MODELING OF PROSTATE CANCER SCREENING

The future directions

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Modeling of prostate cancer screening:
The future directions

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toekomstige ontwikkelingen

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1 General introduction

1.1. THE PROSTATE AND PROSTATE CANCER

The prostate is a part of the male reproductive system located between the bladder and penis, just in front of the rectum (Figure 1). It has the size of a chestnut, and as a man gets older, it tends to increase in size. Its main function is production of fluid that makes up part of the semen. Benign abnormalities of the prostate include prostatic hyperplasia and prostatitis, which should be differentiated from prostate cancer. Prostate cancer is a disease marked by a malignant or uncontrolled proliferation of cells in the prostate.

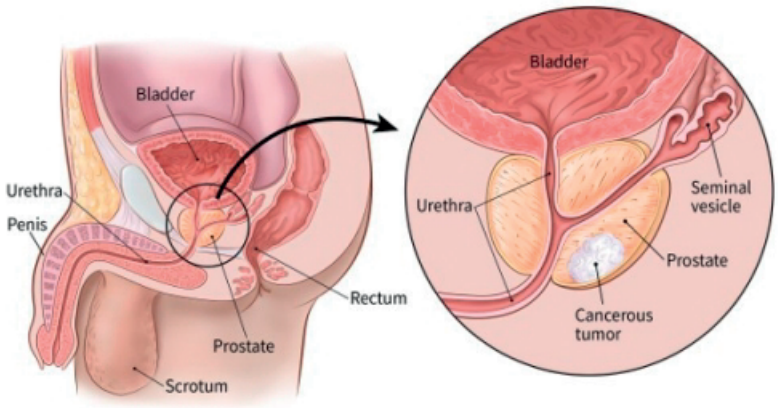

Figure 1. Side view of the male genitourinary system with cancer located in the prostate. Adapted from https://cancer.org/cancer/prostate-cancer/detection-diagnosis-staging/tests.

1.2. EPIDEMIOLOGY OF PROSTATE CANCER

Prostate cancer is the second most common diagnosed malignancy and the 5th leading cause of cancer mortality in men across the world[1,2]. Out of an estimated 1.3 million men that were diagnosed with prostate cancer in 2018 worldwide (accounting for about 14% of men diagnosed with cancer), almost 76% of them were in more developed regions[3]. The worldwide burden is expected to increase to almost 2.3 million new cases and 740,000 deaths by 2040[4]. The disease is most common in Oceania, North America, Northern and Western Europe, and the lowest incidence rates can be found in Asia and North Africa[5] (Figure 2). In Europe, registry data have shown that death from prostate cancer has override death from colorectal cancer, being the second frequent cause of cancer-related death in men behind lung cancer[6].

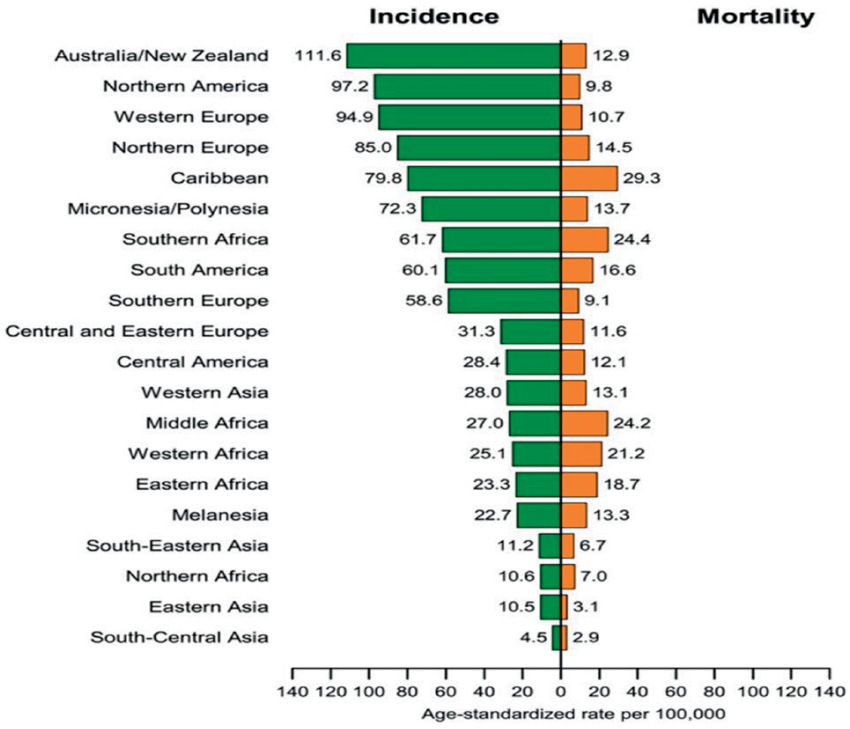

Figure 2. Age standardized prostate cancer incidence and mortality by geographical area. (Adopted from Taitt, 2018)[2]

1.3. DETECTION OF PROSTATE CANCER

Prostate cancer can be detected with a blood test, measuring the level of prostate specific antigen (PSA) in the blood (in ng/mL). PSA is a protein produced by healthy as well as malignant cells in the prostate. An elevated PSA level in the blood may indicate an increased risk for prostate cancer[7]. However, a PSA test lacks specificity, since PSA can also be elevated due to other prostate abnormalities such as benign prostate hyperplasia (enlargement of the prostate) and prostatitis (inflammation of the prostate)[8]. A digital rectal examination (DRE) is another test used for the detection of abnormalities, such as nodules or irregularities, in the prostate. The location of the prostate, as indicated in Figure 1, allows for palpation with the index finger through the anus. The presence of abnormalities up on palpation may indicates an increased risk of prostate cancer[9].

When the PSA or DRE test is suspicious, a prostate biopsy is indicated. This can be transrectal ultrasound-guided biopsy (the standard and widely used method) or

magnetic resonance imaging (MRI) targeted biopsy. The latter is conducted after offering a multi-parametric magnetic resonance imaging (mpMRI) test for those men with suspicious PSA test result.

The introduction of mpMRI and targeted biopsy has improved the diagnosis of prostate cancer. The mpMRI can be used as a reflex test to avoid biopsy if the results are negative, whereas positive results can be used for targeting abnormal areas in the prostate during biopsy[10-12]. Areas on the mpMRI that are suggestive of prostate cancer are categorized according to the Prostate Imaging–Reporting and Data System (PI-RADS), on a scale from one to five[13]. Multiple studies reported that an MRI-targeted biopsy is superior to the standard Transrectal Ultrasonography Guided Biopsy (TRUSGB), because it reduces the detection of clinically insignificant prostate cancer while increasing the detection of significant prostate cancer [10,13,14]. Barentsz etal., recommended that mpMRI should be an integral part of prostate cancer diagnosis and treatment [15].

Staging

The stage/extent of prostate cancer is determined or classified according to the Tumor, Node, and Metastasis (TNM) system[16] (Table 1).

Table 1. Tumor, Node, Metastasis (TNM) stage definitions for prostate cancer.

T- Primary tumor	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Clinically unapparent tumor not palpable or visible by imaging
T1a	Tumor incidental histological finding in 5% or less of tissue resected
T1b	Tumor incidental histological finding in more than 5% of tissue resected
T1c	Tumor identified by needle biopsy (e.g. because of elevated PSA)
T2	Tumor confined within the prostate
T2a	Tumor involves one half of one lobe or less
T2b	Tumor involves more than half of one lobe, but not both lobes
T2c	Tumor involves both lobes
T3	Tumor extends through the prostatic capsule
T3a	Extracapsular extension (unilateral or bilateral) including microscopic bladder neck involvement
T3b	Tumor invades seminal vesicle(s)
T4	Tumor is fixed or invades adjacent structures other than seminal vesicles: external sphincter, rectum, levator muscles, and/or pelvic wall

Table 1. Tumor, Node, Metastasis (TNM) stage definitions for prostate cancer. (continued)

N-Regional lymph nodes	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
M-Distant metastasis	
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis
M1a	Non-regional lymph node(s)
M1b	Bone(s)
M1c	Other site(s)

Grading

Prostate cancer is graded based on the Gleason grading/scoring system[17]. The score ranges from two to ten. A Gleason score of six and below is low-grade, seven is intermediate-grade, and a score of eight to ten is high-grade cancer. The Gleason score is very important for predicting the behavior of prostate cancer. It is used to determine the aggressiveness of the tumor, and helps to choose appropriate treatment options.

1.4. TREATMENT

Treatment of men diagnosed with localized prostate cancer with curative intent includes radical prostatectomy (RP), radiation therapy (RP), and active surveillance (AS).

Radical prostatectomy is a curative treatment of prostate cancer that involves surgical removal of the prostate and seminal vesicles. According to the Scandinavian Prostate Cancer Group Study Number 4 (SPCG-4), in men with localized prostate cancer, RP is associated with a substantial reduction of both overall and cancer-specific mortality (relative risk of 0.71 and 0.56 respectively) as compared to watchful waiting[18]. The study also suggested that the mortality benefit of RP declines with age, where the benefit was largest in men younger than 65 years of age.

RT involves radiation of the prostate and can be given either by an external beam radiation source or by brachytherapy[19]. There are no data from a randomized controlled trial that compare the treatment outcomes of RP and RT.

Active surveillance is a method of closely monitoring men with low-risk prostate cancer rather than treating them immediately after diagnosis. It involves a series of PSA testing, DRE, prostate biopsies, or a combination of these to monitor progression with an intent to start curative treatment (RP or RT) for those who develop significant disease[20]. AS should be differentiated from watchful waiting (WW). In WW, treatment is initiated when symptoms arise (no curative intent). WW is usually a reasonable choice in men with localized prostate cancer and a life expectancy of less than 10 years[21].

1.5. SCREENING FOR PROSTATE CANCER

Screening is the use of tests across a population in order to identify individuals who have a disease but do not yet show clinical symptoms[22]. Likewise, a PSA test is used as a screening tool for detecting early prostate cancer among asymptomatic men[7]. The time by which screening advances the detection of (prostate) cancer by symptom is called the lead-time[23] (Figure 3). Prostate cancer is characterized by slow development and therefore has a long lead-time[24-26]. Conversely, in most of the time

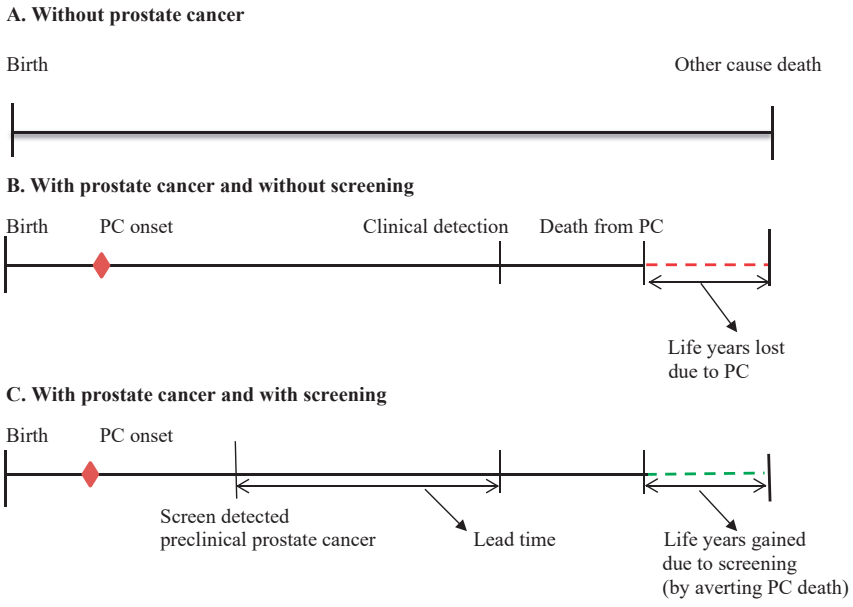

Figure 3. Schematic representation of the basic principle of screening. Prostate cancer onset is the time tumor starts in a preclinical phase. PC= prostate cancer

it is too advanced to be cured when detected without screening[27], because in that case more cancers are diagnosed at stage 3 and above.

Benefits of prostate cancer screening

The aim of PSA screening is to reduce the risk of prostate cancer mortality and metastatic disease by finding and treating prostate cancer at an early stage. The European Randomized study of Screening for Prostate Cancer (ERSPC)[28], the Prostate, Lung, Colorectal and Ovarian cancer Screening trial (PLCO)[29], and The Cluster Randomized Trial of PSA Testing for Prostate Cancer (CAP)[30] were the three large randomized clinical trials on prostate cancer screening.

The ERSPC that included centers in seven European countries was initiated in the early 1990s with the aim of evaluating the effect of PSA screening on prostate cancer mortality[31]. A total of 162,243 men in the core age group (55-69 years) were randomized either to the control (no screening) or intervention group (screening). In most centers, a PSA cutoff 3.0 ng/mL was used to refer suspicious men to biopsy. The screening interval was four years except in the Swedish center, where the interval was two years. The most recent results of the trial, after 16 years follow-up, showed a 20% relative prostate cancer mortality reduction in the intervention arm[28]. The numbers of men needed to invite for screening and the numbers needed to diagnose in order to avert one prostate cancer death were 570 and 18 respectively. Unlike the ERSPC study, the PLCO and CAP trials didn't show a significant mortality benefit[29,30] However, there are many differences in the design and implementation among the trials that could explain the discrepancy. Recently published secondary analyses show that the ERSPC and PLCO trials, in fact, provide compatible evidence that screening reduces prostate cancer mortality[23,32]. Whether the insignificant results from the CAP trial change the evidence of PSA testing was tried to address in this thesis by replicating the trial using a simulation model (Chapter 2).

Harms of prostate cancer screening

The benefits of PSA screening are also accompanied by some adverse effects. PSA testing leads to an overdiagnosis of indolent prostate cancer, which has been further compounded by the limitations of traditional diagnosis by transrectal ultrasound-guided biopsy[33]. Overdiagnosis is defined as detection of cancer because of screening that would not have been clinically diagnosed during the man's life time in the absence of screening. Treating such cancer is considered an overtreatment. The rates of overdiagnosis with PSA screening have been estimated to be up to 50% (based on trials)[34]. Side effects of active treatments of prostate cancer include erectile dysfunction, incontinence, and bowel problems[35,36]. Apart from this, a study indicated that

about 75% of men who have a prostate biopsy due to an elevated PSA level are found not to have prostate cancer[37], and this called a false positive result. False-positive results from a PSA test may leads to psychological problems, and also unnecessary biopsy which is accompanied by pain and sometimes complications[38]. The false-positive and complication rates from a biopsy are higher in older men[34]. All these harms have negative impacts on quality of life.

1.6. GUIDELINES ON PROSTATE CANCER SCREENING

Given the above harms of prostate cancer screening, in 2012 the US Preventive Services Task Force (USPSTF) recommended against PSA screening[39], which resulted in a reduction of the uptake of PSA test for early detection in US after the year 2012[40]. However, in the same period, the incidence of advanced prostate cancer started to rise and the declining trend in prostate cancer mortality stopped[41,42] (**Figure** 4). In the United Kingdom, 4 out of 10 prostate cancer diagnoses are currently diagnosed at a locally advanced or metastatic stage[6].

