# Prostate cancer screening in New Zealand: lessons from the past to shape the future in the light of changing evidence

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#### **ABSTRACT**

Prostate cancer represents a significant health burden worldwide. The cancer incidence had substantially increased since the introduction of prostate specific antigen (PSA) in cancer screening. This had led to considerable debates among health professionals and epidemiologists, since PSA as a screening tool seemed to be far from perfect. In New Zealand, the controversy was quite prominent in the last three decades, with some advocating the benefits of screening, while others concerned regarding the risk of harms. With the absence of an organised screening programme and the appropriate monitoring and quality assurance procedures, the effects of the PSA testing debate had undoubtedly caused a variability in the opportunistic prostate cancer screening practices in the community. This, in addition to the recent rapid advancements in prostate cancer imaging, and updated results from randomised trials, have made it mandatory to question the validity of continuing with the current approach to prostate cancer screening. However, high-quality local data on these aspects had been lacking, which represents an ongoing challenge to developing robust and sound health policies.

rostate cancer (PCa) is the most commonly diagnosed cancer for men in numerous developed countries.1 In New Zealand, PCa is responsible for the death of more than 600 men each year, and approximately 16% of the total cancers-related morbidity and mortality in the society.<sup>2,3</sup> The absence of known modifiable risk factors had shifted the scientific efforts towards early cancer detection, which had led to the discovery of several tumour markers over the past three decades.<sup>4,5</sup> Prostate specific antigen (PSA) is the most commonly used serum marker for PCa management.5,6 It was identified as a normal component of the prostate in the 1970s, and has been used for PCa monitoring thereafter. In 1994, it was approved by the US Food and Drug Administration to be considered in PCa screening and early detection.6

The great uptake for PSA testing in clinical settings had unveiled a major concern in the test characteristics, being prostate rather than cancer specific. This had resulted in a large number of men with benign prostate conditions, undergoing unnecessary invasive procedures. Moreover, it had become apparent that some of the cancers detected through PSA testing were relatively indolent and were unlikely to contribute to significant morbidity during the natural life span of the patients (over-detection).

The limitations of PSA in PCa screening had led to a highly controversial topic in the medical field. On one hand, the presumed benefits of early detection of PCa and possible cure, and the overdiagnosis and treatment on the other. This narrative review aims to summarise the PSA screening



controversy in New Zealand, and highlights the historical and current trends in the screening practices.

### Prostate cancer screening in New Zealand—past practices

Within a similar timeframe to other developed countries (1993–1994), PSA testing for early detection of PCa was introduced in New Zealand.8 This had led to a substantial rise in the cancer incidence (Figure 1).

Shortly after, a debate regarding the validity of PSA as a screening tool commenced.9-13 Some expert voices were against PSA-based screening in asymptomatic men, while others promoted the potential for improvements in cancer specific mortality. In both cases, clinicians were encouraged to use digital rectal examination (DRE) as an aid in the decision-making process, whenever PCa screening was being considered. These mixed messages were reflected in the responses received from general practitioners (GPs) in a survey conducted in 1997, where half of them believed that asymptomatic men should be screened with PSA.8 Similar results were reported in another survey of New Zealand GPs in 2003, where 50% of the participants supported the implementation of a national PCa screening programme.<sup>14</sup>

The first objective estimation of the extent of PSA testing and DRE in New Zealand was published in 2003.15 The conveyors conducted phone-based survey with 1,225 men aged 40–74 years. Within this group, only 175 men (9.2%) reported previous PSA testing, while 618 (41.0%) had received DRE. Moreover, socioeconomic status and education levels were identified as factors that influence the likelihood to be screened. Shortly after, another phone survey of men aged 40-79 was conducted by Arroll and Colleagues. 16 Of the 120 respondents, 60 men (55%) reported being offered PSA testing, while 40 participants (33%) received PSA screening. The same study identified variabilities in the level of understanding among the participants about PCa screening within this cohort of predominantly New Zealand European men.

