Bracing for the Flood: How Should We Manage Prostate Cancer Care by 2050?

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INTRODUCTION

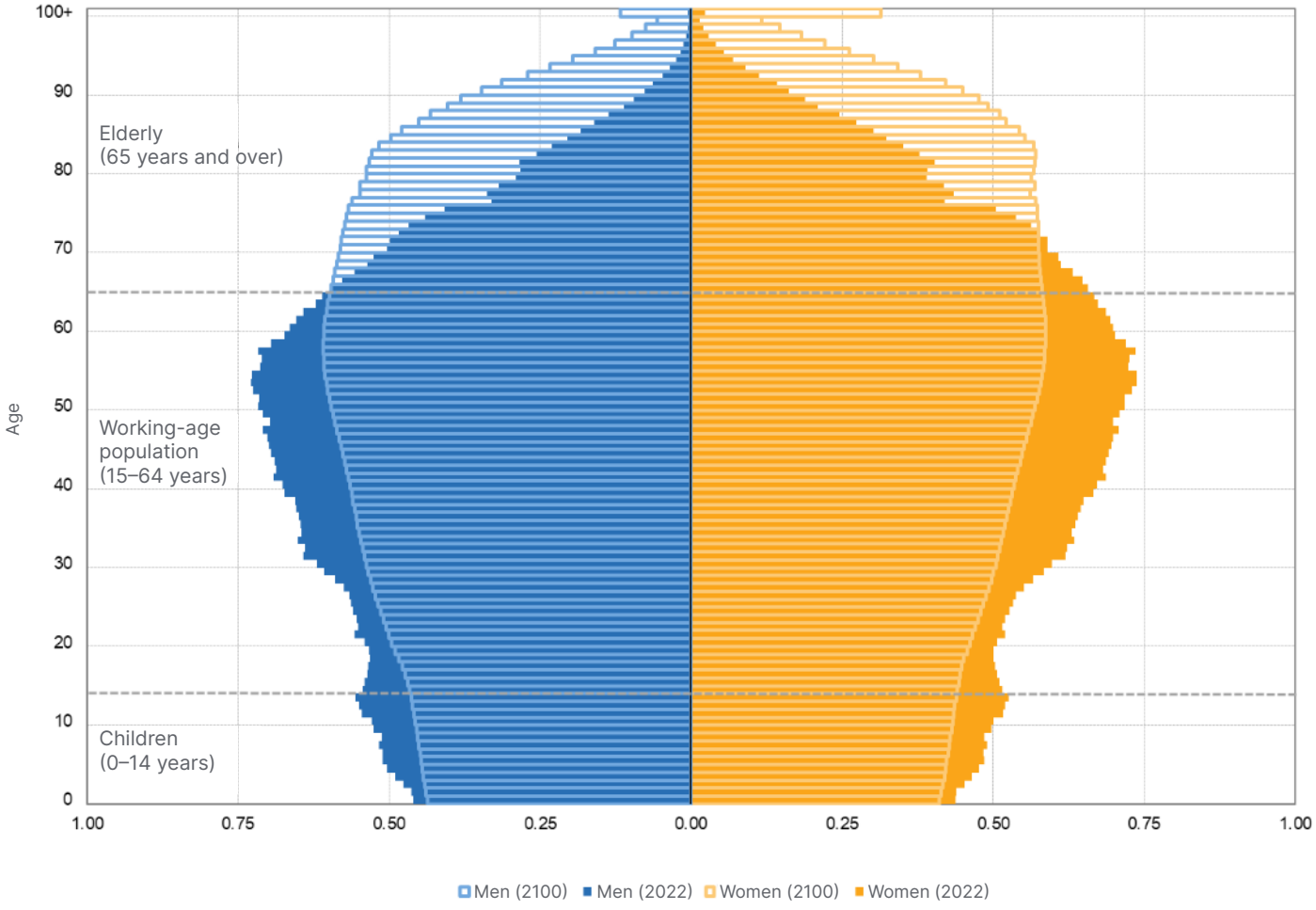
With an ever-growing world population and increasing life-expectancy, the incidence of different types of cancer is expected to rise in the coming decades. Prostate cancer (PCa) is already the most commonly diagnosed cancer among males, ranking as the first to third most common cause of cancer-related death in western countries. PCa worldwide incidence is set to grow from 1.5 million to 2.9 million by 2050, with an estimated 400,000 males already dying from PCa annually as of 2022 and an estimated 940,000 deaths by 2050.[1] In Europe, as seen in Figure 1,[2] this increase will also be felt with a gradual shift towards an older population, with an expected 23.6% increase in diagnoses and 42% more PCa-related deaths by 2040.[3] PCa is generally, though exceptions apply, a slow-growing cancer, with 98% of patients living longer than 5 years past their initial diagnosis.[4]

