The use of PSA testing in general practice

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Prostate cancer





American Joint Committee on Cancer (AJCC) Staging System



- The AJCC staging system is based on 3 factors
 - T: the size, extent, and penetration of the tumor
 - N: the number or location of cancer-involved lymph nodes
 - M: the presence of sites of metastases

American Joint Committee on Cancer. American Joint Committee on Cancer. *Cancer Staging: What You Need to Know?* Chicago, IL: American Joint Committee on Cancer; 2010.



T4 Prostate Cancer – regional/distant spread



Illustration courtesy of the American Society of Clinical Oncology



Background

- 3000 NZ men each year are diagnosed with prostate cancer
- 76% have localised disease with excellent prognosis
- 560 men will die each year from metastatic prostate cancer
- There are 25,000 men in New Zealand with diagnosed prostate cancer



Age standardised incidence of prostate cancer in NZ 1948 to 2007 per 100,000 men





Age standardised death rates from prostate cancer in NZ 1948 to 2007





To screen or not to screen





Should we screen for prostate cancer?

- Will my patient live longer and be healthier if they take part in a screening program for prostate cancer ?
- Will I reduce my risk of dying from prostate cancer if I have a PSA test?



Testing vs screening

- NZ GPs do 350,000 PSA tests per year
- 80% of these are in asymptomatic men and can be considered "opportunistic" testing
- Most NZ GPs think screening is worthwhile (while UK GPs for instance do very little screening)



Midland Study - PSA testing by general practitioners

- Recruited 31 practices (120,000 total pop; approx. 36,000 men over 40yrs) in the Midland Region
- Linked records of men aged 40 plus to community PSA tests in last 4 years
- Excluded men who already had a diagnosis of prostate cancer
- Checked records of all men who had a raised PSA test (lab defined) in 2010



Sample

35,958 men aged 40+ years

1006 (2.7%) diagnosed before 2010 excluded

9344 men (26.0%) had one or more PSA tests in 2010

7936 men (22.1%) were screened in 2010

Estimated 85% of tests were screening

Māori men aged 40+ yrs in Midland: 14.4%

our sample 14%



PSA testing by general practitioners





Who gets tested?





Do Māori get tested/screened as often?





Does being a rural patient matter?





After a raised PSA



22 men referred with normal PSA; 14 had a biopsy, 7 had positive biopsy



Costs per PCa identified

Categories	20% of GP consultation cost included	50% of GP consultation cost included	100% of GP consultation cost included
Age group			
40-49	\$23,919	\$39,892	\$66,513
50-59	\$29,268	\$48,719	\$81,138
60-69	\$6,023	\$8,916	\$13,739
≥70	\$10,301	\$17,132	\$28,516
Ethnicity			
Māori	\$7,529	\$10,673	\$15,912
Non-Māori	\$10,859	\$17,533	\$28,657
PSA testing history			
No PSA tests in	\$8,589	\$12,867	\$19,996
2007-2009			
Had PSA tests in 2007-2009	\$13,361	\$22,673	\$38,194
Overall			
	\$10,399	\$16,587	\$26,899



What is screening?

 Screening is the practice of investigating apparently healthy individuals with the object of detecting unrecognised disease or its precursors so that measures can be taken to prevent or delay the development of disease or to improve the prognosis.



Criteria for screening for early diagnosis

- Disease characteristics
- Population
- Test characteristics
- Intervention
- Evaluation



Disease characteristics

- Important health problem (i.e. severity and frequency)
- Should be a definable entity
- Natural history should be understood
- Recognised latent phase

Gleason's Pattern Scale





Cumulative Incidence of Death from Any Cause, Death from Prostate Cancer, and Development of Metastases.





Prognosis – mortality by Stage from the Midland Prostate Cancer Study





The population

- Identification of risk groups
- Attitudes to screening



Family history

- Prostate cancer seems to run in some families, which suggests that in some cases there may be an inherited or genetic factor.
- Having a father or brother with prostate cancer more than doubles a man's risk of developing this disease.
- The risk is much higher for men with several affected relatives, particularly if their relatives were young when the cancer was found.