In 2018 the USPSTF revised the 2012 recommendation by giving a C recommendation for screening between age 55 to 69 years, and the decision to undergo this screening should be an individual one[43]. The USPSTF gave this recommendation mainly based on the ERSPC and PLCO trials, and the risk of overdiagnosis was calculated by comparing the number of cancers diagnosed in the screening groups with the number diagnosed in the control groups over follow-up years. However, the estimation of

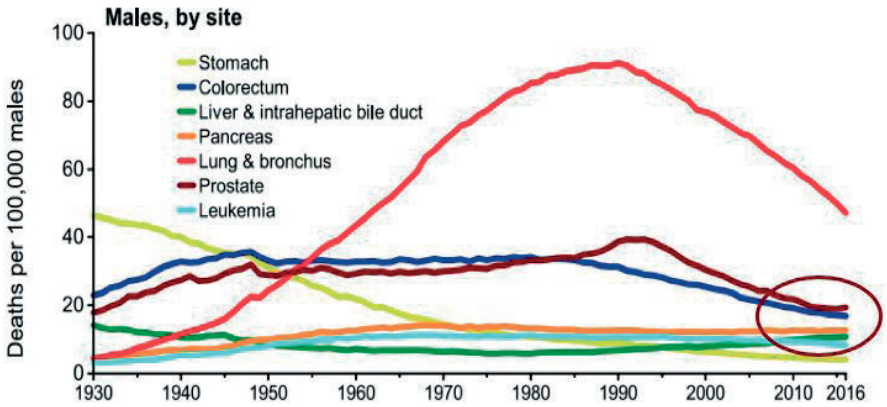

Figure 4. Trends in age-adjusted cancer death rates by site, male, US. Adopted from an European policy paper on PSA screening for prostate cancer[6].

overdiagnosis over the given trial period of 11-13 years only is not enough due to the natural history of prostate cancer. Sufficient length of follow-up periods is essential to account for the effects of lead time in general[44]. Furthermore, in the trials all men with elevated PSA level were receiving systematic biopsy, and did not consider multiparametric magnetic resonance imaging (mpMRI). The European Association of Urology (EAU) on the other hand recommended that baseline PSA should be obtained at the age of 45–50 years to initiate an individualized risk-adapted early detection strategy[45]. Despite the existing guidelines, prostate cancer remains the most common cause of cancer-related morbidity and mortality among men. Recently the EAU emphasized that organized population-based PSA screening programs should be implemented at a European level to reduce prostate cancer mortality[41].

1.7. ORGANIZED POPULATION BASED SCREENING

Despite the evidence about the benefits of prostate-specific antigen (PSA) screening on the reduction of mortality and metastatic disease[23,28,46,47], almost no country has yet introduced a population-based prostate cancer screening program, in contrast with breast, cervical, and colorectal cancers. Lithuania is the only country that has national PSA test program, but the biopsy referral after a positive test is insufficiently low[48]. However, there is high uptake of opportunistic PSA testing in many countries[29,49,50]. This form of screening is usually less efficient and accompanied by a high risk of overdiagnosis[51,52], mainly due to screening at high ages.

However, some important questions such as the age at which PSA screening should start, at what age it should stop, and at what frequency to screen remains debatable and need to be investigated more. Furthermore, assessing the effects of triage tests, like mpMRI, for reduction of the harms of prostate cancer screening (unnecessary biopsy, ovediagnosis, and overtreatment) in a population-based screening setting can have a profound impact. Cost is another important factor that policy-makers need to consider to implement a given strategy. However, finding the optimal screening strategy that can lead to a better balance between the harms and benefits would require comparisons of various alternative screening strategies, which is impossible to do in a single randomized controlled trial (RCT). Additionally, RCTs generally have limited follow-up time and due to this it is impossible to assess the long-term effects of screening such as overdiagnosis, overtreatment and life-years gained. This is particularly true for prostate cancer where the lead time is often long. Therefore, modeling can play a crucial role for bridging the gap between published evidence

and the information we need to develop guidelines, as seen, for example, in breast and colorectal cancer screening[53].

1.8. MICRO-SIMULATION MODEL

Microsimulation is a modeling technique that typically uses a large sample size of individual units (micro units), each with a unique set of attributes, and allows for simulations of downstream events on the basis of predefined states and the transition probabilities between those states over time[54]. In this thesis, a MIcro-Simulation SCreening ANalysis (MISCAN) prostate cancer model is used to assess the long-term effects of various prostate cancer screening strategies (scenarios), mainly in a population-based screening setting. The model has been described throughout the thesis, and further detail descriptions can also be found in previous studies[55,56].

Briefly, MISCAN prostate is a semi-Markov model that simulates individual life histories. By simulating the life histories without and with screening, the effects of screening can be evaluated. The model contains four main parts: demography, natural history of the diseases, treatment, and screening parts. First, the demographic part simulates individual life histories, where each individual in the population has a date of birth and date of other cause of death. Following this, the natural history part simulates prostate cancer histories. Individuals may develop prostate cancer depending on the onset probability. Once a man develops prostate cancer, the cancer can progress to different preclinical states. There are 18 preclinical states as a combination of T-stages, Gleason scores, and metastatic stages. From these preclinical states the cancer has a chance to progress to clinical disease states. Third, the treatment part simulates the life histories after clinical detection. The screening part super-impose screening test(s) on the life histories in the absence of screening. Therefore, screening can alter a life history for a part of screen detected men.

1.9. RESEARCH QUESTIONS AND THESIS OUTLINE

This thesis is subdivided in three parts:

Part 1: PSA screening for prostate cancer

In this first part of the thesis, we will assess the role of modeling in the policy decision making process for (prostate) cancer screening. Furthermore, using the MISCAN-prostate cancer model, we will try to find an optimal prostate cancer

screening strategy at a population level by comparing several screening scenarios. Long-term effects such as prostate cancer mortality reduction, life-years gained, QALYs gained, overdiagnosis, and costs were considered in the comparison.

Research question 1: Can models provide additional insights beyond the observed data of randomized controlled trials? (Chapter 2)

Research question 2: Can we find an optimal cost-effective prostate cancer screening strategy at population level? If so, what are the associated long-term harms and benefits? (Chapter 3)

Part 2: Magnetic resonance imaging in prostate cancer screening

The introduction of mpMRI and targeted biopsy has changed the diagnostic pathway for prostate cancer, and various studies proposed MRI as a means for reducing the harms of PSA-based prostate cancer screening. However, given the natural history of prostate cancer there is lack of reports on the long-term effects of MRI based screening. Therefore, in the second part of this thesis, the long-term effects of MRI based prostate cancer screening will be compared with regular screening in a population-based screening setting.

Research question 3: Does the use of mpMRI as a triage test followed by an MRI-guided biopsy result in a better harm-benefit balance compared to regular PSA screening? (Chapter 4)

Research question 4: Is the MRI-based prostate cancer screening more cost-effective than the regular screening pathway? (Chapter 5)

Part 3: Decision tools

Although various studies have confirmed the benefits of organized PSA screening, almost no country has yet introduced a population-based screening program. Current prostate cancer guidelines recommend that the decision to undergo early PSA testing should be shared between patients and their physicians. However, the path from PSA testing to treating prostate cancer includes several decision points, and making the right decision at each of these points is not straightforward. This has led to the development of various prostate cancer risk prediction tools/calculators. Although the existing calculators have their own strength, they also lack several long-term (lifetime) predictions. Therefore, in the third part of the thesis, we will try to develop a decision tool that can supplement other risk prediction tools and

improve the patient-physician decisions about a PSA test and selection of immediate treatment for localized prostate cancer.

Research question 5: Can we develop an online tool, with long term predictions, for patient-physician decision about prostate cancer screening? (Chapter 6)

This thesis concludes, in chapter 7, with summery answers to and further discussion of the above research questions, as well as recommending future research directions.

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Part 1

PSA screening for prostate cancer

2 The role of modeling in the policy decision making process on cancer screening: example of prostate specific antigen screening

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ABSTRACT

Although randomised controlled trials are the preferred basis for policy decisions on cancer screening, it remains difficult to assess all downstream effects of screening, particularly when screening options other than those in the specific trial design are being considered. Simulation models of the natural history of disease can play a role in quantifying harms and benefits of cancer screening scenarios. Recently, the US Preventive Services Task Force issued a C-recommendation on screening for prostate cancer for men aged 55–69 years, implying at least moderate certainty that the benefit is small. However, modelling based on data from the European Randomized study of Screening for Prostate Cancer, which included quality-of-life estimates, showed that the ratio between benefits and harms is better, and likely to be reasonable, for men screened between the ages of 55 and 63 years (i.e. by using an earlier stopping age than applied in the trial setting). This commentary article considers the importance of simulation modelling in the decision-making process for (prostate) cancer screening. The paper also explores whether the recently published Cluster Randomized Trial of PSA Testing for Prostate Cancer, a trial of a single prostate specific antigen (PSA) testing intervention in the UK, changes the evidence for regular PSA testing for men aged 55–63 years by replicating the trial using a simulation model.

INTRODUCTION

Although randomised controlled trials (RCT) are preferred as the basis for decisions regarding efficacy of cancer screening, it is almost impossible to directly assess long-term effects of screening such as overdiagnosis, overtreatment or life-years gained. This would, for instance, require a long or even lifelong follow-up of individuals in both the screening and control arms of such trials. Furthermore, finding the optimal screening strategy for a population would require formal comparisons of different screening strategies, which is impossible to do in a single RCT. This complexity of decision making has led to the need for (simulation) modelling of the natural history of disease. Modelling allows the impact of various screening strategies, as well as the long-term effects of cancer screening, to be assessed, provided that the model is well calibrated and validated.

There are numerous examples of such quantifications being a valuable source for policy decision making. For example, the US Preventive Services Task Force (USPSTF)[1-3] used results from modelling studies by Cancer Intervention and Surveillance Modeling Network (CISNET) groups on lung, breast and colorectal cancer screening[4-6] to assess the optimum age at which to begin and end screening, the optimal screening interval, and the relative benefits and harms of different screening strategies. Similarly, the Dutch government has implemented a national program for colorectal cancer screening, for which the target age range, the type of test and the cut-off for referral were chosen based on modelling results from several pilot projects and predicted capacity needs for colonoscopy.[7] The BreastScreen Australia Evaluation Advisory Committee (EAC), in its final report[8], used evidence from modelling studies[9,10] on the effectiveness of breast cancer screening by age. A more recent Australian example was modelling to assess the possible benefits and cost-effectiveness of the renewed national cervical cancer screening program in Australia.[11]

PROSTATE CANCER SCREENING

The risks and benefits of prostate specific antigen (PSA) testing for prostate cancer at a population level have been reviewed for decades, yet no country in the world has found sufficient evidence to fund an organised screening program. Reviews, including in Australia, have deemed that the harms outweigh the benefits at a population level, due primarily to the low specificity of the PSA test and the risks of unnecessary invasive treatments with significant side-effects.[12] Prostate cancer is nonetheless a good example of how (simulation) modelling can help to answer important ques-

tions about improved targeting of early detection interventions, such as at what age a man might be encouraged to have his first PSA test and especially at what age a man who had already agreed to be tested might stop.

Existing guidelines on prostate specific antigen screening are contradictory.[13,14] For example, the USPSTF issued a C-recommendation on screening for prostate cancer for men aged 55–69 years, advising clinicians to inform men about the potential benefits (cancer deaths prevented, life-years gained and reduction of risk of advanced disease) and harms (overtreatment and living longer with the knowledge of a cancer diagnosis) of PSA screening.[13] According to the USPSTF, a C-recommendation means there is at least moderate certainty that the benefit is small, and, therefore, selectively offering the test to individual patients based on professional judgement and patient preferences might be appropriate. Based on the 13-year follow-up of the European Randomized study of Screening for Prostate Cancer (ERSPC) trial, the USPSTF concluded that screening may prevent one to two prostate cancer deaths (over 13 years) per 1000 men screened, and 20–50% of men detected by screening may be overdiagnosed. The risk of overdiagnosis was calculated by comparing the number of cancers diagnosed in the screening group with the number diagnosed in the control group over follow-up years. However, estimating overdiagnosis over the given trial period only is often not enough, and, given the natural history of prostate cancer, longer follow-up is needed or has to be simulated.

Pashayan et al.[15] concluded that the benefit of prostate cancer screening in reducing advanced stage disease is counterbalanced by overdiagnosis, the latter being especially more frequent at older ages (65–69 years). Pinsky et al[16] concluded that the burden from diagnosis of indolent disease (i.e. tumours that are unlikely to become symptomatic during a man's lifetime) should be reduced by not diagnosing indolent disease at all and by not aggressively treating diagnosed indolent disease. One of the possible solutions for this could be stopping screening before the age of 69. A model which had been developed in the Australian context did not clearly indicate a favourable harm–benefit ratio for prostate cancer screening.[17] A comprehensive Australian evaluation of the evidence also found no case for a PSA-based population screening program.[18] There may, however, be a role for modelling to help inform targeted approaches, beyond the guidance available through conventional evidence review.

PREDICTIONS FROM A MICRO-SIMULATION ANALYSIS MODEL (MISCAN)

A study using micro simulation analysis (MISCAN) model ,calibrated on ERSPC data and included quality-of-life estimates showed that the ratio between benefits and harms is better for men screened at 55–63 years of age than for the broader age band (55-69/74) screened in the trial.[19] The estimated effects of screening men in different age groups are shown in Table 1. Model simulation is over the lifetime and thus the numbers of prostate cancer deaths averted (5–10 per 1000 men) are larger than the prostate cancer mortality reduction found in the ERSPC trial at 13 years of follow-up. Screening in the 55–63 years age group leads to a smaller number of prostate cancer deaths averted – 7 per 1000 men, compared with 10 for the 55–69 years age group. However, the percentage loss in quality-adjusted life years (QALYs) – the difference between life years gained and QALYs gained divided by the life years gained – is smaller in the 55–63 years age group than in the 55–69 years age group; the number of overdiagnoses is also much lower (23 per 1000 men, compared with 49). Although the ratio between harms and benefits (overdiagnosis per prostate cancer death averted) is better for the initial core age group (55–69 years) than for the 64–69 years age group (who have the highest PSA test uptake in daily clinical practice), it is inferior to that for the 55–63 years age group (5.4 vs 3.2, respectively). This ratio of 3.2 between harms and benefits is almost similar to the ratio of 3 found by the UK independent breast screening panel.[20] The UK panel concluded that this ratio is acceptable for breast cancer screening.

Screening in the 55–63 years age group was found to have the best benefit and harm balance in this analysis. In such circumstances there may be a case for the USPSTF to consider a B-recommendation for PSA testing for the 55–63 or 55–59 years

Table 1. Estimated effects of screening men at 2-year intervals compared with no screening

Screening age group (years)	PC deaths averted[a]	Over-diagnosed cases[a]	Over-diagnosed cases per PC death averted	Life years gained[a]	Life years gained per PC death averted	QALYs gained[a]	QALYs gained per PC death averted	% loss in QALYs[b]
55–63	7.0	23	3.2	62	9.0	51	7.3	17
64–69	5.0	35	7.0	39	7.8	22	4.4	43
55–69	9.8	49	5.4	83	8.4	61	6.7	27

PC = prostate cancer; QALYs = quality-adjusted life years

[a] Per 1000 men screened

[b] Percentage loss in QALYs calculated as the difference between life years gained and QALYs gained, divided by the life years gained.

Note: Men are followed lifetime. A prostate specific antigen threshold of 3 ng/mL and an 80% attendance to the screening was assumed.

age groups, as this modelling indicates there is moderate certainty that the net benefit is moderate to substantial. Further work, including research that improves understanding of the complexities of overdiagnosis in these specific age groups, would add to the quality of information necessary to confidently recommend such a change.