Before the introduction of prostate-specific antigen (PSA)-based testing, up to one in five men diagnosed with PCa were diagnosed with advanced, incurable disease.[5] Following the introduction of the PSA test, urologists and general practitioners gained a tool to detect PCa at an earlier stage. This led to years of research into the early detection of PCa and, together with advancements in the treatment of advanced PCa, it led to less men being diagnosed with advanced stages of PCa and an increase in the life-expectancy of men with PCa.[4,6] However, during this longer life-expectancy, a whole assortment of different and increasingly expensive medical interventions may take place, such as repeat visits to the urologist, novel scans, surgery, radiation therapy, and systemic therapies in metastatic disease, for which costs are several times higher than therapy for organ-confined disease.[7]

A challenge presents itself in the coming decades: to keep providing high-quality care to men diagnosed with PCa with a decreasing workforce. As the population ages and birthrates decline, not only are there more men at risk of PCa, but also less doctors and nurses to care for them. Currently, there is already a shortage of over one million healthcare professionals in Europe, and up to one-third is expected to retire over the coming years.[8] As such, effort should not only be focused on what more can be done to improve cancer-related outcomes for patients, but also on what we can, safely, do less of: de-escalating PCa care. The following paragraphs will list a few examples of steps in the de-escalation of

Figure 1: Current estimated and projected future population of the EU.

Population pyramids, EU, 2022 and 2100
(% of total population)



Adapted from Eurostat.[2]

PCa care and will discuss possible future directions, focusing on early detection and active surveillance (AS).

ORGANISED SCREENING

As the proverb goes, 'prevention is better than cure'. One of the first steps in de-escalating PCa care would be to invest in the prevention of the disease. However, primary prevention is virtually impossible, as there are currently no thoroughly established modifiable risk factors for PCa.[9] Through the use of organised screening programmes, it has been proven that PCa-related morbidity and mortality can be reduced. In the latest analysis of the European Randomized Study of Screening for Prostate Cancer (ERSPC), PSA screening was found to reduce PCa-related mortality by 16% (rate ratio: 0.84; 95% CI: 0.76–0.92).[10] However, PSA was first introduced as a marker for follow-up of PCa and not for screening. In the ERSPC, this came at the cost of overdiagnosis and overtreatment, as more men were diagnosed with forms of PCa that might not have caused symptoms later in life. For every averted death due to PCa, 12 men are diagnosed with PCa on top of those diagnosed in a clinical situation. On the other hand, the risk of diagnosis

for advanced, incurable PCa was lower for screened males than controls (risk ratio: 0.66; 95% CI: 0.60–0.74).[10]

In the ERSPC and most, if not all, of the first PCa screening trials, screening was done in a one-size-fits-all approach. If a participant's PSA level exceeded a set threshold of 3 ng/mL, further evaluation was done through prostate biopsies.[10] Because of the overdiagnosis found in these trials, organised screening programmes for PCa have been hotly contested in the past decades. To improve the characteristics of these organised screening programmes, the use of risk stratification tools is vital.

Risk stratification in screening for PCa can be done in a multitude of different ways and at different points of the screening pathway. Using risk calculators, novel biomarkers, and MRI, patients at risk of a PCa diagnosis can be identified more clearly and, just as importantly, patients at low or no risk for PCa can also be identified.[11] Incorporating MRI into risk calculators has shown to be able to reduce the number of biopsies by 36%, while missing only 4% of high-grade PCa in men who did not receive a biopsy.[12] To reduce overdiagnosis of insignificant PCa (i.e., forms of PCa that would not cause symptoms later in life), these modalities should be combined in an organised screening programme. As for other ways to reduce the inflow of men into these screening programmes, attention should be turned to which men should be invited for screening. Upfront selection of patients is currently only done through age restrictions on participation in a screening programme. To further de-escalate the overdiagnosis of men with insignificant PCa, attention can be turned towards who to invite for screening and what to consider as 'clinically significant' PCa.

