rectal examination, participants were requested to submit to a transrectal ultrasound-guided

diagnosis of prostate cancer. Slides for all patients diagnosed with cancer were reviewed by the ACS-NPCDP review pathologist at the Armed Forces Institute of Pathology.⁵ Classification of clinical stage was based originally on the Whitmore paradigm, but for the purpose of comparison with data from the NCDB, cancers were assigned to American Joint Committee on Cancer (AJCC) pathologic stages I through IV.^{6,7}

Tumor grade was assessed in the biopsy specimen according to the scoring system described by Gleason and Mellinger.⁸ AJCC pathologic stage was assigned for patients treated by radical prostatectomy based on the surgical pathology report.

The original protocol required five

The ACS-NPCDP database now includes results from 12,414 digital rectal examinations, 12,226 PSA tests, and 10,589 ultrasound examinations.

biopsy. When only the digital rectal examination could locate the suspicious area, a digitally guided biopsy was performed. A PSA level of more than 4.0 ng/ml was the usual indicator of the need for further evaluation.

The most common exception to this guideline occurred when the transrectal ultrasound and digital rectal examination were normal and the elevation in PSA was consistent with benign gland enlargement. In these instances subjects would continue to be followed by transrectal ultrasound, digital rectal examination, and PSA assessment without immediate biopsy.

Subjects who had normal biopsy outcomes continued to be monitored by transrectal ultrasound, digital rectal examination, and PSA level; they underwent biopsy again if these examinations again indicated the need.

The principal study outcome was the

repeat annual evaluations. That phase is complete, and subjects continue to be seen annually and to receive the PSA testing and digital rectal examination as recommended in the ACS checkup guidelines.⁹

As result of this protocol, the ACS-NPCDP database now includes results from 12,414 digital rectal examinations, 12,226 PSA tests, and 10,589 ultrasound examinations. A total of 1,290 biopsy procedures were done at one or more visits in 920 men. Seven hundred forty-nine men had biopsies done on only one occasion, and 171 had several visits that resulted in biopsies being done.

The initial objectives of the ACS-NPCDP were addressed by internal comparisons of the yields of the different modalities studied, but the project design did not incorporate a control group receiving usual care. Although it does not

constitute a true control group, contemporaneous data may provide reference points to place the ACS-NPCDP results in the context of the general patterns of detection prevalent in the United States during the time of this investigation.

The NCDB data used for comparison herein are the aggregated reports of more than 1,300 hospitals participating in the American Cancer Society–American College of Surgeons Commission on Cancer patient care evaluation program. To approximate the time frame of and age range of patients in the ACS-NPCDP, only prostate cancers diagnosed between 1987 and 1992 in men age 55 to 70 years at diagnosis were used for these analyses.

A further subset of patients treated by radical prostatectomy was used for the comparison to ACS-NPCDP patients with respect to pathologic stage. Total numbers tabulated for both the ACS-NPCDP and the NCDB vary among analyses because of missing data about staging, treatment, or other variables. The method used to collect and process NCDB data has been described elsewhere.¹⁰

Results

The average age of the participants at entry was 62.5 years. Whites made up 88.1% of the cohort, African-Americans constituted 7.2%, and other racial and ethnic groups (including Hispanics, American Indians, and Asians) accounted for 4.7%.

Of the initial 2,999 eligible subjects, 1,383 were examined for all of the first 5 years. Adjustment for cancer cases detected in earlier years yielded a total compliance rate at year 5 of 49.0%. The greatest loss occurred after the first examination, after which 70.7% of initially eligible men were examined. Thirty-one of the 854 men (3.6%) who did not return after the initial visit had been recommended for biopsy but did not return for that further evaluation in spite of follow-up contact. Biopsies were obtained in 89.1% of instances in which an examina-

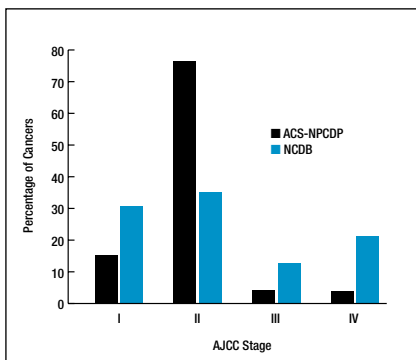


Fig. 1. American Joint Committee on Cancer (AJCC) clinical stage of 204 prostate cancers detected in the ACS National Prostate Cancer Detection Project (ACS-NPCDP) compared with the AJCC clinical stage of 56,910 prostate cancers reported in the National Cancer Data Base (NCDB). To approximate the age range and time frame of the ACS-NPCDP, the NCDB data used were only from men age 55 to 70 years who were diagnosed from 1987 to 1992.

tion visit resulted in a recommendation for biopsy.