ONE-TIME TESTING (CAP TRIAL) VERSUS REGULAR PSA TESTING (ERSPC)

The Cluster Randomized Trial of PSA Testing for Prostate Cancer (CAP), conducted in the UK with 408 825 men, is now the largest RCT on PSA screening.[21] However, in the CAP trial men were offered only one PSA test, and about 36% of them accepted that offer. Therefore, in practice, the number of PSA tests in the CAP trial is less than performed in the ERSPC trial (82 299 and 140 040, respectively). The result from the CAP trial must therefore be interpreted bearing in mind the low acceptance rate (36%) and single test applied only at age 50.

We used a well-validated natural history model (MISCAN) to replicate the CAP trial, as best as we could, based on UK life tables, men screened by age, ERSPC incidence, treatment and survival rates, and assuming an 80% biopsy compliance and limited contamination rate of 2% per year. Analogue to PLCO (Prostate, Lung, Colorectal, and Ovarian) Cancer Screening Trial-experiences[22], we assumed no difference in the natural history of prostate cancer, the performance of PSA testing and the benefit per screen in the UK compared with other countries in Europe or the US. Figure 1 shows our expected prostate cancer mortality curves for the screen and control arms of CAP. The small expected difference between the arms (given the one test at low compliance) is striking. We have estimated a prostate cancer mortality rate ratio of 0.94 after 10 years of follow-up, not much different from the observed point estimate of 0.96, and well within the 95% confidence interval (0.85, 1.08).

Extending the prostate cancer mortality prediction to 15 and 20 years of follow-up did not alter our estimate (0.94 and 0.95 mortality rate ratio, respectively). Therefore, our conclusion is that although the CAP-trial of a single PSA testing intervention did not show statistically significant differences in prostate cancer mortality after 10 years of follow-up, there may still be a potential mortality benefit demonstrated by microsimulation modelling. The low point estimate (4% statistically nonsignificant prostate cancer mortality reduction) observed in CAP cannot be interpreted to be inconsistent with the 27% benefit per screen as estimated from ERSPC, and con-

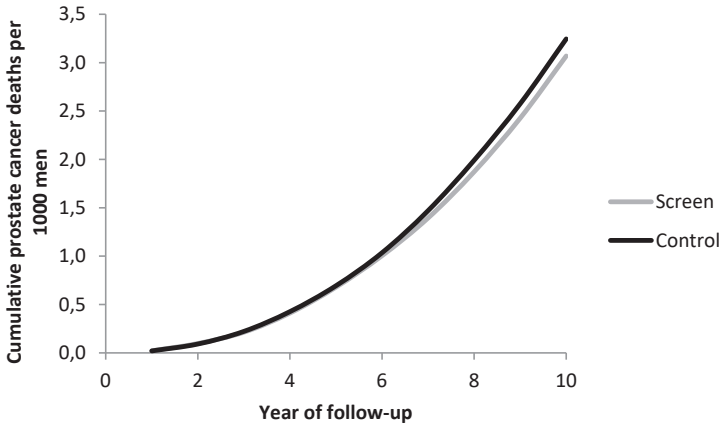

Figure 1. Cumulative number of prostate cancer deaths in both arms of the CAP trial by follow-up years, as predicted by MISCAN model.

firmed in PLCO. This implies that, even when a trial shows no mortality benefit, well-validated modelling can strengthen the evidence on targeted interventions for improved early detection.

MODEL VALIDATION

Validation is one of the main methods for achieving trust and confidence in healthcare models.[23] Model validation methods include: face validity, verification (or internal validity), cross validity, external validity and predictive validity; the latter has been suggested to be the most desirable method.[23] In several modelling studies, the CISNET models have been replicated by independent researchers (with external validation by others). For example, the MISCAN prostate model was replicated by independent researchers based on the reporting of all basic parameters in our papers.[24, 25] We have also described how the MISCAN model prediction of the impact of breast cancer screening fulfils predictive validity.[26] In short, MISCAN model predictions for the impact of breast cancer screening on incidence, made in 1994 for a steady-state screening situation[27], closely resemble the actual breast cancer incidence rates in 2010 in the Netherlands.

CONCLUSIONS

A well-validated (simulation) model can play a crucial role in the development of sound cancer control policies, particularly when RCTs and other empirical studies are unable to give information regarding the harm–benefit ratio in the long run, and an optimum age or interval to screen, because of a lack of diverse trials. In this commentary article, we showed how modelling is useful to quantify the ratio between harms and benefits, and evaluated an age category with a better harm–benefit balance for prostate cancer screening than was applied in the trials to show efficacy.

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3 Assessment of Harms, Benefits and Cost-effectiveness of Prostate Cancer Screening: A Micro-Simulation Study of 230 Scenarios

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ABSTRACT

Background: Prostate cancer screening incurs a high risk of overdiagnosis and overtreatment. An organised and age-targeted screening strategy may reduce the associated harms while retaining or enhancing the benefits.

Methods: Using a micro-simulation analysis (MISCAN) model, we assessed the harms, benefits and cost-effectiveness of 230 prostate-specific antigen (PSA) screening strategies in a Dutch population. Screening strategies were varied by screening start age (50, 51, 52, 53, 54 and 55), stop age (51-69) and intervals (1, 2, 3, 4, 8 and single test). Costs and effects of each screening strategy were compared with a no-screening scenario.

Results: The most optimum strategy would be screening with 3-year intervals at ages 55 to 64 resulting in an incremental cost-effectiveness ratio (ICER) of €19,733 per QALY. This strategy predicted a 27% prostate cancer mortality reduction and 28 life years gained (LYG) per 1,000 men; 36% of screen-detected men were overdiagnosed. Sensitivity analyses did not substantially alter the optimal screening strategy.

Conclusions: PSA screening beyond age 64 is not cost-effective and associated with a higher risk of overdiagnosis. Similarly, starting screening before age 55 is not a favoured strategy based on our cost-effectiveness analysis.

BACKGROUND

The incidence of prostate cancer has increased in most European countries, whereas prostate cancer mortality rates have declined.[1,2] Most Western European countries have experienced a sharp rise in the incidence of prostate cancer. The observed trend change in the incidence and mortality of prostate cancer may be partly related to opportunistic prostate-specific antigen (PSA) screening and advances in prostate cancer treatment and diagnostic procedures.[3] However, this progress is usually accompanied by a high risk of overdiagnosis. Various studies indicated that opportunistic PSA testing is less efficient and associated with a higher risk of overdiagnosis compared to organised screening.[4,5] An organised and age-targeted screening strategy may reduce the associated harms while retaining or enhancing the benefits.

While screening for prostate cancer remains controversial, various large-scale studies have confirmed the benefit of PSA screening.[6-8] Similarly a secondary analysis confirmed that the Prostate, Lung, Colorectal and Ovarian screening Trial (PLCO) and European Randomized Study of Screening for Prostate Cancer (ERSPC) provide a compelling and consistent evidence that screening reduces prostate cancer mortality.[9] However, the question as to the age at which PSA screening should start and especially at what age it should stop remains debatable, mainly because of the associated harms and costs. Finding the optimal screening strategy can lead to a better balance between the harms and benefits for citizens. Recently, the European Association of Urology (EAU) recommended that a baseline PSA test should be offered to men aged > 50 and, men > 45 years of age having a family history of prostate cancer or men of African-American origin,[10] whereas the US Preventive Services Task Force (USPSTF) recommended age 55 as the starting age and that the decision to undergo periodic PSA-based screening for prostate cancer should be an individual one.[11]

Even though evidence for the benefit of prostate cancer screening under age 55 seems less conclusive, there are some studies that suggest a benefit of screening between ages 50-54. Recently, the 18-year follow-up study from the Goteborg randomised control trial, one centre of the ERSPC trial, showed a large and statistically significant relative prostate cancer mortality reduction (RR = 0.31) for the attendees in this age group.[8] Similarly, two other recent studies indicated a possible benefit of screening for this age group.[12,13]. Although the overall result reported from the CAP (Cluster Randomized Trial of PSA Testing for Prostate Cancer) trial was insignificant, the highest prostate cancer mortality reduction was seen in this age group.[13] The

insignificant result from the CAP trial may be related to the single screening offered and its lower acceptance rate (36%).[14]

Although multiple studies on prostate cancer screening have been conducted, they have mainly focused on screening starting at age 55[6,7,15,16] or did not calculate life years gained or quality-adjusted life years (QALYs) gained.[17-19] Furthermore finding an optimum screening strategy requires comparison of several screening strategies. The present study aimed to assess the harms, benefits and an optimum cost-effectiveness scenario of prostate cancer screening for men from age 50 onwards in a Dutch population. 230 screening strategies were evaluated using a micro-simulation analysis model.

MATERIALS AND METHODS

Model description

For this study we used a micro-simulation screening analysis (MISCAN) model in order to assess the effects of prostate cancer screening. MISCAN prostate model has been described extensively before[6,20]. In short it is a stochastic model that simulates individual life histories of men and the natural life histories of prostate cancer. Overall, the model consists of 18 preclinical detectable states combined with three stages (T1, T2 and T3), three Gleason scores (7, less than 7 and greater than 7) and two metastatic states (local-regional and distant). Each individual in the simulation starts with no prostate cancer. Once the individual has prostate cancer, the cancer can progress to different screen-detectable preclinical states. From each preclinical state, the cancer has a probability to progress to clinical prostate cancer (detected by symptoms) (Figure 1).

In the model, prostate cancer incidence and mortality are first simulated in the absence of screening. Prostate cancer survival in the absence of treatment (baseline survival) was estimated at clinical detection based on surveillance, epidemiology and end results data from the pre-PSA era (1983-1986). Those clinically detected men with local disease and having received primary treatment (radical prostatectomy or radiation therapy) have improved survival rates with a hazard ratio of 0.56 compared to baseline survival.[21] For distant cases it is assumed that treatment has no effect on survival. Following this, the effect of PSA screening on the natural history of prostate cancer is simulated. In our model, the effect of PSA screening on prostate cancer mortality is dependent on the lead time using a lead time-dependent cure probability.[22]

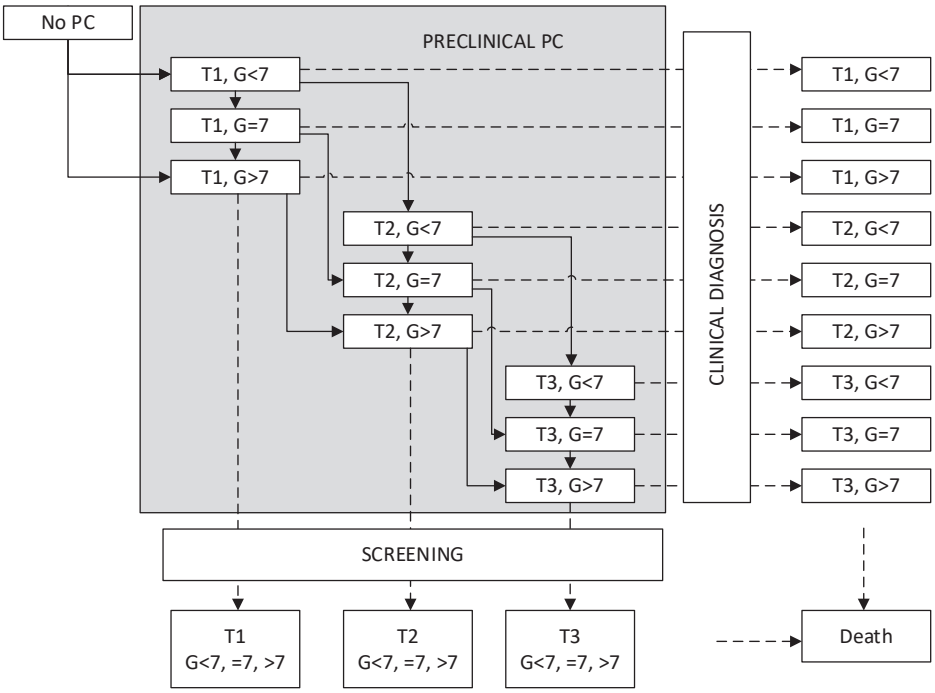

Figure 1. The MISCAN prostate cancer model. The model also contains a distinction between local and distant stages, but for the sake of simplicity it is not illustrated here. T= tumor stage and G = Gleason score

In our model, the allocation of treatments (radical prostatectomy, radiation therapy and active surveillance) after the diagnosis of prostate cancer was based on age, stage and Gleason score as described in previous studies.[3,22] It was assumed that 30% of men switch from active surveillance to secondary treatment during the first seven years.[6] A Dutch life table was applied to model non-prostate cancer related death.[23]

Model calibration

The MISCAN prostate model was previously calibrated to ERSPC data by estimating parameters on duration, sensitivity and lead time dependent cure probability.[15] In order to adapt the model to the Dutch situation and also account for younger age groups (50-54), the model was calibrated to prostate cancer incidence among the Dutch population between 1989 and 2013 by 5-year age categories from age 50 to age 75.[24] Furthermore, prostate cancer mortality predicted by the model was compared with observed prostate cancer mortality (among the Dutch population) over the same period (1989-2013) to validate our model. More information on the calibration of the model is available in the supplementary part of this manuscript. Additional

descriptions about the four components of MISCAN prostate model (demography, natural history, screening and treatment) can be found at https://cisnet.flexkb.net/mp/pub/CISNET_ModelProfile_PROSTATE_ERASMUS_001_12152009_69754.pdf.

Screening strategies

A hypothetical cohort of 10 million men in the Netherlands aged 50 in 2020 was sampled and simulated over a lifetime period. The reason why we used a larger sample size than the male population in the Netherlands is to avoid a stochastic noise in the model. This number was selected by increasing the sample size until the model outputs get stable. Screening strategies were varied by screening start age, stop age and screening intervals. The screening start age varied between 50 and 55 years, and the age at which screening was stopped varied between the screening start ages and age 69. Screening intervals of one, two, three, four and eight years and once-in-a-lifetime screenings were applied.

In our study the biopsy compliance rate after a positive screen test result was assumed to be 90%, with a sensitivity of 90% as observed in the ERSPC Rotterdam data[25,26]. Most ERSPC centres used a PSA cutoff value of 3 ng per milliliter as an indication for biopsy[27], and a similar cutoff was used in our model. A screening attendance of 80% was assumed. For each strategy a total number of invitations, PSA tests done, prostate cancer detected (with and without screening), overdiagnosed cancer, prostate cancer death (with and without screening) and life years gained were predicted. The total number of biopsies was estimated by using the number of screen detected cancers and a mean positive predictive value of 22.7% of a biopsy in the screen arm of the ERSPC[26] and by using the number of clinically detected cancers and the positive predictive value of 35.8% of a biopsy in the control arm.[28]

For each screening strategy, overdiagnosis was estimated as a proportion of screen-detected prostate cancers (i.e. overdiagnosed prostate cancers divide by screen detected prostate cancers). The screen detected prostate cancers composed of both overdiagnosed prostate cancers and relevant (non overdiagnosed) prostate cancers. The term overdiagnosis was defined as the detection of a prostate cancer during screening that would not have been clinically diagnosed during the man's lifetime in the absence of screening. All the outcomes (costs and effects) were estimated over a lifetime period and presented per 1,000 men.