No two people are the same, as much as no two cases of PCa are the same. Currently, clinical significance is defined on the pathologic characteristics of the tumour. However, an International Society of Urologic Pathology Grade Group (ISUP GG) 1 PCa diagnosis for a 74-year-old with end-stage kidney disease does not carry the same weight as the same diagnosis for a 52-year-old man with no medical history. The same disease that could be clinicopathologically, and appropriately, defined as 'insignificant' or 'not clinically significant' for the first man, whose life-expectancy is to be counted in years, could very well become 'clinically significant' for the second man, as he may have a life-expectancy of several decades where the disease may become more aggressive. As symptoms of PCa often take years to manifest, in light of efficient use of resources, remaining life expectancy should be used as a tool, more so than chronological age, to determine both who to invite to screening and what to consider clinically significant PCa.

As of yet, there are no large-scale organised screening programmes. Although their use in the reduction of PCa-related mortality has been proven, much discussion still exists around overdiagnosis and overtreatment. PSA tests are, however, available outside of the organised screening setting. Through their general practitioner, informed men can get access to a PSA test. This practice, where asymptomatic men take the initiative to get a PSA test, is labelled 'opportunistic screening'. This opportunistic screening poses several problems: first and foremost, that it may not have any effect on PCa-related mortality and has higher overdiagnosis than organised screening, with up to twice the number of men needing to be diagnosed to prevent one PCa-related death.[13] Second, having opportunistic screening be dependent on public initiative could disadvantage men who are less medically informed.

A challenge in both opportunistic and organised screening is how to handle those at a higher risk of PCa, especially at a younger age due to hereditary forms of PCa. As mentioned, in opportunistic screening, initiative is dependent on a man's own knowledge of the disease and, in this case, his increased risk. In organised screening, the pathway proposed for the general population might not be suitable for these men, as they are at greater risk of developing PCa and at younger ages than those without a genetic predisposition. In organised screening, this could be taken

into account by reaching out to these men earlier and evaluating if an adapted programme would be of greater benefit.

Organised screening is, however, not yet a widely accepted and applied practice, and opportunistic screening will probably still exist for several years, if not longer. So, de-escalating opportunistic screening is an equally important endeavour to explore. Much the same as organised screening programmes, opportunistic screening can benefit from the use of risk stratification tools. In addition, part of this risk stratification can be outsourced from the hospital, as Hogenhout et al.[14] describe in their article on shifting PCa detection to primary care. By performing risk-stratification at a diagnostic centre, over two-thirds of referrals could be prevented, and at a reduced cost compared to a hospital visit.

ACTIVE SURVEILLANCE

With the introduction of PSA-based screening of PCa and the subsequent inflow of men with low-risk PCa, AS was introduced as a way to defer or avoid invasive treatment by closely following these men. Critically distinct from watchful waiting, when higher-grade PCa is detected in men on AS, definitive treatment is initiated. Though initially only performed in a research setting, as time passed and results were published, AS evolved into the preferred treatment for low-grade PCa. Oncological outcomes are comparable to definitive treatment, such as radical prostatectomy or radiotherapy, for men on AS.[15] The introduction of MRI in the AS pathway allows for a theoretical improvement of the initial selection of patients eligible for AS by more precisely sampling tumours during biopsy. Also, MRI may identify men with elevated PSA but no prostatic lesions, and thus reduce unnecessary biopsies in up to a quarter of patients.[16] However, due to the reduction in undersampling, men who would have been diagnosed with a low-risk form of PCa could show higher grade PCa although the underlying disease was the same. Though a heterogeneous group, multiple studies have shown that a subgroup of men with ISUP GG 2 can be safely monitored with AS.[17] Even though expensive, definitive treatments can be avoided, most AS strategies include an intensive follow-up protocol. This consequently strains the urologist's practice with frequent appointments for repeat PSA-tests, MRI, and biopsy results.

