The great American pseudo-epidemic of cancer of the prostate

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Introduction

A pseudoepidemic of prostate cancer is sweeping USA, with no real increase in the actual number of patients with this disease. The increase in the number of cases detected is largely because of the widespread use in USA of a screening test - measurements of prostate specific antigen (PSA) - in asymptomatic, apparently normal males 50 years of age or older (40 years of age in black Americans).

Use of the test has increased the rate of treatment (surgery, radiation, drugs) without improving mortality from prostate cancer. In fact, the mortality and morbidity associated with treatment have increased. In USA, screening with the test has been enthusiastically endorsed bv the American Urologic Association and the American Cancer Society. It has been rejected by the National Cancer Institute. It has been specifically rejected in Canada.

To date, the epidemic has not spread to Europe. Nor is the test used as a mass screening method in India. We attempt to warn physicians about the dangers of PSA screening in normal males and provide some important lessons about the hazards of poorly conceived screening approaches.

Early history

There is an interesting and instructive coincidence involving the surgical treatment of prostate cancer and India. In 1901, P. Johnston Freyer introduced the use of radical prostatectomy for the treatment of prostate cancer.[1] The surgical treatment consisted of suprapubic prostatectomy.[2]

Freyer was a surgeon in the Indian Medical Service and it is almost certain that the procedure was performed on Indian subjects without informed consent. How could the patients have been provided informed consent? Johnston Freyer himself had no idea of the risks versus benefits of his surgical procedure. Nor did he have any clear idea of the natural life history of prostate cancer, so different from the natural life history of most visceral cancers. He simply obeyed an intuitive impulse - 'diagnose cancer; remove as'much of the organ as feasible.' That impulse is still commonly followed today. At any rate, it is almost certain that he caused net loss of life and/or deterioration of the quality of life.

The 'credit' for the introduction of radical prostatectomy for prostatic cancer is usually given in the U.S. to Hugh Hampton Young at Johns Hopkins Medical School. He probably performed the first radical perineal prostatectomy in 1904.[2] For purposes of establishing priority, Young did manage to push back the date to 1898 when he performed a total perineal prostatectomy as a surgical resident. In a review extolling his own contributions published almost 50 years later, Young displays a profound ignorance of the natural life history of cancer of the prostate as well as risk/benefit analysis.[2] The major purpose of his review was to prove that his form of radical prostatectomy cured cancer of the prostate. The proof consisted of a collection of 38 cases which have been followed for '5 to 27 years without evidence of recurrence.'

Young seemed unaware that by age 50-60, about one third of all apparently normal males have cancer of the prostate without showing adverse manifestations. By age 90 or more, almost all males have carcinoma of the prostate as demonstrated by post-mortem examination.[3] Thus, 20 year survival without surgery or other treatment is common in prostatic cancer. Without a control group, Young's results were meaningless. The claims of cure, however, were eagerly accepted by urologists.

The overwhelming majority of patients with prostatic cancer show-no evidence of prostatic disease during their lifetime and will die of disorders entirely independent of the existence of prostatic cancer. This fact has enormous implications for any screening program in apparently normal males. Not only would an accurate test be required but the test would need to distinguish the relatively few patients with progressive disease from those who would show no ill effects from their carcinoma without treatment. No such screening test appears to be in prospect. Certainly, none would dare claim such an ability for PSA testing.

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Stated another way, one perceptive urologist has stated 'The only patients we can cure are precisely those who will live the longest without intervention.'[4]

Natural life history of cancer of the prostate

Precise knowledge on the natural life history of a disease is required to evaluate the effects of therapy. Until 1935, knowledge of the natural life history of prostatic cancer was negligible. The view (which is still held by many urologists and most physicians) was that cancer is cancer. In 1935, Rich showed, using autopsy data, that in 220 patients who died of a variety of causes (not including cancer of the prostate), about one third of the patients had cancer of the prostate.[5]

Franks, also using autopsy material, showed a progressive increase in the percent of silent, clinically insignificant cancer of the prostate with advancing age. By age 50, about 30% of all males showed carcinoma of the prostate; by age 69, about 40%; by age 89, over two thirds of all males dying of causes other than cancer of the prostate and, by age 99, there was a 100% incidence![5] It should be emphasized that the cancers detected by this and subsequent post-mortem studies was not confined to a few nests of isolated cells. Advanced stages of prostatic cancer were found in some patients as well.