Cancer detection rates across the five annual examinations averaged 2.0%, with a high of 2.7% yielded by the first examination. Earlier reports from the ACS-NPCDP and other studies have provided detailed assessments of the comparative sensitivity, specificity, and predictive value of PSA level, transrectal ultrasound, and digital rectal examination in the early detection of prostate cancer, and those results are not included in this report.^{4,5,11-13}

To summarize those other reports, PSA assessment shows a good balance of sensitivity and specificity compared with both transrectal ultrasound and digital rectal examination. More than 70% of tumors were sensitive to detection by PSA at every annual examination. The digital rectal examination was most productive in the first examination, but by the fifth year, the digital rectal examination was sensitive to only 25% of the cancers that were detectable by other modalities.

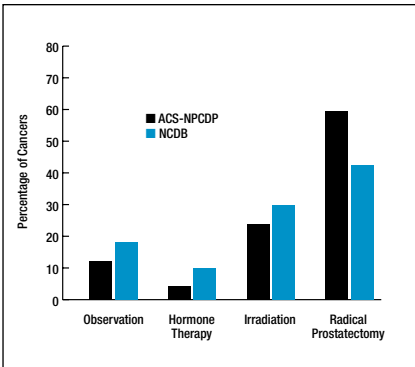


Fig. 2. Primary treatment for 230 cancers detected in the ACS National Prostate Cancer Detection Project (ACS-NPCDP) compared with primary treatment for 131,775 prostate cancers reported in the National Cancer Data Base (NCDB) in men age 55 to 70 years diagnosed from 1987 to 1992.

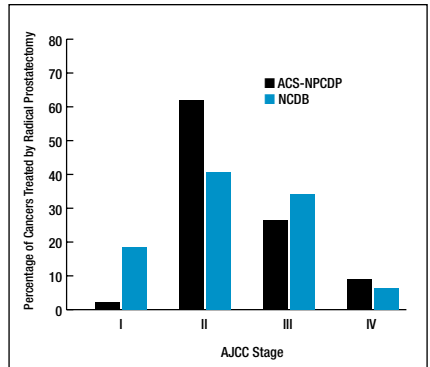


Fig. 3. American Joint Committee on Cancer (AJCC) clinical stage of 133 prostate cancers in patients in the ACS National Prostate Cancer Detection Project (ACS-NPCDP) treated by radical prostatectomy compared with AJCC clinical stage of 43,172 prostate cancers reported in the National Cancer Data Base (NCDB) in men (age 55 to 70 years, diagnosed from 1987 to 1992) treated by radical prostatectomy.

Transrectal ultrasound, in contrast, achieved high sensitivity but low specificity; only one in 20 lesions that were suspicious on ultrasound proved to be cancer unless the digital rectal examination or PSA test also supported the suspicion.

To date, complete staging data have been obtained for 204 of the 233 cancers detected (Fig. 1). When the clinical stage of cancers detected in the ACS-NPCDP was compared with that of cancers reported to the NCDB, two trends were seen. More advanced prostate cancers (stages III and IV) and more cancers in the earliest stage (stage I) were seen in the NCDB data (34% versus 8.3% for advanced cancers and 30.9% versus 15.2% for stage I cancers). Conversely, the proportion of cancers classified as stage II in the ACS-NPCDP results was more than twice that reported in the larger database (76.5% versus 35.1%).

The tumors showed a limited range of aggressiveness. For the 218 patients on whom Gleason grade data have been obtained, 192 (88.1%) were Gleason grades 4 through 7. The most common Gleason grade was 5, accounting for 25.7% of all

patients with known grades.

Figure 2 describes the primary treatments used for both the ACS-NPCDP and NCDB cancers. The selection of treatment for the ACS-NPCDP patients was not dictated by the project; patients freely selected from among the range of options appropriate to their disease. These data show more frequent selection of radical prostatectomy in the ACS-NPCDP cohort (59.6% versus 42.4%), similar rates of radiation therapy (23.9% versus 29.8%), and less frequent use of medical or surgical hormonal therapy (4.3% versus 9.8%) and observation (12.2% versus 18.0%). Distributions of treatment by stage are not shown, but in ACS-NPCDP data, 97% of patients treated by radical prostatectomy were clinical stage I or II.