Attitudes

- Gender
- Socio-economic status
- Ethnicity



Test characteristics

- Simple and cheap
- Safe
- Acceptable/ non invasive
- Sensitive and specific
- Valid and reliable



PSA test

- Identifies men who are likely to suffer from symptomatic prostate cancer from men in whom symptomatic prostate cancer is unlikely.
- PSA identifies a significant proportion of men who have no evidence of cancer as well as some men who have evidence of cancer but in whom it is unlikely to become symptomatic and thus have no increased risk (false positives).
- Cut off point of 4 ng/ml will miss some men with cancer including a small number who may have undifferentiated tumours with a high Gleason score (false negatives).
- Lowering the cut off point to 3 ng/ml as was done in the European prostate screening trial increased the sensitivity but also increased the number of false positives.



DRE

- 7/172 (4%) cases identified had a normal PSA
- Most men (73%) said they had received a DRE.
- Māori (71%) and non-Māori men (73%) were just as likely to receive a DRE
- Men aged 60–69 years (86%) were most likely to receive a DRE by their GP.



Treatment

- Is there an effective treatment for the disease?
- Is the treatment acceptable?
- Are there adequate facilities for treatment?



There is an effective and accessible treatment or intervention for the condition

- Options for treatment include radical prostatectomy, radiotherapy (focussed beam, or brachytherapy), or hormonal treatment.
- We have evidence from an RCT of radical prostatectomy versus watchful waiting fewer men in the radical prostatectomy group died of prostate cancer (Bill-Axelson et al).
- There is little convincing evidence that brachytherapy or focussed bean radiotherapy have different survival outcomes than prostatectomy.
- Treatment options in New Zealand vary from DHB to DHB and differences in outcomes of the various options have not been evaluated in the local setting.

Cumulative Incidence of Death from Any Cause, Death from Prostate Cancer, and Development of THE UNIVERSITY

OF AUCKLAND

Metastases.



Bill-Axelson A et al. N Engl J Med 2011;364:1708-1717.

PIVOT study

 Trial of watchful waiting vs prostatectomy in localised cancer





Subgroup	Observation	Radical Prostatectomy	Hazard Ratio (95% CI)	P Value for Interaction
	no. of even	ts/total no.		
Overall	183/367	171/364	- 0.88 (0.71-1.08)	
Age				0.85
<65 yr	50/131	43/122	0.89 (0.59-1.34)	
≥65 yr	133/236	128/242	- 0.84 (0.63-1.08)	
Race				0.81
White	119/220	117/232	0.84 (0.65-1.08)	
Black	53/121	46/111	0.93 (0.62-1.38)	
Other	11/26	8/21	0.85 (0.34-2.11)	
Charlson score				0.79
0	86/220	82/224	0.90 (0.66-1.21)	
≥1	97/147	89/140	0.84 (0.63-1.13)	
Performance score				0.66
0	146/310	139/312	0.89 (0.71-1.13)	
1-4	37/57	32/52	0.82 (0.51-1.31)	
PSA				0.04
≤10	101/241	110/238	1.03 (0.79-1.35)	
>10	77/125	61/126	0.67 (0.48-0.94)	
Risk				0.07
Low	54/148	62/148	1.15 (0.80-1.66)	
Intermediate	70/120	59/129	0.69 (0.49-0.98)	
High	49/80	42/77	0.74 (0.49-1.13)	
Gleason score				0.87
<7	125/261	113/254	- 0.86 (0.67-1.12)	
≥7	47/86	50/98	0.84 (0.56-1.25)	
			Radical Prostatectomy Observation	



