

Published in final edited form as:

Int J Epidemiol. 2007 April ; 36(2): 278–281. doi:10.1093/ije/dym049.

Prostate cancer is omnipresent, but should we screen for it?

Richard M Martin

Department of Social Medicine, University of Bristol, UK

Introduction

In 1935, the pathologist Arnold Rice Rich reported on a study investigating his impression that microscopic prostate cancers could be detected at autopsy more commonly than were being diagnosed clinically.¹ This study has been cited 215 times up to July 2006, and along with a 1954 autopsy series reported by LM Franks² (cited 371 times), made a major contribution to our understanding of the natural history of prostate cancer. Rich's study confirmed his intuition of a large disparity between microscopic prevalence of prostate cancer and its clinical incidence, in contrast with many other solid tumours where these differences are not as marked. This commentary discusses the contemporary relevance of these findings 71 years on, with a focus on their implications for understanding the epidemiology of prostate cancer and its early detection and treatment.

What were the main findings?

There were at least three key findings, and each of these still raise important questions today. Firstly, despite the observations being retrospectively based on single, random microscopic sections from the prostates of unselected men dying of any disease, Rich demonstrated prostate cancer in 41 (14%) of 292 men older than 50 years of age, a result he described as 'surprising'. In only 14 of the 41 cases had the tumour been recognized clinically. Rich wrote '... the actual incidence of this condition is, in all probability, still higher; for the tumours ... (are) so small and so inconspicuous microscopically that it was only a matter of chance that the routine section passed through them'. Secondly, Rich eloquently described how difficult it would have been to clinically recognize most of the cancers in the series, despite a high prevalence of capsular invasion; these early tumours were impalpable ('they were neither seen nor felt even by the pathologist who was able to hold the dissected prostate in his hands and to examine the cut surface visually'), and the presence of tumour was not associated with any specific pre-morbid clinical symptoms or signs. Thirdly, Rich recognized that many men with prostate cancer died of other diseases, stating this was probably because prostate cancer is rare in people under 50 years and is slow growing. The questions raised by this study, therefore, include: (i) what is the prevalence of early prostate cancer? (ii) Is it possible to detect these early cancers in alive men? (iii) Given that many men with these histological prostate cancers die of other diseases, is it worth detecting them?

What is the prevalence of early prostate cancer?

Several autopsy studies published in the 1940s and 1950s confirmed high rates of tumour foci in the prostate gland,³ including the study by Franks, which estimated that 31% of men aged >50 years who died of other causes had some evidence of prostate cancer.² A recent

autopsy study reported on 314 African American and 211 Caucasian (sic) men aged 20-80 years who died of trauma in Detroit, USA. Microscopic evaluation in each case was based on 10-14 whole-mount step sections that were 2-3 mm thick.⁴ This study demonstrated a high prevalence of prostate cancer that increased progressively with advancing age and was similar at all ages in African American compared with Caucasian men (around 10%, 30%, 40%, 45%, 70% and 80% in the 3rd, 4th, 5th, 6th, 7th and 8th decades, respectively). When this ubiquity of microscopic prostate cancer is placed in the context of lifetime risks of clinical or fatal prostate cancer (about 10% and 3%, respectively for a man aged 50 years in the USA),⁵ these data indicate that local or distal progression of early cancer is far from inevitable within a man's lifetime. Put another way, only a minority of prostate tumours are highly aggressive and life-threatening, while the majority are slow-growing and indolent.⁶

The autopsy studies, started by Rich, offer insights into prostate cancer aetiology. For example, the similarity in prevalence of autopsy prostate cancer in African American and US white men⁴ is mirrored by findings of little variation in autopsy prostate cancer between countries.⁷ Yet, paradoxically, compared with US white men, African American men have higher prostate cancer incidence (137 per 10⁵ vs 100 per 10⁵) and mortality rates (34 per 10⁵ vs 16 per 10⁵) and there are 60-fold and 12-fold higher rates of prostate cancer incidence and mortality, respectively, amongst African American vs Chinese men.⁸ The explanation for the inconsistencies in patterns of disease between autopsy compared with incidence and mortality data remain unclear, but could reflect a role for environmental or genetic factors in prostate cancer progression, and/or indicate differences in the availability and use of healthcare.