Over the years, these findings were confirmed by a number of workers,[6,7] under such terms as the incidental cancer of the prostate,[6] occult cancer of the prostate, and latent prostatic cancer. Urologists failed to perform acceptable, rigorous, prospective randomized clinical trials to compare the efficacy of no treatment with radical prostatectomy, external or interstitial radiation or drugs.

An analysis of cancer of the prostate in 1983 included an estimate of the ratio of incidental, asymptomatic prostatic cancer to the number of patients dying each year of the disease.[8]

The results are staggering. There are about 380 men with cancer of the prostate for every patient who dies of the disease. Even recognizing the substantial errors in this kind of estimate, these figures suggest that radical prostatectomy with a mortality of perhaps 1% and a morbidity of at least 15% results in outcomes that are far worse than those from untreated disease! The net effect of mass screening would almost certainly increase the number of men needlessly treated and the number of men injured or killed, say, by surgery.

The basis for the relatively favorable natural life history of cancer of the prostate is not completely understood. One important factor is the advanced age of those who develop cancer of the prostate. Their age dictates that many patients of advancing age die of other causes before cancer of the prostate becomes clinically significant. It has also been suggested that there are two populations of cancer cells, one indolent and the other aggressive.

The biological behavior of cancer of the prostate appears to differ from that of most other visceral cancers. One third of asymptomatic women over the age of 50 do not show evidence of breast cancer at post-mortem examination. Nor is there evidence that one third of asymptomatic women at age 50 have evidence of cervical cancer. To be certain, a relatively small percent of women have intraductal papillary carcinoma of the breast and a small percent of women have intraepithelial cervical neoplasia. Mass screening for those two diseases have their own limitations and risks. But those are relatively minor as compared with mass screening for cancer of the prostate.

The implication on screening males to detect slow, benign, non-progressive prostatic carcinoma is clear. A test which was epidemiologically perfect (100% specificity, 100% sensitivity) would not, on these grounds alone, be acceptable for screening apparently normal males. The test would also be required to separate males with progressive disease (candidates for treatment) from those with indolent disease (not candidates for treatment).

The clinical inadequacies of the test as carried out today can be inferred from the large number of proposed modifications. PSA velocity, PSA density, age-specific PSA, measurement of various forms of circulating PSA and, of course, computer analysis - in which various other findings are lumped in with a given value of PSA to provide a 'more accurate' result. All these attempts have one common characteristic. None has been adequately validated. None has been shown to improve patient survival or to improve patient outcome.

Risk/benefit analysis of current therapies for cancer of the prostate

This is a pertinent issue because, as emphasized by the World Health Organization, mass screening for specific diseases requires that an effective treatment be available for the disorder being detected.

In this context, the summary statement of an oncologist, made in 1981, and still true today is relevant: 'After a number of good controlled trials, there is yet no convincing evidence that surgery, radiation or endocrine therapy, alone or in combination, improve life expectancy in the patient with cancer of the prostate."

Numerous attempts have been made to establish an acceptable risk/benefit ratio for radical prostatectomy.

The most rigorous and acceptable study was reported in 1981.[10] When radical prostatectomy was compared to estrogen therapy, it was noted that there were more deaths in the group treated with estrogen. In the second trial, in which placebo therapy was compared to placebo plus radical prostatectomy, the patients in the placebo group did at least as well as those treated with radical prostatectomy. The number of patients studied was small but the study concluded that '... if radical prostatectomy has any value for patients staged in this manner, the advantage must not be very dramatic.' This study has been updated recently with a median follow up of survival of 23 years. No improvement in survival for the treated group could be demonstrated.'[11]

Other studies also raise questions about the efficacy of prostatectomy for the treatment of prostatic cancer. We will analyze specifically only one such investigation. Chodak et al performed a meta-analysis of ten separate studies on what was called clinically localized cancer of the prostate.[12] The term 'clinically localized' was not precisely defined but the study presumably did not include patients whose prostatic cancer was detected by mass screening of PSA. The data from 828 patients were included in the analysis. No clear cut evidence for the benefits of treatment could be demonstrated. For patients with grade 1 cancers, mortality among the patients was actually less than for the general population of men of comparable ages. Inclusion of patients with early stages of cancer who were older, had worse than average health, or who underwent delayed radiation therapy or radical prostatectomy, did not affect mortality significantly.