B Death from Prost	ate Cancer			
		Radical		P Value for
Subgroup	Observation	Prostatectomy	Hazard Ratio (95% CI)	Interaction
	no. of even	s/total no.		
Overall	31/367	21/364	0.63 (0.36-1.09)	
Age				0.63
<65 yr	12/131	6/122	0.52 (0.20-1.39)	
≥65 yr	19/236	15/242	0.68 (0.34-1.33)	
Race				0.76
White	22/220	15/232	0.57 (0.30-1.10)	
Black	7/121	5/111	0.80 (0.25-2.54)	
Other	2/26	1/21	0.56 (0.05-6.17)	
Charlson score				0.63
0	19/220	14/224	0.69 (0.34–1.37)	
≥1	12/147	7/140	0.54 (0.21-1.38)	
Performance score				0.57
0	25/310	18/312	0.67 (0.37-1.23)	
1-4	6/57	3/52	0.41 (0.10-1.71)	
PSA				0.11
≤10	15/241	14/238	0.92 (0.44-1.91)	
>10	16/125	7/126	0.36 (0.15-0.89)	
Risk			. ,	0.11
Low	4/148	6/148	1.48 (0.42-5.24)	
Intermediate	13/120	6/129	0.50 (0.21-1.21)	
High	14/80	1/77	0.40 (0.16-1.00)	
Gleason score			. ,	0.57
<7	15/261	11/254	0.68 (0.31-1.49)	
≥7	15/86	10/98	0.51 (0.23-1.14)	
	· · · · ·		0.05 0.14 0.27 1.00 2.72 7.20	
			0.05 0.14 0.37 1.00 2.72 7.39	
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Harm of treatment

Table 2. Patient-Reported Urinary, Erectile, and Bowel Dysfunction at 2 Years, According to Study Group.*						
Dysfunction	Radical Prostatectomy	Observation	P Value			
	no./total	no. (%)				
Urinary incontinence†	49/287 (17.1)	18/284 (6.3)	<0.001			
Erectile dysfunction:	231/285 (81.1)	124/281 (44.1)	<0.001			
Bowel dysfunction§	35/286 (12.2)	32/282 (11.3)	0.74			



Harm of treatment ("Let sleeping dogs lie")

Table 9: Prevalence of urinary incontinence, bowel problems and sexual impotence, three years after treatment and in untreated controls (percentages). EBRT, external beam radiation therapy; ADT, androgen deprivation therapy.

-	Active surveillance ("watchful waiting")	RP total	Nerve sparing RP	Non-nerve sparing RP	EBRT	ADT	Combined EBRT/ADT	Low dose brachy- therapy	High dose brachy- therapy	Controls
Urinary incon	tinence	-		-						-
Baseline	6.0	. 1.1	0.6	1.5	0.0	б.б	3.0	0.0	0.0	1.0
three years	3.4	12.3	9.4	15.1	2.7	4.3	3.9	5.4	7.0	
Moderate to s	severe bowel pr	oblems		-						
Baseline	13.5	4.4	3.6	5.3	10.6	10.0	9.0	0.0	2.1	6.3
three years	6.3	3.5	4,1	2.7	14.5	6.4	12.5	0.0	9.3	
Impotence										
Baseline	27.3	21.5	15.6	27.6	30.2	42.1	39.1	19.0	25.5	22.3
three years	54.3	77.4	67.9	86.7	67.9	97.8	82.3	36.4	72.1	



Evaluation of a screening programme

- Effectiveness proven by RCT
- Efficiency cost effective
- Equitable
- Acceptable
- Accessible
- Appropriate



So is there evidence from RCTs that screening is beneficial?

