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Stage shift in PSA detected prostate cancers - effect modification by Gleason score:

Gleason score interaction with stage shift

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Abstract

Objective—This paper aims to investigate whether the stage shift (where more cancers are detected at an earlier stage) in PSA-detected cancers differs by Gleason score.

Methods—Between 2002 and 2005, 1,514 men 50-69 years were identified with prostate cancer following community-based PSA testing as part of the ProtecT study. In the same period, 2021 men 50-69 years with clinically diagnosed prostate cancer were registered at a population based cancer registry in East of England. Using logistic regression analysis and controlling for age, the odds ratio (OR) for advanced stage (TNM stage T3 and above) prostate cancer among the PSA

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Authors' contributions

NP and SD contributed to the conception and design of the study, analysis, interpretation of the findings, and drafting the manuscript. NP and SD are the guarantors. PP contributed to the interpretation of the results and revising of the manuscript. JD, FH, DN are the principal investigators of the ProtecT study and have collected data on the PSA-detected prostate cancer cases. DG, JD, RM, FH, and DN provided the data and contributed to the interpretation of the results and revising of the manuscript.

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detected group was compared to the clinically diagnosed tumours. The evidence that stage shift differs by Gleason score was assessed using the likelihood ratio test for interaction.

Results—Advanced stage disease among the PSA detected cancers was less common than among the clinically detected cancers (OR = 0.47, 95% CI 0.39-0.56). PSA detected tumours had a substantial shift to earlier stage disease where the Gleason score was <7 (OR=0.52; 95%CI 0.36-0.77, P<0.001) but showed no such shift where the Gleason score was 7 or more (OR=0.84; 95% CI 0.66-1.07, P=0.1). There was evidence of interaction between detection mode and Gleason score (p=0.03).

Conclusion—The observed stage shift could be partially explained by length bias or overdiagnosis. These findings may have implications on understanding pathways of prostate cancer progression and on identifying potential targets for screening, pending further investigation of complexities of associations between PSA testing, Gleason score, and stage.

Keywords

Prostate cancer; PSA testing; Stage shift; Gleason score; Effect modification

INTRODUCTION

In cancer screening, there is considerable interest in which tumours benefit from early detection, and in the association between early detection and biological measures of aggression of the tumour. [1; 2] For example, in breast cancer screening, there is evidence that the majority of the mortality reduction associated with early detection is due to the detection of invasive cancers at an early stage, rather than to detection of carcinoma in situ. [2] In prostate cancer screening, there has been considerable interest in estimation of the proportion of tumours detected which would not have been diagnosed in the host's lifetime if screening had not taken place. [3; 4] Less well researched is the issue of which prostate cancers manifest the greatest stage shift (where more cancers are detected at an earlier stage) as a result of prostate specific antigen (PSA) testing.

The two randomised prospective trials on prostate cancer screening, the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial [5] and the European Study of Screening for Prostate Cancer (ERSPC) [6] showed no reduction and a 20% reduction respectively in mortality following screening with PSA. In the midst of this controversial and relatively modest reduction in mortality reported by these two randomised trials, it is of importance to find out which prostate cancers benefit from early detection.

In prostate cancer, the histological grading based on the Gleason grading system is predictive of the biological behaviour and prognosis of the cancer. Gleason grading takes account of the structural arrangement of the glandular cells and their extent of differentiation. A grade from 1 (least aggressive) to 5 (most aggressive) is assigned to the most common pattern and a second grade to the next most common pattern. The two grades are added to give the Gleason score, ranging from 2 to 10. Prostate cancers with high Gleason score are more aggressive and have worse prognosis. [7]

It is likely that tumours with higher Gleason score may progress more quickly during the preclinical phase, thus giving a lesser opportunity for PSA testing to shift the stage at diagnosis. To test this hypothesis, we compared PSA detected prostate cancers with clinically diagnosed cancers with respect to stage of disease and examined whether the stage shift in PSA detected cancers differed by Gleason score.

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METHODS

PSA detected cancers

Data on 1,514 PSA detected prostate cancers were obtained from the Prostate Testing for Cancer and Treatment (ProtecT) study, an ongoing national study of community-based PSA testing and randomized trial of subsequent prostate cancer treatment. [8] The PSA testing in the ProtecT study is equivalent to prevalence screening.