These opinions have resulted in a peculiar paradox. Asymptomatic men are urged to undergo a screening test for the early detection of a disease that may well be treated with 'watchful waiting.' Watchful waiting will result in a large population of men (up to 15,000,000 in the U.S. alone)* held captive by urologists.

The most conservative conclusion that can be reached is that an adequate prospective, randomized, controlled clinical trial involving treatment by radical prostatectomy is mandatory. It appears almost certain that this form of treatment will show no statistical benefit of increased survival.

It is, of course, probable that radical prostatectomy will be shown to prolong life in some individuals. The probability of this outcome (as low as that value might be) should than be provided to prospective patients so that they can make an informed choice.

It may safely be predicted that under these conditions the performance of radical prostatectomy would drop precipitously. These considerations appear to be valid, even with a new mass influx of patients provided by PSA screening.

Clinical surveys on the use of ionizing radiation to treat cancer of the prostate have also failed to show a significant improvement in survival time. The use of radiation does have one advantage over surgery: peritherapy mortality is essentially zero and perioperative morbidity is low. Despite extensive pragmatic use, there is no convincing evidence that either external or interstitial radiation reduces mortality. This is likewise true of many forms of malignancy for which therapy with ionizing radiation is used. But there is an important difference. In prostatic cancer, only about 1/400 patients will show progressive disease. The use of PSA screening could only increase the percent of patients being treated needlessly.

A whole host of drugs are in use, either in primary treatment of cancer of the prostate or in the treatment of metastatic disease. The use of estrogen was terminated due to a significant excess of cardiovascular deaths in patients with stage 1 cancer of the prostate treated with estrogen. Currently used drugs include luteinizing hormone releasers (LHRH) and anti-androgens (flutamide, cyproterone acetate and nilutamide). There is no claim that these agents are curative and indeed doubt exists on their efficacy in prolonging survival in patients with metastatic disease.

In clinically detected disease, independent of any mass screening survey, there is no acceptable evidence that any current treatment of cancer of the prostate improves mortality. If this conclusion is true, detection of larger numbers of patients with asymptomatic cancer of the prostate would render them vulnerable to increased use of such therapies without reducing mortality. A recent study confirms this prediction of a marked increase in treatment with no improvement in patient outcome![13]

*PSA **measurements as a test***

The efficacy of PSA detection of prostatic cancer depends heavily on the clinical, chemical and epidemiologic validity of the measurement per se. It will be seen that there are major problems in all of these areas.

Its sensitivity has been estimated at 60% and specificity at 40%.[14] The sensitivity and specificity of PSA screening are not improved by adding findings on digital rectal examination (DRE).[8] This leaves us with a screening test for cancer of the prostate which is statistically no better than a flip of a coin. We know, further, that elevations of PSA are found in patients with benign disease such as benign prostatic hypertrophy (BPH), chronic prostatitis, recent manipulation of the prost[illegible] cystoscopy, DRE) and, simply

put, reasons unknown. Thus, the term 'prostate specific' is misleading. The antigen is a general tumor marker with many false positives.

PSA levels are not used only to diagnose - or attempt to diagnose - cancer in asymptomatic males. The PSA level is also used as a surrogate criterion to measure success of therapy (on the basis of a drop in PSA levels) by, for example, radiation oncologists? No study, to date, has shown that patients so treated live longer or better for having received the therapy.

PSA is not an ideal test by another criterion, namely the frequent changes and modifications which have appeared since its introduction.

The conclusion is simple and obvious: an elevated PSA does not mean the patient has cancer of the prostate; a normal PSA does not mean the patient does not have cancer of the prostate.

Ethical considerations

A major issue is informed consent. Should patients who are to be screened by PSA measurement be told that the test is inaccurate? Should they be told that therapies available to treat the disease, if detected, are of no proven benefit? Should they be informed, prior to being screened for PSA, that they are subjects in an experiment?