Quality of life, costs and cost effectiveness

All utility estimates, unit costs (costs of screening, biopsy, primary treatment, follow-up and palliative care for advanced cases) and durations in screening, biopsy

and treatment phases were obtained from a previous study[6] (Supplementary Table 1). Our analysis did not consider indirect costs. As described in a previous study[15], the utility estimates for the post recovery period was obtained by combining the percentage of men with side effects from treatment with the utility estimates for those side effects. This resulted in a utility estimates of 0.95 for all men during the period of 1-10 years after diagnosis and after receiving radical prostatectomy or radiation therapy. The utility estimates range between 0 (death) and 1 (perfect health) and one minus the utility estimate gives a loss in utility at each health state. The total loss in quality of life was estimated as follows:

$$\sum_{i=1}^{k} (1 - u_i) * d_i * n_i$$

where u, d and n represent the utility estimate, duration (in years, e.g. 2 months = 1/6 year) and number of men in each health state (i) respectively. The utility estimates and durations are presented in Appendix Table 1. The number of men in each health state was based on the model prediction. The letter "k" indicates the total number of health states.

QALYs gained were calculated by subtracting the total loss in quality of life from the net life years gained as a result of screening.

After determining the costs and effects of each screening strategy, the results were compared with a no-screening scenario. Both strategies that were at least as expensive as and less effective (also called "strongly dominated strategies") than an alternative option and weakly dominated strategies were excluded from the cost-effectiveness analyses. A weakly dominated strategy is defined as a strategy whose incremental cost-effectiveness ratio (ICER) is greater than that of a more effective strategy[29]. The remaining strategies were regarded as efficient strategies and listed from lowest to highest according to their ICER. The ICER was calculated as the additional costs divided by additional QALYs gained compared with the previous less expensive strategy. The optimum efficient strategy was identified by comparing the ICERs with the willingness-to-pay (WTP) threshold per QALY. Considering a commonly used WTP threshold of €20,000 in a Dutch situation[30], a strategy (among efficient strategies) with the highest ICER below this threshold was taken as the optimum strategy. All costs and effects were estimated at a discount rate of 3.5% and presented in comparison with the no-screen scenario, unless otherwise stated.

Sensitivity analysis

Univariate sensitivity analyses were conducted to test the robustness of the model results under different assumptions. Utility estimates of different health states and costs of screening, diagnosis and treatment were the selected parameters for these analyses. The utility estimates in each health state (except for the terminal illness and palliative therapy) was varied using the highest (favourable) and lowest (unfavourable) value (Appendix Table 1). For the terminal illness and palliative therapy, it is favourable for screening when the utility is low [15]. All costs were varied by ±20%.

RESULTS

Calibration and validation

Our model adequately predicted the prostate cancer incidence trends in the Netherlands between 1989 and 2013 (Supplementary Figure 1). Furthermore, the model reasonably predicted the prostate cancer mortality in the Netherlands (except for the 70-74 age group) over the same time period (1989-2013), and this was taken as validation of the model (Supplementary Figure 2).

Effects of various screening strategies

For single screening strategies (once only), screening at age 57 was found to be most efficient which resulted a 9.5 life years gain and 8.2 % prostate cancer mortality reduction, with 31 % of screen detected cancer overdiagnosed. Screening at 4- years interval from age 55 to 59 (2 tests) and at 3- years interval from age 55 to 61 (3 tests) were found to be other efficient strategies with ICER below the optimum cost effectiveness cut-off (Table 1). Screening at 3-years intervals from age 55 to 64 (4 tests) was regarded as the optimum screening strategy with an ICER closest to the optimum cost effectiveness cut-off. Biennial screening between 51-69 (9 tests) and annual screening between age 50-69 (20 tests) were accompanied by a maximum life years gain of 41 and 47 years per 1,000 men with a 42% and 47% life time prostate cancer mortality reduction respectively. However, these benefits were accompanied by a higher risk of overdiagnosis (39 % and 41% respectively) (Table 1) and higher net costs for the corresponding life years or QALYs gained (Appendix Figure 3, and Figure 2) compared to other strategies. The fewest life years were gained with a single screening at age 50. In a one-time screening strategy the highest QALYs were attained at age 62. For all screening intervals used in our study, screening between an age group 50-54 generally yielded a lower number life years gain and prostate cancer mortality reduction than screening in age groups 55-59 or 55-64. The harms,

Table 1. Harms, benefits and ICER for the efficient screening strategies. Results per 1000 men invited.

Screening age	Number of tests	Screening interval	PCM reduction %	Overdiagnosis, as % of screen detected men	ICER in € Per QALY
56 single test	1	-	6.9	29.3	10,211
57 single test	1	-	8.2	30.7	10,946
55-58	2	3	12.2	31.4	12,814
55-59	2	4	13.8	31.6	13,129
55-61	3	3	19.8	34.6	14,738
54-63	4	3	25.1	34.7	18,417
55-64	4	3	27.2	35.8	19,733
54-64	6	2	30	34.9	22,395
55-65	6	2	32.2	36	24,589
53-65	7	2	33	35.6	24,819
54-66	7	2	35	36.7	28,053
53-67	8	2	37.6	37.4	29,565
52-68	9	2	39	38.1	36,805
50-68	10	2	40.3	37.9	43,831
51-69	10	2	42	38.9	50,572
53-69	17	1	46	38	55,083
52-69	18	1	46.4	37.9	57,448
50-69	20	1	46.9	41.3	97,784

ICER= incremental cost-effectiveness ratio; PCM= prostate cancer mortality; QALY = quality adjusted life years

benefits and total net costs for each screening strategy are presented in the appendix (Supplementary Table 2).

Cost effectiveness

The total costs of prostate cancer screening, diagnosis and treatment ranged from €739,561 at no screening to €1,583,786 with annual screening of age 50-69 per 1,000 men (3.5% discounted). The ICER of efficient strategies, strategies on the efficient frontier, increased from €10,211 per QALY (single test at age 56) to €97,784 per QALY (annual screening between ages 50-69). As indicated in Table 1, most of the efficient strategies use a screening interval of three years or less, and screening strategies beyond age 64 were found to be less cost-effective and associated with higher probabilities of overdiagnosis. Screening at 3-year intervals from ages 55 to 64 resulted in an ICER of €19,733 per QALY, which is closest to the WTP threshold of €20,000 per QALY, and regarded as the optimum strategy. A 27% prostate cancer mortality reduction and 28 life years gained per 1,000 men were predicated in association with this strategy. Of all screen-detected men using this strategy, 36%

were overdiagnosed. Extending the screening start age before age 55 (age 50 at the earliest) is less desirable (Table 1).

Sensitivity Analyses

The results from the sensitivity analyses showed that for 77% of the analyses, screening from age 55-64 with 3-year screening intervals remained an optimal strategy, as in the base case scenario. Varying the utility estimate of the post-recovery period produced the greatest effect on screening stop age, screening frequency and incremental cost-effectiveness ratio of the optimum strategy. Using an unfavourable utility estimate for this parameter shifted the screening stop age of the optimum strategy from 64 to 61 (compared with the base case) with an ICER of €15,816. When the highest utility estimate was assumed for the same parameter, the screening stop age increased from 64 to 65, the screening frequency went from 3 to 2, QALYs gained rose from 24 to 33 (with a proportionate increase in the probability of overdiagnosis) and the ICER fell by 30%. A ±20% variation in unit costs caused the ICER of the optimum strategy to vary between €17,429 and €19,986 and also proportionately increased the effect of changing treatment costs (Table 2).

Table 2. Optimal strategies in base case and under a variety of different assumptions with their incremental cost effectiveness ratio.

Parameter	Optimum strategy		ICER in €
	Screening age	Interval	
Base case	55-64	3	19,733
Highest utility for screening attendance	54-63	3	17,960
Lowest utility for screening attendance	55-64	3	19,416
Highest utility for diagnostic phase	55-64	3	19,371
Lowest utility for diagnostic phase	54-63	3	18,582
Highest utility for diagnosis	55-64	3	19,615
Lowest utility for diagnosis	55-64	3	19,853
Highest utility at 2 months after RP treatment	55-64	3	19,284
Lowest utility at 2 months after RP treatment	55-64	3	19,956
Highest utility at 2 months after RT treatment	55-64	3	19,516
Lowest utility at 2 months after RT treatment	55-64	3	19,771
Highest utility at 2 months to 1 year after RP treatment	55-64	3	18,427
Lowest utility at 2 months to 1 year after RP treatment	54-63	3	19,427
Highest utility at 2 months to 1 year after RT treatment	55-64	3	18,835
Lowest utility at 2 months to 1 year after RT treatment	54-63	3	19,494
Highest utility for AS	55-64	3	17,630

Table 2. Optimal strategies in base case and under a variety of different assumptions with their incremental cost effectiveness ratio. (continued)

Parameter	Optimum strategy		ICER in €
	Screening age	Interval	
Lowest utility for AS	55-61	3	19,217
Highest utility for post recovery period	55-65	2	19,150
Lowest utility for post recovery period	55-61	3	15,816
Highest utility for Palliative therapy	55-61	3	17,085
Lowest utility for Palliative therapy	55-67	2	18,133
Highest utility for terminal illness	54-63	3	18,732
Lowest utility for terminal illness	55-64	3	19,380
Costs of PSA test +20%	54-63	3	18,710
Costs of PSA test -20%	55-63	2	19,472
Costs of invitation +20%	55-64	3	19,673
Costs of invitation -20%	55-64	3	19,794
Costs of biopsy +20%	54-63	3	18,664
Costs of biopsy -20%	55-64	3	19,343
Costs of RP +20%	55-64	3	19,562
Costs of RP -20%	55-64	3	17,697
Costs of RT +20%	54-63	3	19,986
Costs of RT -20%	55-64	3	17,429
Costs of AS +20%	54-63	3	18,710
Costs of AS -20%	55-64	3	19,267
Costs of staging +20%	55-64	3	19,815
Costs of staging -20%	55-64	3	19,651
Costs of follow-up +20%	55-64	3	19,783
Costs of follow-up -20%	55-64	3	19,683
Costs of advanced case +20%	55-64	3	18,940
Costs of advanced case -20%	54-63	3	18,989

AS = active surveillance; ICER= incremental cost-effectiveness ratio; RP = radical prostatectomy; RT= radiation therapy

DISCUSSION

According to the model predictions, the highest QALYs were estimated for age 62 in a one-time screening strategy; extending once-only screening to age 69 resulted in a loss in QALYs. However, extending the screening stop age yielded additional QALYs for the other strategies (Figure 2). This study shows that screening strategies with intervals of four years or shorter were more efficient than strategies with longer intervals. With 3-year intervals, screening between ages 55 to 64 was found to be the

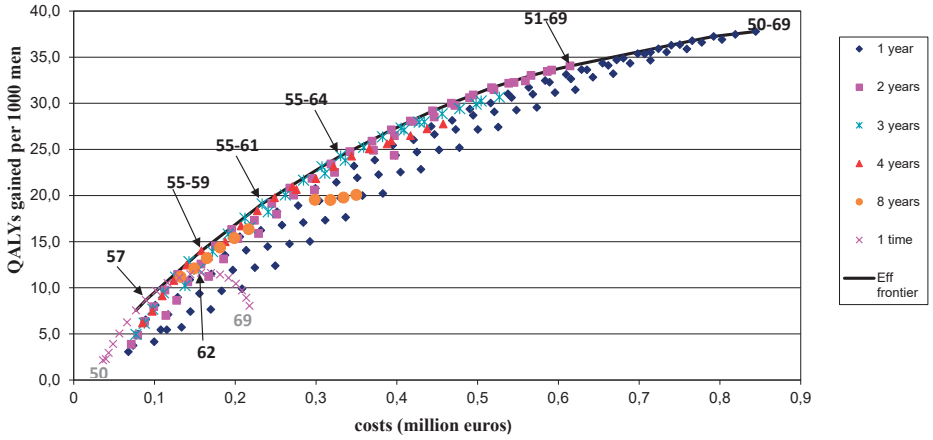

Figure 2. Net costs and QALYs gained per 1,000 men. The start and end age of most optimal strategies given 1,2,3,4,8 and once depicted in the figure. Numbers in the legend indicate the screening intervals used in the model. Eff frontier = efficient frontier.

optimum strategy. Screening beyond age 64 is less cost-effective and associated with a higher risk of overdiagnosis.

When comparing screening between age group 50-54 and age groups 55-59 or 55-64, the former resulted in lower life years and QALYs gain, and lower prostate cancer mortality reduction than the other two age groups. The difference in prostate cancer mortality benefit between these strategies may be due to the lower chance of lethal prostate cancer among younger age groups.

An earlier study with our model showed an increasing trend in QALYs gained only up to age 63. QALYs started to fall when screening stop age extended beyond this age.[6] A possible explanation for these contradictory results could be more effectiveness, and the lower overdiagnosis predicted in this study using the updated model compared to the previous one, because treating overdiagnosed cancer is the main cause of QALY loss. Updates in the model inputs (hazard of clinical prostate cancer detection and/or hazards of onset of a pre-clinical prostate tumor) in the current study could be the reason for the different overdiagnosis projections in the present and earlier study[6]. On the other hand our findings are consistent with the earlier study with our model that screening is less cost effective at higher age and with longer screening intervals. When the optimum strategy in the current study was compared with that in the previous study (age group 55-59 with 2-year intervals), it resulted in ten more life years gained at a much lower ICER and a 3% higher probability of overdiagnosis.[6] The 27% prostate cancer mortality reduction estimated for

the optimum strategy in the present study is in the same order as the 30% breast cancer mortality reduction reported in population-based breast cancer screening, which is already established in the Netherlands[31].

Generally, much lower net costs of screening and higher QALYs were predicted in the present study (Figure 2) as compared with some previous cost-effectiveness studies.[6,32,33] Factors that could explain this difference include differences in background risk (incidence), model assumptions and proportions of cases assigned in each treatment category (radical prostatectomy, radiation therapy and active surveillance). The higher QALYs gained reported in our study is in line with two previous studies.[15,34]

Most of the results in our study are robust for the univariate sensitivity analyses. However, there are some parameters that produced a considerable effect on quality of life, which in turn altered the optimum strategy. Among these, the utility of post-recovery treatment is the principal one. This is due to the longer duration (nine years in our study) of this health state compared to the other health states. The use of a favourable utility estimate for this health state increased the QALYs gain by 8 at a lower ICER, whereas an unfavourable utility reduced the QALYs gain by 6 compared to the base case scenario. Men undergoing prostatectomy or radiation therapy for localised prostate cancer experience a decline in all functional outcomes (urinary, sexual and bowel functions) throughout early, intermediate and long-term follow-up.[35]

To our knowledge, the present study is the first that assesses the harms, benefits and cost-effectiveness of prostate cancer screening using Dutch population data. In addition, the existing studies, none of which are specific to the Netherlands, mainly focused on screening starting at age 55.[6,7,15,16] Therefore, the main strength of our study is that we were capable of considering screening before age 55, unlike several previous studies that mentioned this point as one of their study limitations.[6,15,16] Another strength of this study is that we evaluated 230 screening scenarios, and find possible to be recommend strategies when choosing for 1,2,3 or 4 tests.