The discrepancies between the reported proportions of men screened in the surveys (9.2–33%), and the attitudes of GPs towards screening (50% tend to offer PSA testing), could stem from three areas.<sup>8,14–16</sup> First, relying on the participants' recollection of receiving PSA testing. Some of the key limitations of survey research are self-reporting and recall biases.<sup>17</sup> This element can be viewed from the results of the study

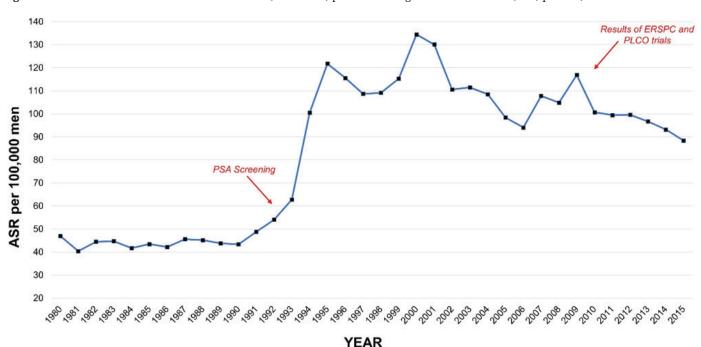


Figure 1: Prostate cancer Incidence in New Zealand (1980–2015) presented as age-standardised rate (ASR) per 100,000 men.\*

<sup>\*</sup>Age standardised rates (ASR) adopted from the Ministry of Health publications (2)



by Sneyd et al, where the participants might have remembered the DRE (41.0%) but forgotten the PSA test (9.2%).15 The second contributor to the discrepancy may arise from men who did not undergo PCa screening. For instance, these men could have been asymptomatic and hence less motivated towards receiving the PSA test with the DRE.18 This may be presented in the study by Arroll and colleagues, where 55% of the total respondents were offered PSA testing, while only 33% reported receiving it.16 Also, some men might not have access to primary care. Results from the New Zealand national health survey at the time had suggested that approximately 10% of the adult male population did not have regular GPs.19 Lastly, the third element to explain the survey's results is the limited generalisability to the total New Zealand population, since both studies had intermediate response rates (66 and 77%, respectively), and restricted the inclusion to married men in the former, and those living in Auckland region in the latter. 15,16

## Prostate cancer screening—impact of initial results from randomised trials

To develop a better understanding of the validity of PSA for population-based screening of PCa, and to provide a scientific perspective, two large randomised control trials, namely: the European Randomized Study of Screening for Prostate Cancer (ERSPC) and the Prostate, Lung, Colorectal and Ovarian Cancer Screening trial (PLCO), were initiated in 1994. After 15 years, the first glance of evidence from these trials were available to the public in 2009.

The ERSPC study, which collected data from seven European centres, and included 162,387 men aged 55–75 years, reported a PCa specific mortality reduction by 21% in men screened regularly every 2–4 years, when compared to the control group. 20 Moreover, the number needed to screen (NNS) and number needed to treat (NNT) to prevent one PCa death, were 1,410 and 48 men, respectively. Conversely, the PLCO trial, which was conducted in 10 US centres and included 76,693 men aged 55–75 years, did not demonstrate a significant difference in PCa-specific mortality between the control and the screening groups. 21

Both studies had acknowledged weaknesses.<sup>20-22</sup> The ERSPC had protocols for screening that varied between the recruitment centres, with PSA cut-offs for prostate biopsy ranging from 3.0–4.0ng/ml. Additionally, the level of contamination in the control arm was not clearly reported. The PLCO had a uniform PSA cut-off (4.0ng/ ml) for prostate biopsy but reported a rather high level of contamination in the control group. Nevertheless, the long follow-up time with a median of nine years for ERSPC and 10 years for PLCO, and the high participants' compliance rates in both trials, represented areas of major strengths. The results reported by the ERSPC and PLCO had failed to provide a conclusion on the PSA screening argument locally and internationally.23 Some voices endorsed the ERSPC results and advocated for population screening, while others were the opposition. In 2012, after considering the evidence, the US Preventative Services Task Force (USPSTF) released their recommendations against the utilisation of PSA for screening in asymptomatic men.24 This decision was met with disapproval from entities such as the American Urology Association and members of the public.25,26The impact of the USPSTF recommendations on PCa screening and characteristics was noticeable. Multiple reports suggested a decrease in the PSA testing rates for men aged 50-75 years and consequently, a decrease in PCa incidence.27,28 Moreover, the effect of these recommendations spilled over beyond the US. In a study from Australia using Medicare data, there was a clear decline in PSA testing and prostate biopsy rates after 2012.29 Similarly, Bhindi et al reported a 38% reduction in rates of prostate biopsy and PCa detection in a Canadian institution, following the recommendations.30 Additionally, several studies demonstrated a change in the pathological characteristics of the detected cancers.<sup>27,28,31</sup> A report from the American Cancer Society suggested an increase in the incidence of high-grade PCa and rates of distant metastasis at time of diagnosis.28 Also, the incidence of localised PCa had dropped by 6% in the US within one year of the recommendations' release.31