Should they be told that only some cancerous glands are undoubtedly rendered less dangerous to the patient by their surgical removal or by irradiation or even by exposure to pharmacologic agents? Should they be told that our problem is that no one, not the screening physician, not the operating surgeon, not the irradiating oncologist knows which patients will benefit from therapy? Should they be told that since those who do benefit from therapy do not emerge as a group from any of the clinical trials available to date, their numbers are probably small?

Should they be told that a new risk of radical prostatectomy has recently emerged? Twelve of 14 consecutive patients undergoing this treatment have been shown to have seeded prostatic epithelial cells in the general circulation when their disease was shown to be organ-confined prostate adenocarcinoma. The implication is that surgery for a tumour with a low metastatic potential, itself, may be an important metastatic mechanism.[16]

Surgical dissemination, of course, may prove to be of little importance in patient outcome but, alternatively, this possibility may represent an important risk for cancer surgery generally.[17]

A number of experts using and urging mass screening in apparently normal males acknowledge that there is no firm evidence that screening produces improved patient outcome. This revelation is then usually followed by a promissory statement: 'In two years . ..'or 'In five years ....'or '... at some indefinite future time we'll know'... because study A or study I3 or study C is underway . . . '

In the absence of definite knowledge of outcome the entire mass screening program represents an experiment. The experiment may result in harm or death to the participants. Such an experiment is not acceptable without the informed consent of those who are the experimental subjects. A written - or even oral - acknowledgement by the patient of the experimental nature of PSA screening is, at this time, in the U.S., seldom, if ever used.

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References

1. Freyer PJ: Described in Garrison FM: ***An introduction to the history of medicine.*** Philadelphia: WB Saunders Co., 1914
2. Young HH: The cure of cancer of the prostate by radical-perineal prostatectomy (Young's operation). ***Journal of Urology*** 1945;188-256
3. Franks LM: Latent carcinoma of the prostate. ***Journal of Pathology and Bacteriology*** 1954;68:605
4. Whitmore WF: The natural history of prostatic cancer. ***Cancer*** 1973;32: ***1104***
5. Rich AR: On the frequency of occurrence of occult carcinoma of the prostate. ***Journal of Urology*** 1935;33:215
6. Fullis I: Incidence of prostatic cancer in the elderly. ***Urology*** 1975;6:295
7. Halpert B, Shmalhorst WR: Carcinoma of the prostate in patients 70-79 years old. ***Cancer*** 1966;19:695
8. Stamey Ta: Cancer of the prostate. ***Monographs in Urology*** 1983;4:85-92
9. Zumoff B: Carcinoma of the prostate. In Fries J, Elliot G. (Eds.) ***Prognosis:*** Chapter 30. Maryland: Charles Press, ***1981***
10. Byar DP, Corle D: VACURG randomized trial of radical prostatectomy for stages I and II cancer of the prostate. ***Urology*** (Suppl) 1981;17:7-11
11. Tversen P, Madsen PO, Corle DK: Radical prostatectomy versus expectant treatment for early carcinoma of the prostate: 23 year follow up of prospective randomized study. ***Scandinavian Journal of Urology and Nephrology*** 1995;172:65-72
12. Chodak GW, Thisted RA, Gerber GS et al: Results of conservative management of clinically localized prostate cancer. New ***England Journal of Medicine*** 1994;330:242-248
13. Yu-Lao GL, Greenberg ER: Changes in prostate cancer incidence and treatment in USA. ***The Lancet*** 1994;343:251-254
14. Magiminiyi OA, Rege V: Multiple forms of PSA in serum and clinical significance of results. Letter. ***The Lancet*** 1995;345:125-***126***
15. Schild SE, Wond WW, Grado GL et al: Radiotherapy for isolated increases in serum prostate specific antigen levels after radical prostatectomy. *Mayo Clinic* ***Proceedings*** 1994;69:613-619
16. Eschwege P, Dumas F, Blanchet P et al: Haematogenous dissemination of prostatic epithelial cells during radical prostatectomy. ***The Lancet*** 1995;346:1528-1530
17. Oliver RTC: Does **surgery disseminate** or accelerate cancer. The ***Lancet*** 1995;346:1506-1507