Another important implication is that the high prevalence of autopsy prostate cancer reported by Rich and others complicates the study of its epidemiology, as incidence rates⁹ and attribution of prostate cancer mortality,^{10,11} are driven by surveillance intensity, such as screening with prostate-specific antigen (PSA), more frequent use of transurethral resection of the prostate and refined diagnostic procedures (biopsy).¹² For example, recent marked increases in prostate cancer incidence in the USA, Canada, Australia and France (25-114% between 1973-77 and 1988-92) were greatly influenced by intensive screening with PSA tests.⁸ Increases of a similar magnitude that occurred in Asian and other low-risk countries may be partly due to enhanced diagnostic efforts in developing countries or could indicate a role for changes in environmental and lifestyle exposures such as increased calorie and fat consumption.⁸

Finally, many studies of the aetiology of prostate cancer are based on clinically identified prostate cancer compared with unscreened controls, many of whom are likely to harbour foci of prostate cancer. Selection bias in such studies is possible if prostate cancer in men with benign prostatic hyperplasia (BPH) is more likely to present symptomatically and hence be diagnosed than in men without BPH.¹³ Hence positive associations of a putative aetiological factor with prostate cancer could be observed if that factor causes BPH, but not cancer. On the other hand, in studies of screen-detected cases, exposures that are more important later in carcinogenesis, as opposed to its initiation, may not be detectable as prostate cancer risk factors.

Is it possible to detect these early cancers in alive men?

Rich reported that the early prostate cancers in his dissected pathology specimens were impalpable.¹ Little wonder then that digital rectal examination (DRE) has subsequently been shown to have no value as a screening test in the general population.⁵ In the late 1980s, the serum concentration of PSA, a strong predictor of prostate cancer incidence and mortality,^{14,15} was introduced as the main screening test used to indicate when further investigation by transrectal biopsy is required. Men are selected for biopsy if their PSA level exceeds the

'normal' level. There is, however, considerable controversy over what is an appropriate cut-point,⁶ and there is a continuum of increased risk of prostate cancer with increasing PSA, even at levels well below currently recommended cut-offs.¹⁶ No threshold PSA value for undertaking a diagnostic biopsy offers simultaneously high sensitivity and specificity.¹⁷

The key issue, however, is not what the properties of the screening test are, but what it is that is being detected.¹⁸ The large difference between a man's small risk of death from prostate cancer and life-time risk of having microscopic disease, suggests that the majority of prostate cancers detected by screening are clinically unimportant.⁵ As screening intensity increases, the likelihood of over-detection of clinically unimportant prostate cancers becomes greater.¹⁹ Given the ubiquity of prostate cancer, especially in old age, demonstrated by the autopsy studies of Rich and others, 'any excuse to biopsy has an excellent age-dependent chance of being positive.'¹⁹ Seventy-one years after Rich's paper, the critically important question now is: can we identify localized prostate cancers destined to progress and result in clinical disease and mortality? Unfortunately, although advances in genomics and proteomics may provide useful prognostic markers in the future, no measures of biologically aggressive prostate cancer have yet been identified.¹⁸

Given that many men with these histological prostate cancers die of other diseases, is it worth detecting them?

Screening offers the potential to identify almost all prostate cancers that could previously only be detected in autopsy specimens.¹⁹ Intuitively, this could appear as an important scientific advance since Rich's day, since we can now detect asymptomatic, small and well-differentiated cancers that are clinically confined to the prostate and hence potentially curable.¹⁹ Indeed, a randomized controlled trial from Scandinavia showed that radical prostatectomy for localized prostate cancer reduced the risk of all-cause and prostate cancer-specific mortality at 10 years by approximately 25% and 44%, respectively, compared with watchful waiting.²⁰ However, the absolute reductions in risk of all-cause and prostate cancer-specific mortality were small (around 5%), and this study has limited relevance for screening as only 11% of the men had screen-detected prostate cancer.⁶ Treatments for localized prostate cancer can have deleterious side effects, and evidence from randomized trials about the effectiveness and side-effects of treatment for screen-detected disease is urgently required.²¹