In the ProtecT study, between 1 January 2002 and 31 December 2005, 43,842 men aged 50 to 69 years, from randomly selected general practices in nine regions in the UK, had PSA testing. Participants with PSA of 3mg/dl or more were invited for transrectal ultrasound guided systematic prostate biopsy involving 10 core specimens. Pathologic examinations were carried out by specialist uropathologists in each study centre. Tumours were assessed by histological grading using the Gleason scoring system (6-10), [7] tumour staging using the 2002 TNM Classification.[9] All laboratories have participated in the UK National External Quality Assessment Service (UK NEQAS) programme for PSA testing. [8]

Clinically diagnosed cancers

Over the same study period and age range of the participants of the ProtecT study, data on clinically diagnosed prostate cancers were identified from the Eastern Cancer Registry and Information Centre (ECRIC) - a population-based cancer registry covering a current population of 5.5 million in the East of England. ECRIC is known to have high level of ascertainment of cancer cases, as reflected in the Death Certificate Only (DCO) index for prostate cancer of 0.1%, a figure twenty times lower than the figure deemed acceptable for Registration practice across England. [10] Between 2002 and 2005, 2,435 men aged 50 to 69 were registered with prostate cancer. Information on stage and Gleason score were available on 100% and 83% of the registrations respectively. The staging and grading of prostate cancer are verified at the registry by an oncologist on the basis of the clinical and pathological information available.

Statistical analysis

Prostate cancer was classified as localised disease with tumour-node-metastasis (TNM) stage T2 and below; and advanced disease (regional-distant) with TNM stage T3 and above. Prostate cancer was further classified into low aggressive tumour, Gleason score <7, and intermediate to high aggressive tumour, Gleason score ≥ 7.

Data were analysed by logistic regression, [11] with advanced stage as the outcome variable and controlling for age. In particular we estimated the odds ratio for advanced stage for PSA detected compared to clinically diagnosed tumours, and tested whether this varied by Gleason score using the likelihood ratio test for interaction based on the age adjusted model. Analysis was done using STATA 10.

RESULTS

Table 1 shows the numbers tested and those detected with localised and advanced tumours in ProtecT, and the numbers of clinical cancers by stage from ECRIC. Out of 1,514 prostate cancers detected by PSA testing in 43,842 men, 1,322 (87%) were localised disease and 1,071 (71%) had Gleason score <7. Whereas out of the 2,021 clinically diagnosed prostate cancers, 1,531 (76%) were localised and 901 (45%) had Gleason score <7.

After adjustment for age, there was strong evidence that the proportion of PSA detected advanced stage cancers within ProtecT were lower than that of the clinically diagnosed tumours, as expected (OR = 0.47, 95% CI 0.39-0.56, p<0.001).

Table 2 shows the frequency of tumours stratified in three dimensions: detection mode (PSA detected or clinical), stage (localised or advanced) and Gleason score (below or 7 and above). The association between detection mode and stage was stronger in those with Gleason score <7 than in those with Gleason score 7 or above (p=0.03). The age-adjusted OR for the former group was 0.52 (95% CI 0.36-0.77, p<0.001), whereas for the latter the OR was 0.84 (95% CI 0.66-1.07, p=0.1). When the data were stratified into four five-year age groups, the same phenomenon was observed in all four groups (data not shown).

DISCUSSION

Shifts in both the clinical stage and Gleason score distribution with use of PSA for prostate cancer screening have been reported in studies from the UK (Moore et al, submitted manuscript), Europe [12] and the USA. [13;14] However, to our knowledge, the effect modification by Gleason score has not been reported.

This study shows that early diagnosis of prostate cancer through PSA testing in asymptomatic men reduced the rate of advanced stage disease, but this reduction appeared to be mainly confined to tumours with a Gleason score<7. It may be that higher grade advanced cancer detection is less affected by PSA testing due to more rapid progression of the tumour. From Table 2, it can be seen that where the Gleason score was 7 or above, the proportion of advanced disease was high (35-40%) regardless of mode of detection. For tumours of Gleason score<7, the proportion of advanced disease was low (<10%), but proportionally lower in PSA-detected tumours.

In common with other researchers [12] we observed a more favourable Gleason score in the PSA detected cancers. In clinically diagnosed tumours, 55% had Gleason score 7 or more, whereas in PSA detected tumours the figure was 29%. Part of this reduction may be due to diagnosis prior to dedifferentiation, but part is also likely to be due length bias or overdiagnosis. In other words, it is possible that screening is inducing a stage shift amongst cancers that may never affect a man's quality or quantity of life. Our previous work [4] suggested overdiagnosis rates of 10-31% depending on age. If we assume an average of 20% overdiagnosis for the age group 50 to 69, all occurring in localised tumours with Gleason score less than 7, the proportion of 'true' Gleason ≥7 tumours in PSA detected cancers would be 37% suggesting that around one third of the effect of PSA testing on Gleason score is a genuine effect of early detection. Similar analysis using age-specific estimates of overdiagnosis, suggests that for the age groups 50-59, 60-64, and 65-69 around 43%, 37% and 12% respectively of the effect of PSA testing on Gleason score is genuine effect of early detection. Further analysis using multistate disease models is under way to quantify this more robustly and estimate the likely time frame of progression with respect to Gleason score.