In New Zealand, the effects of the PCa screening debates can be inferred from



Figure 2: Prostate cancer mortality in New Zealand (1980-2015) presented as age-standardised rate (ASR) per 100,000 men.\*

\*Age standardised rates (ASR) adopted from the Ministry of Health publications (2)

observing the temporal trends in PCa incidence and mortality. As demonstrated in Figure 1, the age-standardised rates of PCa had dropped markedly from 134 cases per 100,000 men in 2000 to 98 cases per 100,000 men in 2005. This drop coincided with the local concerns regarding the potential risks of PSA testing for PCa screening.9-13 Similar decline was also observed between 2009 and 2015, which could be linked to the ERSPC and PLCO results, and subsequently the USPSTF recommendations. On the other hand, the observed steep decline in mortality rates following the introduction of PSA screening stagnated from 2009 to 2015 (Figure 2).

This may reflect a stage-shift towards detecting more aggressive cancers in response to the decline in PCa screening. This hypothesis is supported by the results from ERSPC since the mortality benefits from PSA-based screening, would only be tangible after approximately 10 years. Additionally, the changes in the cancer's characteristics following USPSTF recommendations towards more advanced diseases at diagnosis represents another supporting argument to the hypothesis. PR. Nevertheless, this cannot be ascertained without

high-quality data on PCa stage at diagnosis in New Zealand, which are currently unavailable.<sup>32</sup>

## Prostate cancer screening in New Zealand—status quo

In light of the extensive PCa screening debate in New Zealand, the Health Select Committee presented an inquiry to the House of Parliament on this subject in July, 2011.<sup>33</sup> This had generated several recommendations to the Government and the Ministry of Health (MoH), with particular focus on equitable access to screening for well-informed men, and the necessity of establishing quality improvement strategies to monitor the early detection and treatment of PCa in the country.

In response to the Parliament inquiry, the MoH formed the Prostate Cancer Taskforce.<sup>34</sup> The recommendations from this group of clinical and population health experts led to the publications of the "Prostate cancer management and referral guidelines" in September 2015, which are still in use to this date. These guidelines offered primary healthcare providers with directions regarding the PSA-based screening, and when to seek specialist input for



further investigations. However, since PCa screening has always been opportunistic, no formal (governmentally funded) educational and monitoring facilities were established to review and update these guidelines.<sup>35</sup> These services are provided by the National Screening Unit (NSU) for diseases with organised screening programmes, such as breast and colorectal cancers.

While the national guidelines were being drafted, few studies were conducted to offer an insight into the local PCa screening practices. In a report prepared to the NSU in 2010, the prevalence of opportunistic PCa screening of asymptomatic men in the community was estimated to be 21%, with age and socioeconomic status proportionally increased the screening rates. Also, it demonstrated that 51% of the population never had a PSA test. This was based on a phone survey of 518 men aged 40–74 years, identified through the electoral role. The survey design was weighted to include higher proportion of Māori men (30%).

In a study of PSA testing in 31 general practices in the Midland region, the authors reported that 22.1% of the practice enrolled men, aged 40 years or above, were screened in 2010.37 The majority of these men (84.9%) received PSA testing while being asymptomatic. Also, Māori men were less likely to be screened when compared to non-Māori (11.2% vs 22.6%). In another analysis of all the PSA tests performed in New Zealand, Van Rij and colleagues estimated the prevalence of PSA testing in the population to be 28.3% in 2011, for men aged 40 years or above.<sup>38</sup> The same report demonstrated that 93% of the GPs in the country offer some form of PSA screening.

The aforementioned three studies have several limitations. The first, being a survey, with questionable representativeness of the cohort, due to the higher proportion of Māori men than the total New Zealand population (30% vs 12% as reported in the national census in 2013). 36,39 This is particularly relevant, since the Midland study clearly demonstrated lower PSA testing rates in Māori men. 37 The second and third studies were both cross-sectional, and did not account for men receiving PSA testing every two or three years. 37,38 Lastly, all three studies were conducted before the USPSTF

or the New Zealand guidelines, which render them deeply outdated.