Our study also had some limitations. Firstly, we did not use risk-stratified screening. Several studies suggest risk-based screening (for instance, screening based on PSA level) as one method to reduce overdiagnosis.[36,37] Similarly, various studies suggest that a magnetic resonance imaging (MRI) guided biopsy could minimise the risk of overdiagnosis,[38-40] but MRI is not included in our screening protocol. We did not consider indirect costs in our analysis. Therefore, the actual total costs of prostate cancer screening may turn out to be higher than estimated in our study. Finally,

our results are from a population based screening, and this may not be directly applicable in clinical practice under certain conditions. For instance a man with high risk of prostate cancer may benefit from screening/rescreening beyond the screening stop age recommended in our study. Further studies that include selection of men based on their risk, such as using baseline PSA, comorbidity status or using nomograms and/or MRI as triage test may allow to screen older age groups with a minimal harm, or may improve the cost-effectiveness.

In conclusion, our results indicate that PSA screening beyond age 64 is not cost-effective and associated with a higher risk of overdiagnosis. Likewise, starting screening before age 55 is not a favoured strategy based on our cost-effectiveness analysis. Screening men with 4 tests maximum, from ages 55 to 64 with 3-year intervals is considered the optimum screening strategy at a WTP threshold of €20,000.

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SUPPLEMENTARY MATERIALS

Calibration and validation of the model

We used the model of Heijnsdijk et al. 2015 as a base for this study[15]. Model parameters for the natural history of prostate cancer (including transition probabilities and mean dwelling time), stage dependent test sensitivities and lead time dependent cure probability were estimated based on the following data:

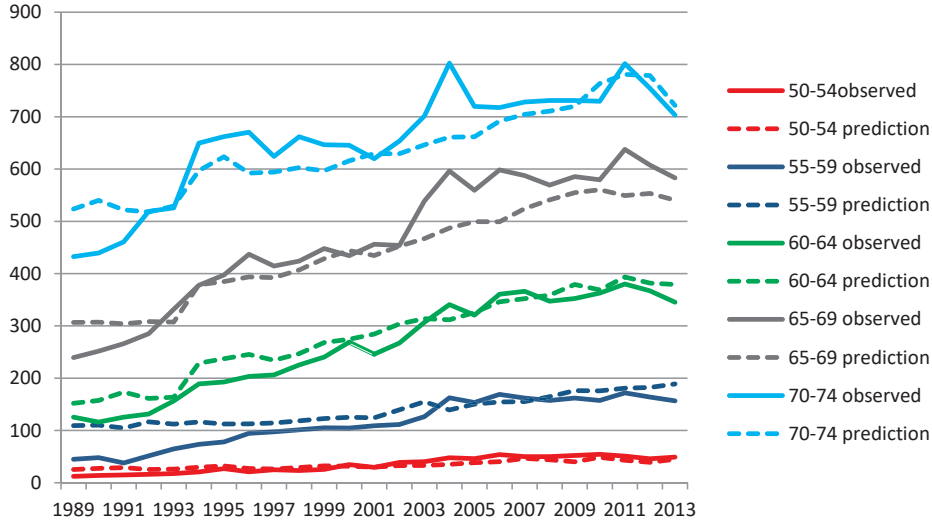
- Baseline incidence and stage distribution in 1991-1993 in the Netherlands,
- ERSPC Rotterdam trial data up to July 2004 (screen results until 2006) for both arms of the trial,
- Baseline incidence in Sweden in 1990, and
- ERSPC results of Göteborg up to end of 2004.

During the calibration, the baseline incidence and incidence in control arm, detection rate in first and subsequent screens, interval cancers, clinical T-stage distribution, metastatic state and biopsy Gleason score distribution were used. In addition, the model was calibrated to the incidence of the Dutch population in 1992–2002.

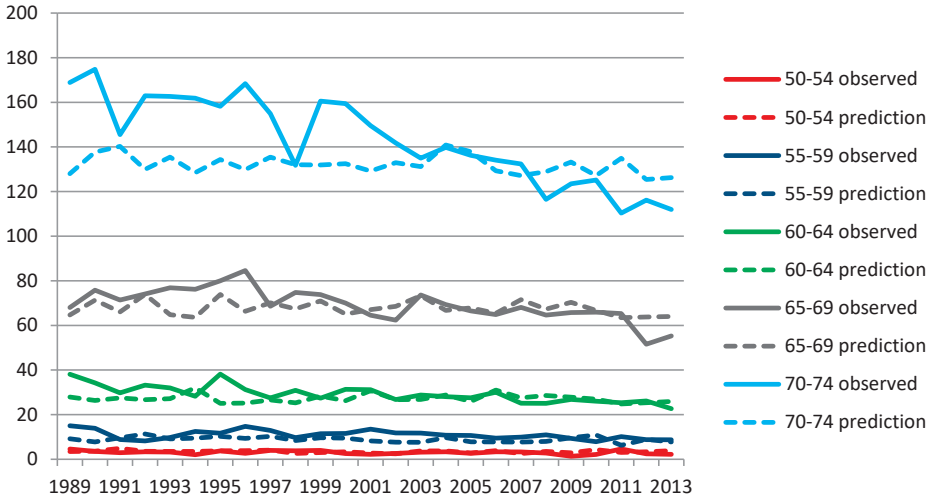
Model updates in the current study

Because the previous model didn't account for men younger than 55 years, we recalibrated the model to Dutch incidence between 1989 to 2013 by 5-year age categories from age 50 to age 75. Parameters for the hazards of onset of a pre-clinical prostate tumor and clinical prostate cancer detection were calibrated to these data. During the calibration, for the period 1989 to 1992 we used no screening, and after 1992 we used an estimate of increasing opportunistic PSA screening in the Netherlands, varying from 16% (within five years) for age group 50-55% to 41% (within five years) for age group 65-75% (based on CBS.nl).

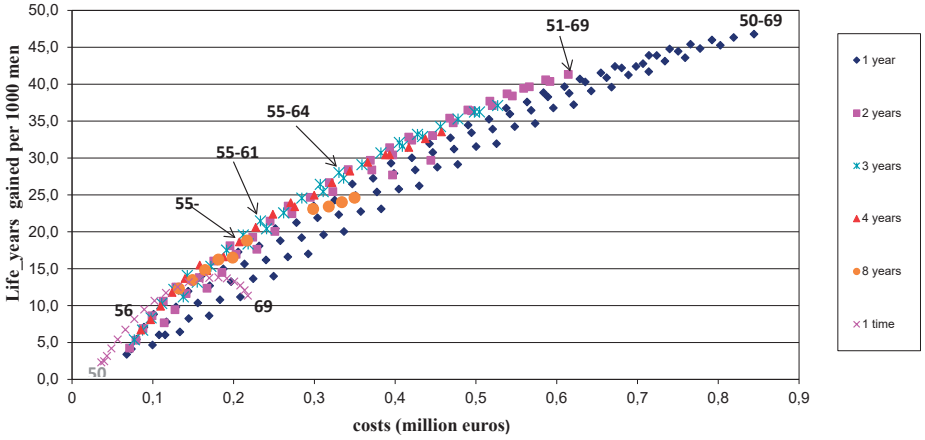
Following this, we projected the incidence of prostate cancer (to check the performance of the calibration) over the period from 1989 to 2013 by 5 years age category from age 50 to 75 (with no screening scenario from year 1989 to 1992, and with opportunistic screening from year 1993 to 2013 (Supplementary Figure 1). We also predicted the prostate cancer mortality over the same period, age categories and screening strategies, and compared with the observed prostate cancer mortality among the Dutch population to validate our model, Supplementary Figure 2. (**Note:** the model was not calibrated to the Dutch prostate cancer mortality data).



Supplementary Figure 1. Observed and predicted prostate cancer incidence rates per 100,000 men across different age categories.



Supplementary Figure 2. Observed and predicted prostate cancer mortality rates per 100,000 men across different age categories.



Supplementary Figure 3. Net costs and life-years gained per 1000 men. The start and end age of most optimal strategies given 1,2,3,4,8 and once depicted in the figure. Numbers in the legend indicate the screening intervals used in the model.

Supplementary Table 1. Costs, utility estimates and durations of the various phases in screening, diagnosis and treatment taken from a previous publication[6] and costs were converted to euro. The utility estimate for the terminal illness was updated.

Intervention	Unit costs in euros	Health states	Utility estimates (range)	Duration
Screening	34	Screening attendance	0.99 (0.98-1)	1 week
Invitation	2.8			
Blood sample taking	13.5			
PSA determination	17.7			
Diagnosis	241.3			
Biopsy	130.7	Diagnostic phase	0.90 (0.87- 0.94)	3 weeks
PA research	47	Diagnosis	0.80 (0.75 -0.85)	1 months
GP consulting	63.6			
PT and follow up				
Staging	283.9	RP		
RP	16,753.7	at 2 month after		
RT	20,128.8	procedure	0.67 (0.56-0.90)	2 months
AS	2,254.1	at >2 month to 1 y	0.77 (0.70-0.91))	10 months
19 PSA tests	592.3	RT		
10 DRE	696.8	at 2 month after		
4 biopsies	965	procedure	0.73 (0.71-0.91)	2 months
Follow-up	213.4	at >2 month to 1 y	0.78 (0.61-0.88)	10 months
		Active surveillance	0.97 (0.85-1.00)	Maximum 7 years
		One year after treatment	0.95 (0.93-1.00	9 years
Advanced disease				
Palliative therapy	17,420	Palliative therapy	0.60 (0.24-0.86)	30 months
		Terminal illness	0.40 (0.24-0.56)	6 months

DRE = digital rectal examination; GP = general practitioner; PA = pathological research; PSA = prostate-specific antigen; RP = radical prostatectomy; RT= radiation therapy; AS= Active surveillance (Active surveillance consists of multiple tests and corresponding costs are presented) .

Supplementary Table 2. Harms, benefits and net costs of each screening strategies per 1000 men‡

Screening age	Interval	LYs_gain#	PCMR %#	Overdiagnosis, as % of screen detected men	Total net costs # in Euro
50-51	1	3.4	2.3	21.6	67,707
50-52	1	4.7	3.3	22.3	99,584
50-53	1	6.4	4.7	23.3	133,498
50-54	1	8.6	6.5	24.4	169,745
50-55	1	11.2	8.6	25.5	208,405
50-56	1	14	11.1	26.5	249,548
50-57	1	17	13.8	27.3	292,412
50-58	1	20	16.6	28.2	336,676
50-59	1	23.1	19.6	29.1	382,703
50-60	1	26.2	22.6	30	429,866
50-61	1	29.1	25.7	30.9	477,467
50-62	1	31.9	28.7	31.8	525,498
50-63	1	34.7	31.7	32.7	573,338
50-64	1	37.2	34.7	33.5	621,025
50-65	1	39.6	37.5	34.4	667,855
50-66	1	41.7	40.1	35.2	713,978
50-67	1	43.6	42.5	36.1	758,951
50-68	1	45.3	44.8	36.9	802,555
50-69	1	46.8	46.9	41.3	844,225
51-52	1	4.1	3	23	73,544
51-53	1	6	4.5	23.8	107,807
51-54	1	8.3	6.3	24.7	144,430
51-55	1	10.8	8.4	25.8	183,186
51-56	1	13.6	10.9	26.6	224,257
51-57	1	16.6	13.6	27.5	267,187
51-58	1	19.6	16.4	28.3	311,373
51-59	1	22.7	19.4	29.2	357,388
51-60	1	25.8	22.4	30.1	404,547
51-61	1	28.8	25.5	31	452,259
51-62	1	31.5	28.5	31.9	500,233
51-63	1	34.3	31.5	32.8	548,052
51-64	1	36.8	34.4	33.6	595,816
51-65	1	39.1	37.2	34.5	642,755
51-66	1	41.3	39.8	35.3	688,839

Supplementary Table 2. Harms, benefits and net costs of each screening strategies per 1000 men‡ (continued)

Screening age	Interval	LYs_gain#	PCMR %#	Overdiagnosis, as % of screen detected men	Total net costs # in Euro
51-67	1	43.1	42.2	36.2	733,941
51-68	1	44.8	44.5	37	777,471
51-69	1	46.3	46.6	37.8	819,072
	1				
52-53	1	5.4	4.1	24.4	79,699
52-54	1	7.8	6	25.2	116,875
52-55	1	10.4	8.2	26.1	155,743
52-56	1	13.2	10.7	26.9	196,943
52-57	1	16.2	13.3	27.7	240,124
52-58	1	19.2	16.1	28.5	284,281
52-59	1	22.3	19.2	29.4	330,255
52-60	1	25.4	22.2	30.3	377,417
52-61	1	28.4	25.2	31.1	424,863
52-62	1	31.2	28.3	32	472,914
52-63	1	33.9	31.3	32.8	520,708
52-64	1	36.5	34.2	33.7	568,380
52-65	1	38.8	37	34.5	615,482
52-66	1	40.9	39.6	35.4	661,786
52-67	1	42.8	42	36.2	706,785
52-68	1	44.5	44.2	37.1	750,387
52-69	1	46	46.4	37.9	792,212
53-54	1	7.1	5.5	25.8	89,035
53-55	1	9.8	7.8	26.6	128,741
53-56	1	12.7	10.3	27.4	170,345
53-57	1	15.7	13	28.1	213,459
53-58	1	18.8	15.9	28.7	257,824
53-59	1	21.8	18.9	29.6	303,889
53-60	1	24.9	21.9	30.5	350,978
53-61	1	27.9	24.9	31.3	398,585
53-62	1	30.8	28	32.2	446,605
53-63	1	33.4	31	33	494,465
53-64	1	36	33.9	33.8	542,079
53-65	1	38.3	36.6	34.7	589,078
53-66	1	40.3	39.2	35.5	635,337
53-67	1	42.2	41.6	36.4	680,448

Supplementary Table 2. Harms, benefits and net costs of each screening strategies per 1000 men‡ (continued)

Screening age	Interval	LYs_gain#	PCMR %#	Overdiagnosis, as % of screen detected men	Total net costs # in Euro
53-68	1	43.9	43.8	37.2	723,806
53-69	1	45.4	45.9	38	765,672
54-55	1	8.8	7.2	27.3	100,959
54-56	1	11.9	9.9	27.8	143,724
54-57	1	15	12.5	28.5	187,272
54-58	1	18.1	15.4	29.2	231,611
54-59	1	21.2	18.5	29.9	277,808
54-60	1	24.3	21.5	30.8	325,116
54-61	1	27.3	24.6	31.6	372,670
54-62	1	30	27.6	32.4	420,723
54-63	1	32.7	30.5	33.2	468,495
54-64	1	35.3	33.4	34.1	516,234
54-65	1	37.6	36.2	34.9	563,323
54-66	1	39.7	38.8	35.7	609,601
54-67	1	41.5	41.2	36.5	654,668
54-68	1	43.2	43.5	37.3	698,195
54-69	1	44.8	45.6	38.1	739,779
55-56	1	10.8	9	28.6	115,304
55-57	1	14.1	12	29.1	160,657
55-58	1	17.3	14.9	29.7	205,699
55-59	1	20.4	17.9	30.4	251,798
55-60	1	23.5	21	31.2	299,239
55-61	1	26.5	24.1	32	347,007
55-62	1	29.3	17.1	32.7	394,898
55-63	1	31.9	30	33.5	442,567
55-64	1	34.5	32.9	34.3	490,374
55-65	1	36.8	25.7	35.2	537,560
55-66	1	38.9	38.3	36	583,689
55-67	1	40.7	40.7	36.8	628,750
55-68	1	42.4	42.9	37.6	672,170
55-69	1	43.9	45	38.4	714,210
50-52	2	4.2	3	22.7	71,321
50-54	2	7.7	5.8	24.7	114,180