It is likely that the progression of tumours in the PSA-detectable preclinical phase occurs simultaneously in the two dimensions of stage and Gleason score. It is not clear which progression events occur first. Our multistate analyses will also address this issue, taking into account length bias and overdiagnosis.

The findings of this study may have implications on designing screening regimens. While the two randomised prospective trials on prostate cancer screening [5;6] showed no reduction and a 20% reduction respectively in mortality following screening with PSA, our results are potentially relevant to the trial findings in two respects. Firstly, if the benefit is

confined to those cases with more favourable Gleason score, then this may partially account for the relatively modest benefit observed. Secondly, in the midst of this controversial and relatively modest reduction in mortality, it is important to identify the prostate cancers that are likely to benefit from screening. If we assume that screening induced stage shift from advanced to localised disease carries with it a disease-specific reduction in mortality,[15] then identifying prostate cancers with early Gleason score would lead to the desired stage shift and consequently to potential reduction in mortality. In a screening programme setting, it will be possible to identify prostate cancer in preclinical screen-detectable phase with early Gleason score, when the inter-screening interval takes account of the transition time from preclinical Gleason score less than 7 to preclinical Gleason score 7 or more.

This study has several limitations. The PSA detected cancers and the clinically diagnosed cases were not derived from randomisation, but from community based PSA testing and cancer registration. Also, although there is no prostate cancer screening programme in the UK, there is ad hoc PSA testing. [16] Thus, ECRIC data also must have included some patients diagnosed by PSA testing, although not in the context of formal screening. However, these figures are likely to be small. [16;17]

In conclusion, there is some evidence that stage shift in prostate cancer with PSA testing may differ by Gleason score. Prostate cancer with low Gleason score could be a potential target for screening, pending further investigation of complexities of associations between PSA testing, Gleason score, and stage. The ongoing randomised controlled trials of prostate cancer screening will determine whether such stage shift will lead to improved outcomes.

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Table 1

Frequency of prostate cancers by detection mode (PSA detected or clinical), stage (localised or advanced), Gleason score (GS) categories (<7 or ≥7) and age groups, in men 50-69 years with prostate cancer diagnosis between 2002 and 2005

	Age group							
	50-54		55-59		60-64		65-69	
	N	(%)	N	(%)	N	(%)	N	(%)
PSA tested	12092		13787		10060		7903	
PSA detected Cancers *	134	(100)	344	(100)	487	(100)	549	(100)
Localised cancers	125	(93)	310	(90)	428	(88)	459	(84)
Advanced cancers	9	(7)	34	(10)	59	(12)	90	(16)
Gleason Score <7	100	(75)	259	(75)	354	(73)	358	(65)
Gleason Score ≥7	34	(25)	85	(25)	133	(27)	191	(35)
Localised & GS<7	99	(74)	246	(71)	342	(70)	338	(61)
Localised & GS ≥7	26	(19)	64	(19)	86	(18)	121	(22)
Advanced & GS <7	1	(0)	13	(4)	12	(2)	20	(4)
Advanced & GS ≥7	8	(6)	21	(6)	47	(10)	70	(13)
Clinically diagnosed cancers †	128	(100)	352	(100)	605	(100)	936	(100)
Localised cancers	96	(75)	279	(79)	458	(76)	698	(75)
Advanced cancers	32	(25)	73	(21)	147	(24)	238	(25)
Gleason Score <7	65	(49)	172	(49)	263	(43)	401	(43)
Gleason Score ≥7	63	(51)	180	(51)	342	(57)	535	(57)
Localised & GS <7	61	(48)	162	(46)	242	(40)	362	(39)
Localised & GS ≥7	35	(27)	117	(33)	216	(36)	336	(36)
Advanced & GS <7	4	(3)	10	(3)	21	(3)	39	(4)
Advanced & GS ≥7	28	(22)	63	(18)	126	(21)	199	(21)

*PSA detected cancers were identified from ProtecT study

† Clinically diagnosed cancers were identified from ECRIC

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Table 2

Odds ratio (OR) for advanced stage prostate cancer by detection mode (PSA detected or clinical) adjusted for age, stratified by Gleason score categories; in men 50-69 years, 2002-2005

Gleason score	Detection mode	Localised Cancers N	Advanced Cancers N	OR (95% CI)
Overall	Clinically diagnosed	1531	490	1.00
	PSA detected	1322	192	0.47 (0.39-0.56)
<7	Clinically diagnosed	827	74	1.00
	PSA detected	1025	46	0.52 (0.36-0.77)
≥7	Clinically diagnosed	704	416	1.00
	PSA detected	297	146	0.84 (0.66-1.06)

PSA detected cancers were identified from ProtecT study

Clinically diagnosed cancers were identified from ECRIC