In 2019, a comprehensive analysis of PSA testing patterns at a population level was conducted in the Northern Cancer Region of New Zealand. 40 Following a review of all PSA tests performed over a 10-year period, the authors reported that 87% of the total region male population, aged 40 years or older, had been tested at least once in the study period, with majority of these tests done in asymptomatic men. This suggested that opportunistic PSA-based screening for PCa in the community was significantly more prevalent than any of the previous estimates. Furthermore, the study highlighted that 65% of men aged 50-69 years underwent regular PSA testing. This figure is well in par with the current national targets for participation in breast (70%) and colorectal (62%) cancers screening programmes.41,42

# Prostate cancer screening in New Zealand—time to reconsider the options

The recent years have witnessed a significant change to the PCa screening paradigm. This was influenced by the extended 16-year follow-up results from the ERSPC trial, demonstrating ongoing mortality benefits for the PSA screening cohort, and a number needed to screen (NNS) of 570 men, to prevent one PCa death.43 This, in fact is comparable to the NNS for mammography and faecal occult blood, for breast and colorectal cancers, respectively.44,45 Additionally, it has become apparent that the other randomised trial (the PLCO), had a significant level of screening contamination in the control arm, with 46% at baseline and up to 80% during the study period.46 This had reduced the applicability of the study results in assessing the benefits of population screening. Furthermore, the most recent screening trial, the Cluster Randomised Trial of PSA Testing for Prostate Cancer (CAP), which compared a one-off "truly opportunistic" screening intervention, to no screening in 415,357 men in the UK, has reported no mortality benefits and significant risk of over-diagnosis in the screening arm after 10 years follow-up.47 Consequently, after reviewing this updated evidence, the USPSTF has changed the recommendations



for PSA usage in PCa screening in 2018, from grade D (discourage usage) to grade C (offer to selected individuals).48 Moreover, the European Association of Urology (EAU) has released a policy statement in 2019, emphasising that only organised population-based PSA screening, rather than opportunistic approaches, has the potential to significantly reduce PCa mortality. 49 Thus, with the well-established role of active surveillance in the management of low-risk PCa, and the implementation of multiparametric MRI in the cancer diagnostic pathway, the balance of risks is currently weighted heavier towards the benefits of cancer screening. Therefore, the EAU has announced a plan to submit a case to adopt PCa screening programmes in the European countries this year.

Locally, the results from the Northern Cancer Region study raised numerous additional concerns regarding the current opportunistic approach to PCa screening in the country. 40,50 First, since PSA testing has been community-led and self-funded, the access to screening has not been uniformly distributed within the population. In contrast to the region ethnic distribution, Māori and Pacific men were evidently under-represented in the screened cohort. Moreover, despite adjustment for socioeconomic status, the frequency of screening was lower for Māori and Pacific men. This disparity in screening may be contributing to the known ethnic disparities in PCa outcomes.34,50 The second concern is regarding the adequacy of counselling these men have received. Multiple reports have demonstrated that most men screened for PCa with PSA were not fully aware of the risks and benefits associated with the screening process. 51,52 This is in spite of the international recommendations to obtain "an informed consent" prior to screening men for PCa.7,34,48,49

One of the main advantages of an organised screening programme is that every participant has the opportunity to receive the same cancer-related information and education, and follow a similar screening pathway.35 This is attributed to the ongoing monitoring and regular conduct of quality assurance procedures. The effect of this on outcomes can be seen from breast cancer survival statistics.53 In 1998, the gap in the five-year relative survival between Māori and non-Māori women was 9%. This improved significantly following the introduction of the national screening programme in 1999 (survival difference of 4% in 2010). Lastly, it is crucial to consider the economical constraint of organised PCa screening. Recent analysis from the Finnish arm of the ERSPC had concluded that organised screening is at least as cost-effective as the opportunistic approach.54 However, the cost of opportunistic PCa screening in New Zealand is largely covered by the screened men.55 This implies that such costs will need to be centrally funded if a national screening programme is to be implemented. Additionally, there currently no local data on the availability of health services that can accommodate a PCa screening programme. Therefore, as demonstrated from the Bowel Screening Programme, a pilot study assessing the feasibility of organised PCa screening in New Zealand is highly needed.

In conclusion, the medical society may be approaching the end of the PCa screening controversy, favouring the implementation of an organised, population-based approach. This, more than ever, calls for greater efforts to support high-quality New Zealand-specific research, to guide the decision makers in constructing policies that assure the delivery of equitable optimum healthcare, and meet the unique demands of our culturally diverse community.



#### **Competing interests:**

Nil.

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