Supplementary Table 2. Harms, benefits and net costs of each screening strategies per 1000 men‡ (continued)

Screening age	Interval	LYs_gain#	PCMR %#	Overdiagnosis, as % of screen detected men	Total net costs # in Euro
50-56	2	12.3	9.8	26.8	167,204
50-58	2	17.6	14.7	28.7	228,879
50-60	2	23.1	20.2	30.8	298,127
50-62	2	28.4	25.7	32.6	371,283
50-64	2	33	31.1	34.4	446,379
50-66	2	37.1	36	36.2	520,377
50-68	2	40.3	40.3	37.9	591,728
51-53	2	5.3	4	24.1	79,266
51-55	2	9.4	7.4	26.2	127,589
51-57	2	14.5	11.9	28.1	185,639
51-59	2	20	17.2	29.9	251,177
51-61	2	25.4	22.7	31.8	322,930
51-63	2	30.4	28.2	33.6	397,136
51-65	2	34.8	33.4	35.4	471,937
51-67	2	38.4	38	37.2	545,195
51-69	2	41.3	42	38.9	614,461
52-54	2	6.9	5.3	25.5	87,856
52-56	2	11.6	9.4	27.2	141,295
52-58	2	16.9	14.3	29.1	203,241
52-60	2	22.4	19.8	31	272,344
52-62	2	27.7	25.3	32.8	396,875
52-64	2	32.4	30.7	34.6	420,685
52-66	2	36.4	35.6	36.4	494,786
52-68	2	39.6	39	38.1	566,150
53-55	2	8.6	6.9	27	99,182
53-57	2	13.8	11.5	28.5	157,624
53-59	2	19.3	16.7	30.3	223,847
53-61	2	24.7	22.3	32.1	295,114
53-63	2	29.7	27.8	33.8	369,373
53-65	2	34	33	35.6	444,315
53-67	2	37.7	37.6	37.4	517,344
53-69	2	40.6	41.6	39.1	586,440

Supplementary Table 2. Harms, benefits and net costs of each screening strategies per 1000 men‡ (continued)

Screening age	Interval	LYs_gain#	PCMR %#	Overdiagnosis, as % of screen detected men	Total net costs # in Euro
54-56	2	10.6	8.7	28.1	113,032
54-58	2	16	13.8	29.5	175,548
54-60	2	21.4	19.1	31.5	245,277
54-62	2	26.7	24.7	33.2	318,595
54-64	2	31.4	30	34.9	393,306
54-66	2	35.4	35	36.6	467,617
54-68	2	38.7	39.3	38.3	538,613
55-57	2	12.5	10.6	29.4	128,653
55-59	2	18.1	16	30.9	195,731
55-61	2	23.5	21.5	32.6	267,681
55-63	2	28.4	27	34.3	342,055
55-65	2	32.8	32.2	36	416,909
55-67	2	36.5	36.8	37.7	490,133
55-69	2	39.4	40.9	39.4	559,212
50-53	3	5.4	4	23.9	77,098
50-56	3	11.2	9	27.3	137,770
50-59	3	18.3	15.8	30.3	217,938
50-62	3	25.4	23.3	33.3	310,874
50-65	3	31.6	30.5	36.1	408,890
50-68	3	36.2	36.7	38.8	504,367
51-54	3	6.7	5.1	25.4	87,369
51-57	3	13.2	10.9	28.4	155,053
51-60	3	20.4	18	31.6	240,855
51-63	3	27.3	25.6	34.3	336,143
51-66	3	32.9	32.5	37.1	433,983
51-69	3	37.1	38.2	39.7	526,931
52-55	3	8.3	6.6	26.9	97,903
52-58	3	15.3	13.1	29.5	171,907
52-61	3	22.6	20.4	32.5	261,920
52-64	3	29.1	27.9	35.3	358,897
52-67	3	34.3	34.4	38.1	456,083

Supplementary Table 2. Harms, benefits and net costs of each screening strategies per 1000 men‡ (continued)

Screening age	Interval	LYs_gain#	PCMR %#	Overdiagnosis, as % of screen detected men	Total net costs # in Euro
53-56	3	10.3	8.4	27.9	111,058
53-59	3	17.5	15.3	30.7	191,329
53-62	3	24.6	22.8	33.6	284,457
53-65	3	30.7	30	36.3	382,326
53-68	3	35.3	36.1	39.1	477,848
54-57	3	12.2	10.3	29.1	126,061
54-60	3	19.6	17.5	31.9	211,981
54-63	3	26.4	25.1	34.7	307,322
54-66	3	32.1	32	37.4	405,265
54-69	3	36.2	37.6	40	498,236
55-58	3	14.1	12.2	31.4	142,724
55-61	3	21.5	19.8	34.6	233,213
55-64	3	28	27.2	35.8	330,487
55-67	3	33.2	33.7	38.5	427,619
50-54	4	6.7	5.1	25.4	85,165
50-58	4	14.7	12.5	29.7	166,997
50-62	4	23.4	21.6	33.8	275,677
50-66	4	30.4	30.1	37.7	393,013
51-55	4	8.1	6.4	27	97,337
51-59	4	16.6	14.5	30.9	187,638
51-63	4	25	23.6	34.9	299,786
51-67	4	31.4	31.8	38.7	417,006
52-56	4	9.9	8.1	28	109,627
52-60	4	18.6	16.7	32.1	207,207
52-64	4	26.7	25.7	36	321,823
52-68	4	32.6	33.5	39.7	437,450
53-57	4	11.8	9.9	29.2	123,846
53-61	4	20.6	18.9	33.1	227,416

Supplementary Table 2. Harms, benefits and net costs of each screening strategies per 1000 men‡ (continued)

Screening age	Interval	LYs_gain#	PCMR %#	Overdiagnosis, as % of screen detected men	Total net costs # in Euro
53-65	4	28.2	27.8	37	344,003
53-69	4	33.5	35	40.6	457,420
54-58	4	13.7	11.8	30.3	139,828
54-62	4	22.4	21	34.2	248,612
54-66	4	29.4	19.6	38	365,978
55-59	4	15.5	13.8	31.6	158,123
55-63	4	24	23	35.3	270,662
55-67	4	30.4	31.2	39.1	388,003
50-58	8	12.3	10.7	31	132,214
50-66	8	23.1	23.6	39.7	298,455
51-59	8	13.5	12.1	32.4	149,097
51-67	8	23.4	24.5	40.9	317,826
52-60	8	14.8	13.7	33.8	164,767
52-68	8	24	25.6	41.9	334,029
53-61	8	16.2	15.3	34.9	181,253
53-69	8	24.6	26.6	42.9	349,793
54-62	8	17.5	16.9	36	198,825
55-63	8	18.8	18.6	37	216,573
50 single test	-	2.3	1.6	20.8	36,229
51 single test	-	2.5	1.7	22.4	39,781
52 single test	-	3.2	2.3	24	43,183
53 single test	-	4.2	3.2	25.3	48,765
54 single test	-	5.4	4.3	26.6	56,535
55 single test	-	6.7	5.5	28.2	66,131
56 single test	-	8.2	6.9	29.3	77,082
57 single test	-	9.5	8.2	30.7	89,394
58 single test	-	10.7	9.6	32	102,211
59 single test	-	11.7	10.9	33.6	116,231

Supplementary Table 2. Harms, benefits and net costs of each screening strategies per 1000 men‡ (continued)

Screening age	Interval	LYs_gain#	PCMR %#	Overdiagnosis, as % of screen detected men	Total net costs # in Euro
60 single test	-	12.5	12	35.3	130,803
61 single test	-	13.2	13.1	36.7	144,401
62 single test	-	13.6	14	38.3	157,753
63 single test	-	13.8	14.7	39.8	169,896
64 single test	-	13.8	15.2	41.4	181,158
65 single test	-	13.7	15.6	43.1	191,658
66 single test	-	13.3	15.7	44.7	200,704
67 single test	-	12.7	15.6	46.4	208,283
68 single test	-	12.1	15.4	48.1	213,560
69 single test	-	11.3	15	49.8	217,594

PCM = prostate cancer mortality reduction; LYs_gain = life-years gain
‡ Life years gain and costs are 3.5% discounted
# Compared to no screening

Part 2

Magnetic resonance imaging in prostate cancer screening

4

The comparative effectiveness of mpMRI and MRI-guided biopsy vs regular biopsy in a population-based PSA testing: A modeling study

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ABSTRACT

The benefit of prostate cancer screening is counterbalanced by the risk of overdiagnosis and overtreatment. The use of a multi-parametric magnetic resonance imaging (mpMRI) test after a positive prostate-specific antigen (PSA) test followed by magnetic resonance imaging-guided biopsy (MRIGB) may reduce these harms. The aim of this study was to determine the effects of mpMRI and MRIGB vs the regular screening pathway in a population-based prostate cancer screening setting. A microsimulation model was used to predict the effects of regular PSA screening (men with elevated PSA followed by TRUSGB) and MRI based screening (men with elevated PSA followed by mpMRI and MRIGB). We predicted reduction of overdiagnosis, harm-benefit ratio (overdiagnosis per cancer death averted), reduction in number of biopsies, detection of clinically significant cancer, prostate cancer death averted, life-years gained (LYG), and quality adjusted life years (QALYs) gained for both strategies. A univariate sensitivity analysis and threshold analysis were performed to assess uncertainty around the test sensitivity parameters used in the MRI strategy.In the MRI pathway, we predicted a 43% reduction in the risk of overdiagnosis, compared to the regular pathway. Similarly a lower harm-benefit ratio (overdiagnosis per cancer death averted) was predicted for this strategy compared to the regular screening pathway (1.0 vs 1.8 respectively). Prostate cancer mortality reduction, LY and QALYs gained were also slightly increased in the MRI pathway than the regular screening pathway. Furthermore, 30% of men with a positive PSA test could avoid a biopsy as compared to the regular screening pathway. Compared to regular PSA screening, the use of mpMRI as a triage test followed by MRIGB can substantially reduce the risk of overdiagnosis and improve the harm-benefit balance, while maximizing prostate cancer mortality reduction and QALYs gained.

INTRODUCTION

The standard and widely used method for the detection of prostate cancer is offering transrectal ultrasound-guided biopsy (TRUSGB) for men with an elevated PSA level or abnormal digital rectal examination (DRE). However, this classical pathway is associated with an underdetection of clinically significant/high-grade prostate cancer and overdetection of clinically insignificant /low-grade prostate cancer [1], which can lead to an unnecessary biopsy, overdiagnosis, and overtreatment. The TRUSGB is also associated with a higher rate of misclassification of grades as compared to magnetic resonance imaging-guided biopsy (MRIGB) that can lead to under or overtreatment [2]. Furthermore, TRUSGB is associated with increased risk of complications like bleeding and pain [3], which can lead to increased health care costs and even-life threatening sepsis [4]. Therefore, looking for an alternative diagnostic pathway that can minimize the risk of overdiagnosis and maximizes the prostate cancer mortality reduction should be at urge.

Using a multi-parametric magnetic resonance imaging (mpMRI) as a triage test followed by MRIGB may reduce the risk of overdiagnosis and overtreatment. Several studies reported that the use of mpMRI and MRIGB is superior to a regular pathway [1,5,6]. The MRI pathway is characterized by having high sensitivity for clinically significant prostate cancer, and low sensitivity for insignificant cancer [7-9], and reduces misclassification rate of grade at biopsy compared to TRUSGB[2]. Furthermore, by using this pathway, a substantial amount of unnecessary biopsies can be avoided [6].

Although various studies reported that the use of mpMRI and MRIGB can reduce the detection of indolent prostate cancer, there is no study so far that quantifies the exact effect of this strategy on the risk of overdiagnosis as well as its effect on prostate cancer related death. However, estimation of the long-term effects of screening such as overdiagnosis is unlikely from trial data. Therefore, the aim of this modeling study was to determine the effects of mpMRI and MRIGB as compared to TRUSGB in a population-based prostate cancer screening setting.

MATERIALS AND METHODS

MISCAN Model

The micro-simulation screening analysis (MISCAN) prostate cancer model [10-12] was used to evaluate the long-term effects of prostate cancer screening using regular pathway (positive PSA test followed by TRUSGB) vs MRI pathway (positive PSA test

followed by mpMRI and MRIGB). Microsimulation is a modeling technique that typically uses a large sample size of individual units (microunits), each with a unique set of attributes, and allows for simulations of downstream events on the basis of predefined states and the transition probabilities between those states over time[13]. Likewise, MISCAN prostate model is a stochastic model that simulates individual life histories, natural history of prostate cancer, effect of treatment at baseline (without screening), and the effect of screening. Each individual in the simulation starts with no prostate cancer, and through time there is a chance to transit to preclinical prostate cancer. There are eighteen pre-clinical detectable states with a combination of three stages (T1, T2, and T3), three Gleason scores (7, less than 7, and greater than 7), and two metastatic states (whether or not the cancer is metastasized). From each pre-clinical state, the tumors can progress to a more advanced state, can be clinically diagnosed, or be screen detected (Supplementary **Figure** 1).

After detection, the person is assigned to either radical prostatectomy (RP), radiation therapy (RT), or Active surveillance (AS). Distribution of the treatments depends on age, stage, and Gleason score as described before [14-16]. Baseline survival (in the absence of treatment) from a clinical diagnosis of prostate cancer was modeled by fitting a Cox model to Surveillance, Epidemiology, and End Results (SEER) survival data from the pre-PSA era (1983-1986), as described in a previous study [14]. The effect of treatment on survival for localized prostate cancer cases was modeled using a hazard ratio of 0.56 for those who received RP as compared with those without treatment [17]. The same effect was assumed for RT. For metastasized prostate cancer cases, it was assumed that palliative treatment has no effect on survival.

The benefit of PSA screening on prostate cancer mortality was modeled using a lead time dependent cure probability (mortality benefit increases with lead time). Lead time is the years by which detection of the cancer is advanced by screening compared with the clinical situation[16]. If a man is cured, he will not die from prostate cancer; but if he is not cured the date and cause of death are not changed due to earlier detection by screening. Death from other causes was modeled based on Dutch life table [18].

The MISCAN prostate model was calibrated to European Randomized Study of Screening for Prostate Cancer (ERSPC) data as has been described before [12]. In order to account the younger age groups (50-54 years), the model was also calibrated to prostate cancer incidence among the Dutch population between 1989 and 2013 from age 50 to age 75 (5-years categories), and the observed prostate cancer mortality over the same period was used for validation [19]. Further descriptions about the four

components of MISCAN prostate model (demography, natural history, screening and treatment) can be found at https://cisnet.flexkb.net/mp/pub/CISNET_ModelProfile_PROSTATE_ERASMUS_001_12152009_69754.pdf

Screening strategy

In our previous study, we compared more than 200 population-based prostate cancer screening strategies, and we found that screening with 3 years interval at ages 55-64 would be the optimum screening strategy [19]. All men with an elevated serum PSA level (cut-off 3ng/mL) were referred to TRUSGB in that study. Those who were positive at TRUSGB were assigned to either RP, RT or AS according to the treatment distribution mentioned before. The biopsy compliance rate after a positive screen test result was assumed to be 90%, with a sensitivity of 90% as observed in the ERSPC Rotterdam data [20,21]. An 80% screening attendance rate was assumed. The total number of biopsies was calculated by using the number of screen detected cancers and a mean positive predictive value of 22.7% of a biopsy in the screen arm of the ERSPC [21] and by using the number of clinically detected cancers and the positive predictive value of 35.8% of a biopsy in the control arm [22].