No robust randomized trials of screening for prostate cancer have yet been published, but a recent modelling exercise suggests that the impact of treating screen-detected disease is likely to be limited.²² This should not come as a surprise, as it has been estimated that 'only 16% of those with disease detected by screening benefit from radical treatments, since their disease would not otherwise have compromised their life expectancy or quality of life'.¹⁸ Proponents of screening advocate that declines in prostate cancer mortality during the 1990s reported in Canada, USA, Austria, France, Germany, Italy and the UK were due to the increased use of PSA screening. However, the pattern of change in mortality is inconsistent between and within countries.^{9,23} In the USA, the mortality decline seems to have occurred very soon after the start of PSA testing, before the effects of any treatment of screen-detected disease would be expected. In the UK and other countries, mortality declined with no major increase in PSA testing. Other factors, including improved treatment of clinically detected disease, are likely to have contributed. The problems of attributing causality in these sorts of observational studies are well known.²⁴ Robust evidence can only come from randomized trials of screening programmes.^{6,25}

Conclusion

The autopsy studies of Rich and, subsequently, several other authors demonstrated the omnipresence of prostate cancer in elderly men, an observation at odds with the relatively low lifetime risk of prostate cancer mortality. The early identification of prostate cancer is worthwhile only if it detects potentially life-threatening tumours among asymptomatic men at a stage when lesions are curable, and if the balance of evidence demonstrates that the prospect of benefit outweighs the potential for harm.^{6,18,25} The key dilemma is that, although most cancers detected by screening are clinically confined to the prostate and hence potentially curable, current screening tests cannot differentiate between the majority of screen-detected cancers that have low biological likelihood of progression (for which radical treatments would probably be unnecessary) from those with aggressive potential, in whom early radical treatment might be beneficial.^{6,25} Seventy-one years since Rich's publication, real progress would be made if we could identify biological factors that predict those localized prostate cancers destined to progress and result in clinical disease and mortality. Such factors would have to be extremely strongly associated with progression, however, to be potentially useful in a clinical setting.²⁶

References

1. Rich AR. On the frequency of occurrence of occult carcinoma of the prostate. *J Urol.* 1935; 33:215–23. Reprinted *Int J Epidemiol.* 2007;**36**:274–77.
2. Franks LM. Latent Carcinoma of the Prostate. *J Pathol Bacteriol.* 1954; 68:603–16. [PubMed: 14354564]
3. Selman SH. 'Latent' carcinoma of the prostate: a medical misnomer? *Urology.* 2000; 56:708–11. [PubMed: 11018643]
4. Sakr WA, Grignon DJ, Haas GP, Heilbrun LK, Pontes JE, Crissman JD. Age and racial distribution of prostatic intraepithelial neoplasia. *Eur Urol.* 1996; 30:138–44. [PubMed: 8875194]
5. Whitmore WF. Localised prostatic cancer: management and detection issues. *Lancet.* 1994; 343:1263–67. [PubMed: 7910280]
6. Donovan JL, Martin RM, Neal DE, Hamdy FC. Prostate cancer: screening approaches. *Br J Hosp Med.* 2005; 66:623–26.
7. Breslow N, Chan CW, Dhom G, et al. The International Agency for Research on Cancer, Lyons, France. Latent carcinoma of prostate at autopsy in seven areas. *Int J Cancer.* 1977; 20:680–88. [PubMed: 924691]
8. Hsing AW, Tsao L, Devesa SS. International trends and patterns of prostate cancer incidence and mortality. *Int J Cancer.* 2000; 85:60–67. [PubMed: 10585584]
9. Oliver SE, May MT, Gunnell D. International trends in prostate--cancer mortality in the "PSA ERA". *Int J Cancer.* 2001; 92:893–98. [PubMed: 11351313]
10. Albertsen PC, Walters S, Hanley JA. A comparison of cause of death determination in men previously diagnosed with prostate cancer who died in 1985 or 1995. *J Urol.* 2000; 163:519–23. [PubMed: 10647669]
11. Penson DF, Albertsen PC, Nelson PS, Barry M, Stanford JL. Determining Cause of Death in Prostate Cancer: Are Death Certificates Valid? *JNCI.* 2001; 93:1822–23. [PubMed: 11734600]
12. Gronberg H. Prostate cancer epidemiology. *Lancet.* 2003; 361:859–64. [PubMed: 12642065]
13. Cohen P. Serum insulin-like growth factor-I levels and prostate cancer risk--interpreting the evidence. *JNCI.* 1998; 90:876–79. [PubMed: 9637133]
14. Gann PH, Hennekens CH, Stampfer MJ. A prospective evaluation of plasma prostate-specific antigen for detection of prostatic cancer. *JAMA.* 1995; 273:289–94. [PubMed: 7529341]
15. Hakama M, Stenman UH, Aromaa A, Leinonen J, Hakulinen T, Knekt P. Validity of the prostate specific antigen test for prostate cancer screening: followup study with a bank of 21,000 sera in Finland. *J Urol.* 2001; 166:2189–191. [PubMed: 11696733]