- ERSPC
- PLCO
- Goteborg



European Randomized Study of Screening for Prostate Cancer (ERSPC)

- Included 182,000 men recruited over 10 years from 7 different European countries
- Men aged 55 to 75 years
- Screened men every 4 years
- Considered positive if test greater than 2.4 ng/ml



ERSPC

- The trial **analysed** men from ages 55 to 69 years
- Absolute risk difference between the screening and control groups of 0.71 prostate cancer deaths per 1000 men.
- 1410 men would have to be screened 1.7 times over 9 years (number needed to screen),
- 48 men would need to be treated (number needed to treat) to prevent one prostate cancer death.
- There was no benefit in all cause mortality



ERSPC

- 13 years of follow up published Lancet 2014
- Absolute risk difference between the screening and control groups of 1.28 prostate cancer deaths per 1000 men.
- 781 men would have to be screened over 13 years (number needed to screen),
- 27 men would need to be diagnosed (number needed to treat) to prevent one prostate cancer death.
- Despite showing a clear prostate cancer mortality reduction, the findings are not sufficient to justify population-based screening.



ERSPC

Table 2. Death from Prostate Cancer, According to the Age at Randomization.*						
Age at Randomization	Screening Group		Cor	ntrol Group	Rate Ratio (95% CI)†	
	No. of Deaths	Person-Yr (Death Rate per 1000 Person-Yr)	No. of Deaths	Person-Yr (Death Rate per 1000 Person-Yr)		
All subjects	261	737,397 (0.35)	363	878,547 (0.41)	0.85 (0.73-1.00)	
Age group						
50–54 yr	6	55,241 (0.11)	4	53,734 (0.07)	1.47 (0.41-5.19)	
55–59 yr	60	316,389 (0.19)	102	402,062 (0.25)	0.73 (0.53-1.00)	
60–64 yr	76	191,542 (0.40)	95	221,113 (0.43)	0.94 (0.69–1.27)	
65–69 yr	78	135,470 (0.58)	129	162,410 (0.79)	0.74 (0.56-0.99)	
70–74 yr	41	38,755 (1.06)	33	39,228 (0.84)	1.26 (0.80–1.99)	



PLCO

- 180,000 men and women recruited in US for a study of prostate, lung, colorectal and ovarian cancer
- 76,693 men randomised
- Aged 55 to 75 years
- Screened men every year
- 2820 cancers in screening group, 2323 in control
- 50 deaths from PC in screening group and 44 in control group



PLCO

- Smaller sample size
- Older patient group
- Significant contamination in control group



Goteborg study (2010)

- 20,000 men aged 50-64 years).
- PSA cut-off 2.4 ng/mL
- Participation rate in at least one screening round was 76% (n=7578) and a total of 29315 PSA tests were performed.
- A total of 4693 positive PSA results were recorded.
- 33% of the participants (n= 2469) received at least one positive result and 93% of these (n=2298) had a biopsy



Goteborg study (2010)

- After 14 years of follow-up, within a core age group of 50 to 64 years, 44 and 78 prostate cancer deaths were observed in the screening group and control groups respectively. The unadjusted rate ratio for death from prostate cancer in the screening group was 0.56 (95% CI, 0.39-0.82 p=0.002).
- This corresponds with a significant absolute risk difference between groups of four deaths per 1000 men.
- The incidence of prostate cancer was almost 60% greater in the screened group (see table) .
- The all cause mortality in the two groups was 1982 in the control group and 1981 in the screened group.



Goteborg study

	Control Group	Screened Group
Number with prostate cancer	718	1138
Number of prostate cancer deaths	78	44
Number with prostate cancer who died of unrelated causes	54	109



There is consideration of cost-benefit

- Screening large numbers of people is expensive and can divert both human and financial resources from other health services.
- The costs of screening for prostate cancer include:
 - GP time in counselling men about the benefits and risks
 - the cost of the test
 - the cost of diagnosis with prostatic biopsy,
 - the pathology costs needed to make the diagnosis,
 - the cost of counselling for those men who treatment is being suggested,
 - the costs of surgery or radiotherapy (or watchful waiting).
- These costs need to be balanced against the cost of investigating and treating symptomatic patients.
- Ideally, a cost-effectiveness analysis should be undertaken before any screening program is considered