In the present study, we included mpMRI as a triage test to this screening strategy (screening with 3-year intervals at ages 55-64) for those men with an elevated PSA level (cut-off 3ng/mL) before referring them to a biopsy (MRIGB) (**Figure** 1). PIRADS scores of 3-5 were considered positive for the mpMRI test. It is important to note that we didn't use a combined biopsy, rather those men with positive mpMRI tests were subjected only to an MRI-guided biopsy (no systematic biopsy). The same screening attendance and biopsy compliance were assumed as in the regular pathway. A positive predictive value of 58% [23] was assumed to calculate the total number of biopsies in this strategy. Men positive at MRIGB were assigned to the same treatment options as in TRUSGB. Grade specific sensitivity values for mpMRI and MRIGB were mainly based on literature that used meta-analysis (**Table** 1). Although a very recent meta-analysis reported by Drost etal, 2020[24] was not included in our study, most of the test sensitivity parameter values reported in that study are within the range of the values that we used for our sensitivity analysis.

We also accounted for misclassification of grades both in the MRIGB and regular biopsy. In our study misclassification of grades represents only wrong classification of clinically significant cancer in to insignificant cancer at biopsy. For the MRIGB we used an 8.7% misclassification rate based on Ahdoot et al [2]. For the regular biopsy

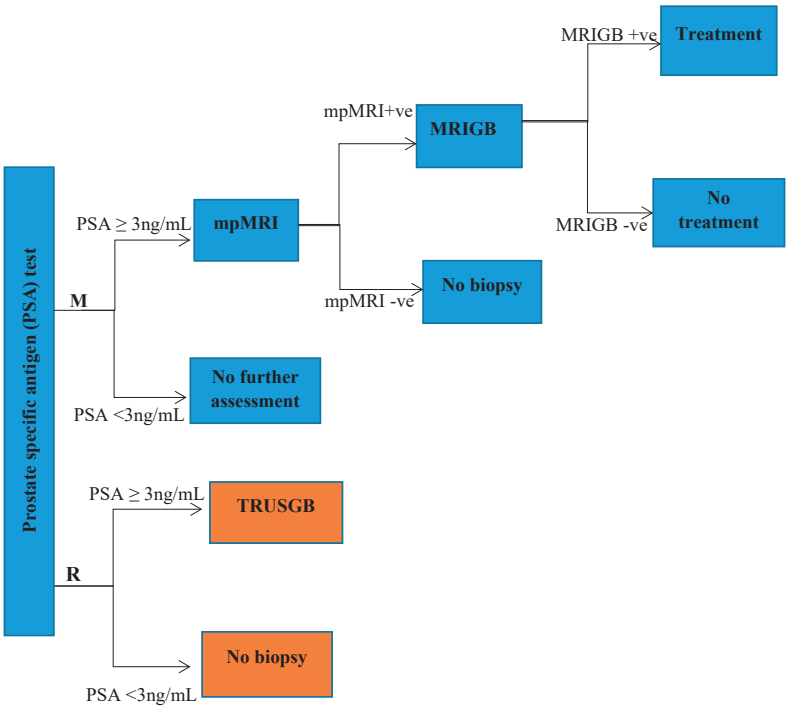

Figure 1. Schematic representation of the MRI pathway (M) and regular pathway (R). mpMRI = multi parametric magnetic resonance imaging ; MRIGB = magnetic resonance imaging-guided biopsy; MRI = magnetic resonance imaging; TRUSGB = transrectal ultrasound-guided biopsy.

Table 1. Sensitivity values for the MRI pathway used in the model.

Variable	Value	Source
Sensitivity of mpMRI for high grade cancer	0.94 (Range 0.70 – 0.97)	Sathianathen etal. 2019[37]
Overall sensitivity of mpMRI*	0.74 (95% CI 0.66 – 0.81)	de Rooij et al. 2014[38]
Sensitivity of MRIGB for low grade cancer	0.44 (95% CI 0.26 – 0.64)	Schoots et al. 2015[29]
Sensitivity of MRIGB for high grade cancer	0.91 (95% CI 0.87 – 0.94)	Schoots et al. 2015[29]

mpMRI = multi parametric magnetic resonance imaging ; MRIGB= magnetic resonance imaging-guided biopsy.
* Used as a sensitivity of mpMRI for low grade cancer in our model.

16.8%, 36.3% and 60% of misclassification were reported [2,25,26,] and we used the intermediate 36.3%.

We compared the two strategies in terms of a harm-benefit ratio (overdiagnosis per death averted), reduction of overdiagnosis, reduction of number biopsied, detection of clinically significant cancer, death averted, life-years gained, life-years gained (LYG) per death averted, QALYs gained and QALYs gained per death averted. In this study, clinically significant prostate cancer was defined as Gleason score 7 or more

and clinically insignificant cancer as Gleason score 6 and less [5]. In both screening strategies, a hypothetical cohort of 10 million men was simulated over a lifetime period. All the results are reported per 1000 men.

Quality of life

The quality adjusted life-years (QALYs) were calculated based on the utility estimates of given health states where patients remain for a certain period of time. The utility values range between 0 (death) and 1 (perfect health), and one minus the utility value gives a loss in utility at each health state. By multiplying the number of men in a given health state with the loss in utility and the duration of the health state, the loss in quality of life was calculated. The utility estimate (0.96) and duration (1 week) for mpMRI were based on Grana et al [27]. There is evidence that MRIGB is associated with less frequent adverse outcomes compared with TRUSGB[3]. Therefore, we assumed 50% lower disutility for MRIGB compared with that of TRUSGB. All other utilities and durations were based on our previous study [12] (Supplementary Table 1).

Sensitivity analysis

To check the robustness of our results, we performed a one-way sensitivity analysis on the harm-benefit ratio (overdiagnosis per death averted) of the MRI pathway. Because the performance and interpretation of both mpMRI and MRIGB are highly influenced by the specialists (radiologist or urologist) skills, we varied the test sensitivity parameters for the analysis using the 95% confidence intervals indicated in Table 1. A threshold analysis was also performed on QALYs per death averted by changing the baseline sensitivity values of the mpMRI and MRIGB simultaneously.

RESULTS

Base model:

The total numbers of men referred to a biopsy were 396 and 278 for the regular and the MRI pathway respectively, a 30% reduction (Table 2). Our model predicted 16 overdiagnosed cases for the regular pathway and 9 (43% reduction) for the MRI pathway (overdiagnosed cancer was defined as a prostate cancer detected during screening but would not have been clinically diagnosed during the man's life time in the absence of screening). The model predicted a 2.7% higher prostate cancer mortality reduction for the MRI pathway than the regular pathway (8.77 vs 8.53). The MRI based screening was also associated with a lower harm-benefit ratio (overdiagnosis per cancer death averted) than the regular screening (1.0 vs 1.8). Our model

Table 2. Predictions of the effects of prostate cancer screening for men between age 55-64 at 3 years intervals using regular pathway and MRI pathway, per 1000 men.

	Regular pathway	MRI pathway	Difference
Number of men biopsied	396	278	118 (-30%)
Total number of clinically insignificant cancer[1] detected at biopsy	80.8	58.9	21.9 (-27%)
Total number of clinically significant cancer[2] detected at biopsy	36.0	51.3	15.3 (+29.8%)
Percent clinical significant cancer missed in the MRI-pathway due to reduction in biopsies	-	10.8 %	-
Number overdiagnosed[3]	15.6	8.9	6.7 (-43%)
Number of prostate cancer deaths averted	8.53	8.77	0.24 (+2.7%)
Overdiagnosed cases per death averted	1.8	1.0	0.8 (- 44%)
Life-years gained LY gained per death averted	81.6 9.57	85.0 9.70	3.4 (+ 4%) 0.13 (+3%)
Quality adjusted life-years gained QALY gained per death averted	77.0 9.0	80.2 9.14	3.2 (+3.9%) 0.14 (+1.5%)

[1] clinically insignificant cancer was defined as Gleason score 6 and below (it contains both screen detected and interval cancer);
[2] clinically significant prostate cancer was defined as Gleason score 7 or more (it contains both screen detected and interval cancer)
[3] overdiagnosed cancer was defined as a prostate cancer detected during screening but would not have been clinically diagnosed during the man's life time in the absence of screening.

predicted a higher LY gained (85 vs 81.6) and QALYs gained (80.2 vs 77) in the MRI pathway than the regular screening pathway.

Clinically significant prostate cancer was detected in 51.3 men in the MRI pathway, as compared with 36 in the regular pathway (30% increment in the detection rate of clinically significant prostate cancer). In contrary, fewer men were diagnosed with clinically insignificant prostate cancer in the MRI pathway than the regular pathway (59 vs 80.8), which resulted in a 27% reduction. However, the MRI pathway was also associated with an 11% risk of missing clinically significant cancer due to not performing biopsy in the mpMRI negative patients.

Sensitivity Analysis:

After varying the baseline sensitivity values of the MRI pathway, using the 95% confidence intervals or ranges, the harm-benefit ratio (overdiagnosis per death averted) remained lower in the MRI pathway than the baseline value (1.8) of the regular pathway (**Figure** 2). The threshold analysis indicated that when the baseline test sensitivity values of the MRI pathway were changed by 14% simultaneously, the QALYs/death averted became the same for the two strategies (Figure 3). To be the

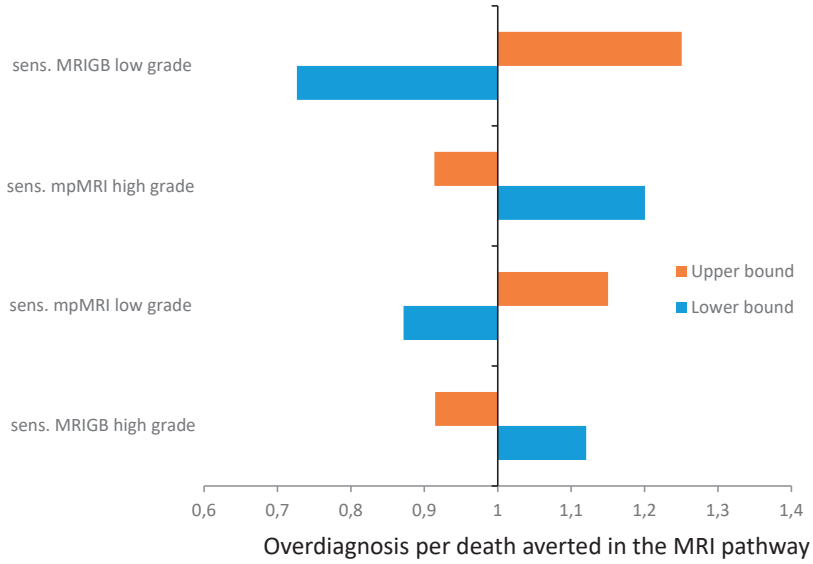

Figure 2. Tornedo diagram of one-way sensitivity analysis on the harm-benefit ratio (over diagnosis per cancer death averted) for the MRI pathway. sens.MRIGB low grade- sensitivity of magnetic resonance imaging-guided biopsy for low grade prostate cancer; sens.MRIGB high grade- sensitivity of magnetic resonance imagingguided biopsy for high grade prostate cancer; sens.mpMRI low grade- sensitivity of multi-parametric magnetic resonance imaging for low grade prostate cancer; sens.mpMRI high grade- sensitivity of multi-parametric magnetic resonance imaging for high grade prostate cancer.

QALYs per death averted in favour of the MRI pathway, the sensitivity of mpMRI and MRIGB for clinically significant prostate cancer should be higher than 81% and 78% respectively; Whereas, for that of clinically insignificant prostate cancer it should be lower than 84% and 50% respectively.

DISCUSSION

The benefit of prostate cancer screening in reducing advanced stage disease or mortality is counterbalanced by the risk of overdiagnosis and overtreatment [28]. In our study, when mpMRI was applied after a positive PSA test and followed by MRIGB, the risk of overdiagnosis was decreased substantially (by 43%) compared with the regular screening. This result can be taken confirmatory for previous studies that proposed the use of mpMRI and MRIGB as a potential means to reduce the risk of overdiagnosis. The lower harm-benefit ratio predicted in the present study could

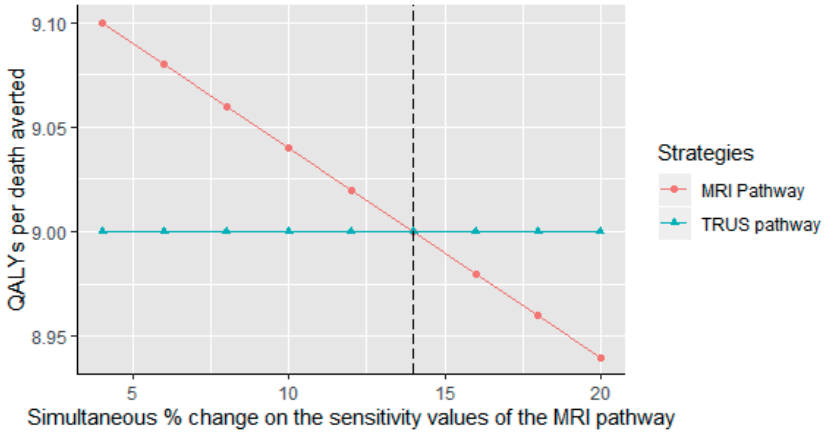

Figure 3. A threshold analysis diagram indicating the QALYs per cancer death averted continues to be in favor of the MRI pathway when the sensitivity values of the MRI pathway were changed simultaneously by up to 14% (this means increasing the sensitivities of mpMRI and MRIGB for low grade cancer and decreasing for high grade cancer by up to 14% simultaneously). Increasing the sensitivity for low grade cancer means detecting more Gleeson 6 cancer and decreasing the sensitivity for high grade cancer means detecting fewer clinically significant cancer which reduce the QALY per death averted.

also inform policymakers about the role of MRI in a population-based prostate cancer screening.

When the MRI pathway was used instead of the regular pathway, 30% of men avoided biopsies. A recent study by Kasivisvanathan et al [5] reported a 28% biopsy reduction due to the use of mpMRI and MRIGB. As compared to the regular pathway, the MRI pathway was also associated with a 30% higher detection rate and 27% lower detection rate for clinically significant and insignificant prostate cancer, respectively. A meta-analysis [29] concluded that MRIGB has a higher detection rate for clinically significant prostate cancer and a lower detection rate for insignificant cancer compared with TRUSGB. More specifically, Siddiqui et al [30] reported MRIGB increases the detection of high risk cancer by 30% (compared to TRUSGB), and Leest et al [31] indicated TRUSGB would over detect insignificant cancer in 20%. The number (percentage) of clinically significant cancers reported in our study (in both pathways) are lower than the number reported by Kasivisvanathan et al. 2018, who used the same definition. The main reason for this discrepancy could be the difference in population characteristics of the two studies. For instance, the upper age limit included in the present study was 64 years, whereas in Kasivisvanathan et al. 2018 the mean age was 64±7. Therefore, the older age groups in the Kasivisvanathan et al.

2018 may contribute to the higher number of high grade cancers (grade 7 and above) than reported in our study. Although it is difficult to directly compare our results with the above studies (because of differences such as, population characteristics, follow-up period and screening strategy), the general conclusion is the same: the use of mpMRI and MRI guided biopsy is superior over that of the regular pathway.