Currently, AS is mostly performed according to static, quite intensive, one-size-fits-all protocols. These protocols generally consist of a combination of recurring PSA-tests, digital rectal examinations, MRI, and biopsies. Different centres have differing protocols, with different combinations of the above-mentioned diagnostic interventions at varying intervals.[17] Given the favourable oncological outcomes observed in men undergoing AS, there is now the concept of the 'overly surveyed patient'. To reduce the workload and keep AS a viable option for all men with low-risk PCa, AS should switch to a risk-based follow-up strategy. This approach has already shown promise with the Stratified Cancer Surveillance (STRATCANS) programme, where most men (214/297; 72%) remained treatment free at a median follow-up of 4.9 years. Apart from diagnostic interventions (digital rectal examination, MRI, and biopsies), follow-up was virtual and men in the lowest risk group (127/294; 43%) only received follow-up biopsy if indicated by PSA or MRI.[18] This risk-based approach addresses the main concern with reducing follow-up: ensuring that those at highest risk of upgrading to higher-risk disease are detected at an appropriate time.

Another challenge arises around keeping men on AS. From a policy and economic point of view, providing a one-time surgery for these low-risk men is more profitable than keeping them in years-long intensive follow-up. Financial incentives to perform definitive therapy in men at low risk of clinically significant PCa are different for a given healthcare system but, for as long as these exist, there will be men at low risk of clinically significant PCa who, possibly to their detriment, undergo definitive treatment. To ensure that men are treated with a focus on what is in their best

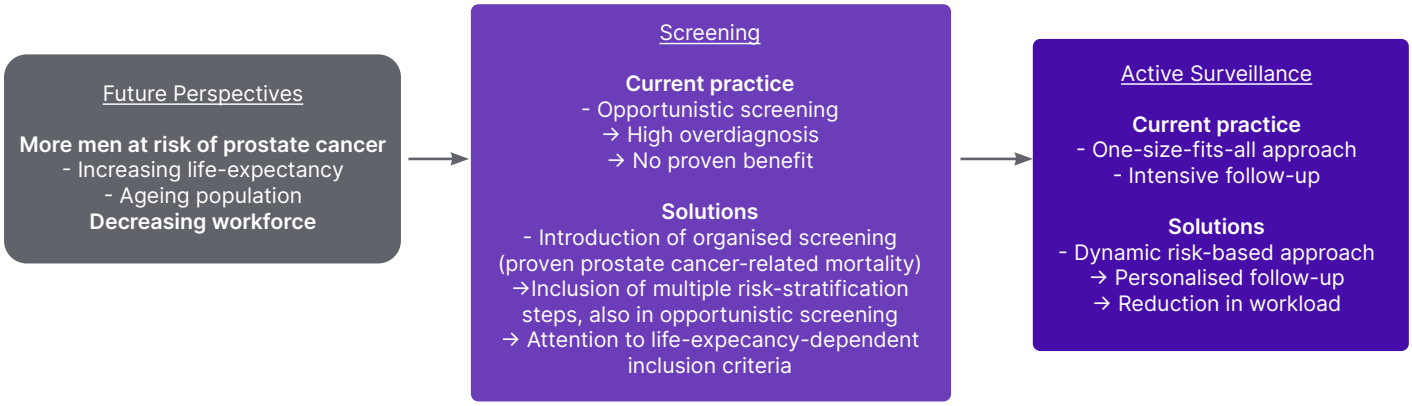
oncological and personal interest (instead of focusing on financials), healthcare systems should ensure that renumeration for AS does not discourage inclusion over performing definitive therapies.

To have AS remain a viable treatment option and reduce definitive treatment, further research should be focused on reducing the workload of AS. Using a risk-based approach, further incorporating MRI and risk-calculators and reducing follow-up intensity for those patients who are expected to have excellent outcomes should assist in keeping PCa care accessible for all men.

CONCLUSION

To continue to manage PCa care in the future, it is essential that we de-escalate parts of PCa care. As discussed, this can be done on different levels and at different points of the diagnostic pathway (Figure 2). Through timely detection, when there is opportunity for curative care, risk stratification, careful selection of who to screen, and efficient use of resources, PCa care will remain accessible and of high quality for all patients.

Figure 2: Steps for de-escalation in the diagnostic pathway.



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