Data on pathologic stage have been obtained for 132 of the 136 ACS-NPCDP patients treated by radical prostatectomy (Fig. 3). Compared with NCDB patients treated by radical prostatectomy, more

ACS-NPCDP patients treated by radical prostatectomy had cancers confined to the organ after treatment. A combined total of 64.4% of ACS-NPCDP radical prostatectomy patients had AJCC stage I or II compared with 59.2% in the national data. More cancers in NCDB patients were pathologic stage I compared with cancers in ACS-NPCDP patients (18.6% versus 2.3%).

The patients with prostate cancer detected in the ACS-NPCDP will receive long-term follow-up. At present, the 233 patients have been followed for an average of 54 months from the time of their diagnosis, and 91.4% have been followed for at least 1 year.

Thirteen patients (6.0%) are known to have died. One death (0.4%) is classified as treatment related because an acute myocardial infarction occurred 9

prostate cancer or its treatment.

Sexual potency status has been reported from physician sources for 123 patients. Six of the 23 patients (26.1%) treated by radiation reported full potency or potency adequate for intercourse. Twenty-two of 83 patients (26.5%) treated by radical prostatectomy reported full or adequate potency. Urinary continence status has been reported from physician sources for 154 patients. Eighty of 95 patients (84.2%) treated by radical prostatectomy reported complete urinary control or only occasional incontinence

Discussion

The collection and evaluation of data from the ACS-NPCDP are continuing. It is, however, 10 years since the project was conceived, and many results now exist

Compared with patients in the NCDB, more ACS-NPCDP patients treated by radical prostatectomy had cancers confined to the organ after treatment.

days after radical prostatectomy. Two men (0.9%) have died of prostate cancer.

One prostate cancer death was in a patient with cancer classified as clinical stage II, Gleason grade 8, who was treated by radical prostatectomy, which yielded positive lymph nodes. He survived 55 months from the time of diagnosis.

The second death was in a patient who had abnormalities on both digital rectal examination and transrectal ultrasound, very high PSA (more than 100 ng/ml), and a Gleason grade 7 tumor when initially seen. This patient declined further treatment after transurethral resection of the prostate. He survived for 48 months from diagnosis.

Eleven (4.7%) other deaths have occurred among the cancer patients being followed from causes unrelated to

that reflect on the efficacy of early detection as a public health intervention.

The compliance results suggest that early detection programs can achieve long-term participation in a well population. The annual cancer detection rates associated with all methods of detection showed a significant decline after the first examination. This effect is to be expected when any previously unscreened population is first examined. Accumulated prevalent cancers in the population are more likely to be detected initially; in subsequent years, only newly incident cancers are detected.

Assessment of PSA level is a particularly useful early detection test because of its balance of sensitivity and specificity. The results of the ACS-NPCDP, however, reinforce the concept that early detec-

tion of prostate cancer may be accomplished best by a multimodality approach. Approximately one-third of the cancers detected in this project occurred in men with PSA levels less than 4.0 ng/ml, the conventional upper limit of normal for this test. Those cancers were detected only because a digital rectal examination or transrectal ultrasound examination (or both) also was done. In addition, Littrup and colleagues¹⁴ have shown that the use of multiple modalities permits a tailored approach to detection and patient surveillance. This approach reduces the overall number of biopsies and false-positive results and enhances the cost-effectiveness of the program.

During the time when the ACS-NPCDP intervention was being applied to the study cohort, prostate cancer de-

This difference may illustrate the gap that exists between what can be achieved in a systematic, coordinated cancer control effort in which all men receive some level of testing and what occurs in the community, where cancer control efforts are episodic. More stage I cancers were seen in the NCDB cohort, but this may be the result of the frequent detection of prostate cancer after transurethral resection of the prostate for benign hyperplasia. Prostate cancer is often detected in this way in the general population, but this type of detection was infrequent in the ACS-NPCDP patients.