16. Thompson IM, Pauler DK, Goodman PJ, et al. Prevalence of Prostate Cancer among Men with a Prostate-Specific Antigen Level ≤ 4.0 ng per Milliliter. *N Engl J Med.* 2004; 350:2239–46. [PubMed: 15163773]
17. Thompson IM, Ankerst DP, Chi C, et al. Operating Characteristics of Prostate-Specific Antigen in Men With an Initial PSA Level of 3.0 ng/mL or Lower. *JAMA.* 2005; 294:66–70. [PubMed: 15998892]
18. Frankel S, Davey Smith G, Donovan J, Neal D. Screening for prostate cancer. *Lancet.* 2003; 361:1122–28. [PubMed: 12672328]
19. Stamey TA, Caldwell M, McNeal JE, Nolley R, Hemenex M, Downs J. The prostate specific antigen era in the United States is over for prostate cancer: what has happened in the last 20 years. *J Urol.* 2004; 172:1297–301. [PubMed: 15371827]
20. Bill-Axelson A, Holmberg L, Ruutu M, et al. Radical Prostatectomy versus Watchful Waiting in Early Prostate Cancer. *N Engl J Med.* 2005; 352:1977–84. [PubMed: 15888698]
21. Stanford JL, Feng Z, Hamilton AS, et al. Urinary and Sexual Function After Radical Prostatectomy for Clinically Localized Prostate Cancer: The Prostate Cancer Outcomes Study. *JAMA.* 2000; 283:354–60. [PubMed: 10647798]
22. Parker C, Muston D, Melia J, Moss S, Dearnaley D. A model of the natural history of screen-detected prostate cancer, and the effect of radical treatment on overall survival. *Br J Cancer.* 2006; 94:1361–368. [PubMed: 16641912]
23. Lu-Yao G, Albertsen PC, Stanford JL, Stukel TA, Walker-Corkery ES, Barry MJ. Natural experiment examining impact of aggressive screening and treatment on prostate cancer mortality in two fixed cohorts from Seattle area and Connecticut. *Br Med J.* 2002; 325:740–43. [PubMed: 12364300]
24. Davey Smith G, Ebrahim S. Data dredging, bias, or confounding. *Br Med J.* 2002; 325:1437–38. [PubMed: 12493654]
25. Martin RM, Davey Smith G, Donovan J. Does current evidence justify prostate cancer screening in Europe? *Nat Clin Pract Oncol.* 2005; 2:538–39. [PubMed: 16270078]
26. Wald NJ, Hackshaw AK, Frost CD. When can a risk factor be used as a worthwhile screening test? *Br Med J.* 1999; 319:1562–65. [PubMed: 10591726]