Author, year	Country	Perspective	Screening strategy	Results
A. Shteynshlyuger [2], 2011	USA	Societal perspective	Screen men aged 55-69 years at an interval of 4 years: ERSPC screening protocol	US \$262,758 per life-year saved
A. J. Martin[3], 2013	Australia	Perspective of the health care system	Screen men aged 50 years at an interval of 4 years	AU \$291,817 per QALY for men with average risk; AU\$110,726 per QALY for men with two times the average risk; AU\$30,572 per QALY for men with five times the average risk
R. Pataky [4], 2014	Canada	Perspective of health system	The most cost-effective strategy: A single screen at age 60 years, followed by a screen at age 65 years for men with PSA above the median	CAN \$340,300 per QALY

- 1. Lao, C., Brown, C., Rouse, P., Edlin, R. & Lawrenson, R. Economic evaluation of prostate cancer screening: A systematic review. *Future Oncology* 11, 467-477 (2015).
- 2. Shteynshlyuger A, Andriole GL. Cost-effectiveness of prostate specific antigen screening in the United States: Extrapolating from the European study of screening for prostate cancer. *J Urol* 185(3), 828-832 (2011).
- 3. Martin AJ, Lord SJ, Verry HE, Stockler MR, Emery JD. Risk assessment to guide prostate cancer screening decisions: A cost-effectiveness analysis. *Med J Aust* 198(10), 546-550 (2013).
- 4. Pataky R, Gulati R, Etzioni R *et al.* Is prostate cancer screening cost-effective? A microsimulation model of prostate-specific antigen-based screening for British Columbia, Canada *Int J Cancer.*(2014).

Prostate Cancer Management and Referral Guidance





Algorithm for supporting men with prostate-related concerns







Man presents with prostate-related concerns

If aged 50 to 70 years, or over 40 years with a family history of prostate cancer, obtain informed consent before testing by discussing:

- the benefits and risks of PSA testing and/or DRE
- the implications of further testing if the PSA or DRE is abnormal. (See Note 1.)

Note: Carefully consider each man's individual context when discussing benefits and risks.





Taskforce Recommendations

Diagnostic guidelines

24. Men meeting the following criteria should be considered for prostate biopsy after taking into account clinical considerations, elimination of benign causes of high PSA, age, co-morbidity and patient choice:

- suspicion of malignancy on digital rectal examination
- men up to the age of 70 years with a PSA \geq 4 ng/mL
- men between 71–75 years with a PSA \geq 10 ng/mL
- men aged \geq 76 years with a PSA \geq 20 ng/mL
- a significant PSA rise in a man with previously low PSA values.



Summary

- Prostate cancer is a common and important cancer with a long lead time before it becomes symptomatic.
- PSA testing with or without DRE has limitations with regards to its suitability as a test. Over-diagnosis is a concern. Research into other tests may find a test with better sensitivity and specificity.
- Radical prostatectomy has been shown to be of benefit over watchful waiting in younger men. The ERSPC study included a variety of local treatment regimes. Treatment options in New Zealand vary from DHB to DHB and differences in outcomes of the various options have not been evaluated.
- The potential benefits of mass screening for prostate cancer are outweighed by the harms caused by over-diagnosis and unnecessary treatment.
- Cost effectiveness analyses suggests that screening is not cost effective
- Current advice is that men seeking a PSA test should be counselled on the potential benefits and harms of screening before a test is carried out



- 67 year old European man attends and says his wife has told him he should have a PSA test. He has no family history of prostate cancer but has had some ED which is causing some marital discord. He has never had a PSA test before.
- What do you tell him?



 58 year old Māori man attends for his CVRA -He has diabetes, BMI 34, smokes 10 cigarettes a day, BP 140/90, total cholesterol of 5.5 mmol/L. He has no family history of prostate cancer and no symptoms. Should you suggest he has a PSA test?



 74 year old man who is generally fit and well – he last had a PSA test 2 years ago which was negative (<1 ng/ml). DRE is normal – what do you advise him?



- 42 year old asymptomatic man whose father died of metastatic prostate cancer 30 years ago at the age of 48.
- He would like to be tested for prostate cancer
 what do you advise him?