Because of the more favorable clinical stage distribution, more patients with prostate cancers detected in the ACS-NPCDP were candidates for treatment with curative intent. In the ACS-NPCDP

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tection was changing dramatically throughout the United States. The general use of both PSA testing and ultrasound increased, and the number of men diagnosed with prostate cancer annually in the United States rose from 96,000 in 1987 to 132,000 in 1992.¹⁵⁻¹⁷ Although recent evidence suggests that the rapid rate of increase in incidence has begun to abate, the estimated number of new cases for 1997 is a noteworthy 209,900.¹⁸

National data suggest that the changes in prostate cancer detection are widespread. The data on clinical stage of disease presented here, however, show that even earlier detection occurred in the ACS-NPCDP compared with the usual pattern of care in the community. Only 8.3% of ACS-NPCDP cancers were clinically advanced (stage III or IV) at the time of diagnosis in contrast to 34.0% of comparable NCDB cases.

cohort, 83.4% received radical prostatectomy or radiation therapy as their primary treatment compared with 72.2% of the NCDB patients. Even in the patients treated by radical prostatectomy, more ACS-NPCDP patients proved to have organ-confined disease (pathologic stage I or II) after radical prostatectomy than did NCDB patients.

The identification of more candidates for treatment with curative intent combined with the greater likelihood that the treatment can actually achieve this aim may be another measure of the benefit that a systematic detection program can yield compared with the usual pattern of care.

The numbers are not large and the follow-up duration is relatively short, but the surveillance of cancers detected in the ACS-NPCDP reveals few adverse outcomes. The one death coincidental to

treatment represents less than 0.5% of the total patient cohort and less than 1% of total patients treated by radical prostatectomy. Other large series have reported death rates related to radical prostatectomy to be between 0.5% and 1%.^{19,20} The two prostate cancer deaths observed both occurred in patients whose disease detected at the initial screening was advanced. No similar events have been observed for cases detected in subsequent examination cycles.

The analysis of the ACS-NPCDP cohort has focused on the subjects who continued to participate in the study. The screening behavior and detection outcomes in men who did not complete the protocol are being assessed through follow-up. Most of the men who did not return had normal examination results be-

in interpreting these comparisons.

Comparison of the outcomes of the ACS-NPCDP with those of other, larger databases may provide an informative perspective but has limited validity. The ACS-NPCDP is not a randomized controlled trial. The subjects in the ACS-NPCDP and the institutions participating in the NCDB are not representative samples. The ACS-NPCDP series is a self-selected population that may differ from the general population with respect to such important characteristics as willingness to follow early detection recommendations and predisposition to prostate cancer.

Randomized controlled trials of screening will result in more rigorous evaluation of the outcomes of prostate cancer early detection. The National Cancer Institute is currently conducting

Prostate cancer was detected earlier in the ACS-NPCDP compared with the usual pattern of care in the community.

fore dropping out, but it is possible that some had prostate cancer diagnosed after they were last seen in this study. This may lead to further adjustment in our estimates of sensitivity and specificity.

In a special survey of radical prostatectomy outcomes in the United States conducted by the Commission on Cancer of the American College of Surgeons, 27.7% of 1,059 patients receiving this treatment reported full or adequate potency.²¹ This is nearly the same percentage observed for the ACS-NPCDP patients treated by radical prostatectomy. In the large survey, 81.1% of radical prostatectomy patients reported complete urinary control or only occasional incontinence, a percentage that also is similar to the rates so far observed in the ACS-NPCDP. However, ACS-NPCDP data on potency and incontinence are not yet complete, and caution should be used

such a trial, the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial. Results from the trial will be more conclusive than the evaluation of efficacy provided by ACS-NPCDP results.²² In spite of these limitations, however, the data reported herein may provide significant information about the effectiveness of digital rectal examination, transrectal ultrasound, and PSA testing in early prostate cancer detection.

Conclusion

It seems intuitively correct that reduced mortality will result from early detection, but this has not been shown in definitive research. Early detection, however, may not yield benefit unless early intervention meaningfully alters the natural history of the disease.

Ultimately, the value of early

prostate cancer detection must be judged in terms of its impact on mortality rates. It may be significant that prostate cancer mortality rates in the United States have recently begun to decline. Between 1990 and 1995, the prostate cancer death rate

declined 6.3%.²³ The decline follows several decades of rising death rates for this disease. Whether this favorable trend is related to the increased use of interventions for early detection deserves careful evaluation. **CA**

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