Using of the MRI pathway resulted in an increased LYG, QALYs gained, and prostate cancer death averted compared to the regular pathway. The increased in LYG and mortality benefit in the MRI pathway can be explained by the increased detection of clinically significant cancer (by about 30%), and the lower misclassification rate of grades by MRIGB (compared to TRUSGB), that were included in our model. On the other hand, the lower detection rate of clinically insignificant cancer in the MRI pathway could explain the higher QALYs gained. However, the MRI pathway also failed to detect around 11% of clinically significant cancer, that would be detected in the regular pathway, and this could explain the smaller difference in mortality benefit between the two strategies. This percentage is in agreement with a previous study by Pokorny et al [6]. The small QALYs difference reported between the two strategies may raise a question of whether the MRI-pathway can be an efficient strategy, especially in relation to the initial additional expenditures required in the MRI-pathway. However, a substantial amount of biopsies were avoided as a result of using the MRI pathway, and this could compensate for the additional expenditures.

Our prediction of the lower harm benefit ratio (overdiagnosis per death averted) for the MRI pathway than the regular pathway was robust to the sensitivity analysis (Figure 2). It is also important to note from the figure that, increasing the sensitivity of mpMRI and MRIGB for high grade cancer resulted in a more better harm benefit ratio, and lowering theses sensitivities relatively worse the ratio. In contrary, lowering the sensitivity of mpMRI and MRIGB for low grade cancer makes the ratio more better, and increasing these sensitivities makes the ratio relatively worse. The threshold analysis showed that when the baseline test sensitivity values of the MRI pathway were changed by 14% simultaneously (this means increasing the sensitivities of mpMRI and MRIGB for low grade cancer and decreasing for high grade cancer by 14% simultaneously), the QALYs per death averted became the same for the two strategies. This may signify the importance of adhering to proper imaging protocol as well as interpretation by the radiologist/urologist. A review by Stabile eta al [32] indicated that there are various factors affecting the performance of mpMRI and MRIGB, among these radiologists' reading experience and urologists'/radiologists' biopsy experience were the main ones.

An important strength of this study is that we were able to quantify the effect of MRI based prostate cancer screening on the risk of overdiagnosis, which is obviously not observable in trial studies. We also quantified the effect of the MRI pathway on the harm-benefit ratio (overdiagnosis per death averted) as compared to the regular pathway, which was also not reported in previous studies. Furthermore, we were able to evaluate the MRI pathway in a population based screening setting. Although our model is calibrated to the Dutch prostate cancer incidence, the results may also be extrapolated to other western populations with similar prostate cancer incidence trends. Study shows that in Western Europe, the incidence of prostate cancer has been on the rise.[33].

Our study has also certain limitations. First, we assumed the same mortality benefit for radiation therapy as that of radical prostatectomy, since there is no clinical trial that compared the two treatment directly. We also assumed that treatment options will not change in both strategies. However, treatment behavior may change in the future, such as more active surveillance than now. Cost is another important factor which was not included in this study. However, avoidance of biopsies and subsequent biopsy related complications and treatment costs, probably make the MRI pathway cost-effective or at least compensate its additional costs. Various studies, though not population-based studies, indicated that the inclusion of mpMRI after a positive PSA test followed by MRI-guided biopsy is cost-effective compared to a regular prostate cancer screening pathway[34-36]. Future studies are needed to evaluate this in a population-based screening settings. Lastly, a probabilistic sensitivity analysis was not included in our study: only a one-way sensitivity analysis and threshold analysis were included.

In conclusion, our modeling results indicated that the use of mpMRI after a positive PSA test followed by MRIGB can substantially reduce the risk of overdiagnosis and improve the harm-benefit ratio, while maximizing prostate cancer mortality reduction and QALYs gained, as compared to the regular screening pathway.

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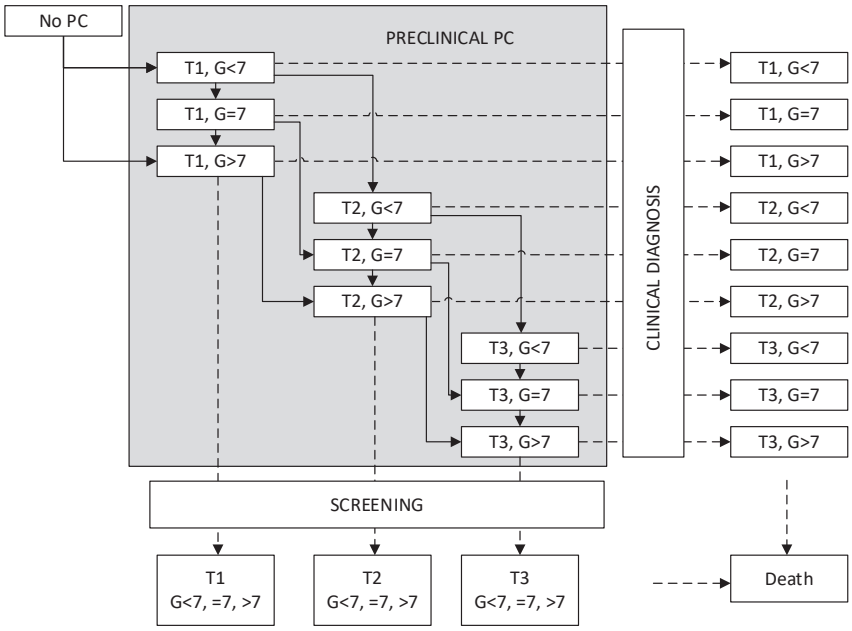
SUPPLEMENTARY MATERIALS

Supplementary table 1. Utility estimates and durations of the various health states, obtained from a previous study[12].

Health state	Utility estimates (range)	Duration
PSA screening attendance	0.99 (0.98-1.00)	1 week
Diagnostic phase	0.90 (0.87-0.94)	3 weeks
Diagnosis	0.80 (0.75-0.85)	1 month
Radical prostatectomy		
At 2 months after procedure	0.67 (0.56-0.90)	2 months
At > 2 months to 1 year after procedure	0.77 (0.70-0.91)	10 months
Radiation therapy		
At 2 months after procedure	0.73 (0.71-0.91)	
At > 2 months to 1 year after procedure	0.78 (0.61-0.88)	
Active surveillance	0.97 (0.85-1)	7 years
Postrecovery period	0.95 (0.93-1.00)	9 years
Palliative therapy	0.60 (0.24-0.86)	30 months
Terminal illness	0.40 (0.24-0.56)	6 months



Supplementary Figure 1.The MISCAN prostate cancer model. The model also contains a distinction between local and distant states, but for the sake of simplicity it is not illustrated here. T- tumor stage ; G - Gleason score

5

Cost-effectiveness of multiparametric magnetic resonance imaging and MRI-guided biopsy in a population-based prostate cancer screening setting using a micro-simulation model

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ABSTRACT

Background: The introduction of multiparametric magnetic resonance imaging (mpMRI) and MRI-guided biopsy has improved the diagnosis of prostate cancer. However, it remains uncertain whether it is cost-effective, especially in a population-based screening strategy.

Methods: We used a micro simulation model to assess the cost-effectiveness of an MRI-based prostate cancer screening in comparison to the classical prostate specific antigen (PSA) screening, at a population level. The test sensitivity parameters for the mpMRI and MRI-guided biopsy, grade misclassification rates, utility estimates, and the unit costs of different interventions were obtained from literature. We assumed the same screening attendance rate and biopsy compliance rate for both strategies. A probabilistic sensitivity analysis, consisting of 1000 model runs, was performed to estimate a mean incremental cost-effectiveness ratio (ICER) and assess uncertainty. A €20,000 willingness to pay (WTP) threshold per quality adjusted life year (QALY) gained, and a discounting rate of 3.5% were considered in the analysis.

Results: The MRI based screening improved the life-years (LY) and QALYs gained by 3.5 and 3 respectively in comparison to the classical screening pathway. Based on the probabilistic sensitivity analyses, the MRI screening pathway leads to total discounted mean incremental costs of €15,413 (95% confidence interval (CI) of €14,556 - €16,272) compared to the classical screening pathway. The corresponding discounted mean incremental QALYs gained was 1.36 (95% CI of 1.31-1.40), resulting in a mean ICER of €11,355 per QALY gained. At a WTP threshold of €20,000, the MRI screening pathway has about 84% chance to be more cost-effective than the classical screening pathway.

Conclusions: For triennial screening from age 55 to 64, incorporation of mpMRI as a reflex test after a positive PSA test result with a subsequent MRI-guided biopsy has a high probability to be more cost-effective as compared with the classical prostate cancer screening pathway.

BACKGROUND

Despite the presence of compelling evidence regarding the beneficial effects of prostate specific antigen (PSA) screening from a trial and modeling studies[1-3], almost no country implemented PSA screening at a population level[4]. This is mainly due to the fact that PSA screening is associated with high risk of overdiagnosis and overtreatment. However, the European Urology of Association (EAU) recently stated that the European union can no longer overlook prostate cancer, and the introduction of PSA screening at a European level need to be rediscussed by taking in to consideration the current evidences about prostate cancer screening[5]. A recent brief correspondence to the European Association of Urology (EAU) emphasized the importance of introducing organized PSA screening at a population level in order to reduce mortality from prostates cancer[6]. The authors indicated that multi- parametric magnetic resonance (mpMRI) should be used as a reflex test after a positive PSA test result to select men for biopsy.

The introduction of mpMRI and targeted biopsy has improved the diagnosis of prostate cancer. Several studies reported that the use of mpMR as a triage before biopsy and followed by MRI-guided biopsy can substantially reduce the detection of low-grade prostate cancers and also result in a better detection of clinically significant cancers compared to the classical screening with an upfront transrectal ultrasound guided biopsy (TRUSGB) for all men with a positive PSA test result[7-11]. While the benefits of using mpMRI with a subsequent MRI targeted biopsy has become more clear, its cost-effective remains uncertain, especially for a screening strategy at a population level.

Although some studies reported the cost-effectiveness of mpMRI and subsequent targeted biopsy[12-15], to our knowledge, no study has yet quantified the cost-effectiveness in a population-based screening strategy, particularly in the European situation. Screening at a population level should have a clear starting and stopping age of screening and intervals to screen. A study by Barnett *et al*.,[16] that modeled screening from 55 to 69 at 2 years intervals reported the cost-effectiveness of mpMRI and targeted fusion biopsy. However, the setting is in the US, where the costs of MRI are much different from the costs in Europe. The aim of this study was to investigate the cost-effectiveness of MRI based prostate cancer screening pathway compared to the classical screening pathway at a population level, using a base model which was calibrated to the European Randomized study of Screening for Prostate Cancer (ERSPC) data and Dutch prostate cancer incidence and mortality data[17]. In this study, the MRI screening pathway represents for a positive PSA test (≥3ng/mL) followed by

mpMRI test and MRI-guided biopsy (for those men positive on mpMRI test), whereas the classical screening pathway refers to a positive PSA test (≥3 ng/mL) followed by TRUSGB.

MATERIALS AND METHODS:

Model overview

In the present study the micro simulation screening analysis (MISCAN) prostate cancer model was used[3,18,19]. Taking variation in to account, the model simulates life histories for each individual starting from birth to death. Everyone in the simulation starts with no prostate cancer. Once a malignant prostate tumor initiated in any individual in the model, the progression of the cancer is simulated as a sequence of preclinical and clinical states. In combination with 3 stages (T1, T2 and T3), 3 Gleason scores (7, less than 7 and greater than 7), and 2 metastatic states (local-regional and distant), the model has 18 pre-clinical states. There is also a chance for the tumor to progress from each preclinical state to the next T-stage, or change to a higher Gleason score, or it may be clinically diagnosed (Supplementary Figure 1). Furthermore, the tumor has a chance to metastasize from a local-regional state into a distant state. For every individual, two life histories are projected by the model: one without screening and the other with screening. A screen detected cancer that would not lead to a clinical diagnosis in case of no screening is considered as an overdiagnosed cancer[11].

Using Surveillance, Epidemiology, and End Results (SEER) data (1983-1986), baseline prostate cancer survival (without screening and localized treatment) in the model was determined at clinical diagnosis[20]. In order to model death other than prostate cancer, we used a life table of Dutch population.[21]. To model the effects of treatment on localized prostate cancer, a 0.56 relative risk of dying was assumed for radical prostatectomy (RP) as compared to watchful waiting[22]. We assumed the same treatment benefit for radiation therapy (RP). The distributions of treatments were based on age, stage, and Gleason score[2,23]. The benefit of PSA screening on prostate cancer mortality was simulated as a function on lead time based on a lead time-dependent cure probability.[2] The years by which cancer detection using screening precede clinical detection is termed as a lead time[11]. Detail information about the model including calibration and validation can be found on literature[3,17,18] and using: https://cisnet.flexkb.net/mp/pub/cisnet_modelprofile_prostate_erasmus_001_12152009_69754.pdf.

Screening protocol

The screening intervals, start and end age in the present study was based on the optimal screening strategy reported in a cost-effectiveness analyses using the same base model, which is from age 55-64 at 3 years interval with an 80% screening attendance[17]. A 90% biopsy compliance rate with a biopsy sensitivity 90% was assumed based on the ERSPC Rotterdam data[24,25]. We kept this screening protocol for the classical screening pathway of the current study. For the MR screening pathway, we added mpMRI as triage test between a positive PSA test and biopsy. This means, men after a positive PSA test were further selected using an mpMRI test before biopsy, and only those men positive at mpMRI (PIRADS scores of 3-5) went to biopsy. Furthermore, for the MRI screening pathway, we replaced the TRUSGB with MRI-guided biopsy (Supplementary Figure 2). The screening attendance rate and biopsy compliance rate that we used in the MRI screening pathway are the same as in the classical screening pathway. The test sensitivity parameters for the mpMRI and MRI-guided biopsy were obtained from literature, mainly meta-analyses (Table 1). Misclassification of grades (misclassifying a clinically significant cancer into an insignificant cancer at biopsy) was also included in the model both for the MRI-guided biopsy and TRUSGB. We used an 8.7% misclassification rate for the MRI-guided biopsy[8]. For the TRUSGB biopsy we obtained different values from literature [8,26,27,] and used the intermediate 36.3% (16.8-60%).

Table 1. The test sensitivity values for the MRI pathway, the utility values and durations of the health states, and the unit costs of interventions.

Parameters included in the probabilistic sensitivity analyses		
Variables	Values	Sources
Sensitivity of mpMRI for HGC*	0.94 (SD: 0.06) †	Sathianathen et al 2019[38]
Overall sensitivity of mpMRI **	0.74 (SD: 0.06) †	de Rooij et al. 2014[39]
Sensitivity of MRI-guided biopsy for HGC	0.91 (SD: 0.05) †	Schoots et al. 2015[34]
Sensitivity of MRI-guided biopsy for LGC#	0.44 (SD:0.05) †	Schoots et al. 2015[34]
Unit costs of mpMRI	€345 (min=€293, max=€397) ‡	de Rooij et al. 2014[13]
Unit costs of MRIGB	€800 (min=€680, max=920) ‡	de Rooij et al. 2014[13]
Unit costs of TRUSGB	€247 (min=€210, max=€284) ‡	Heijnsdijk et al 2015[3]
Remaining unit costs in Euro used in the model (common for both strategies)		
Variables	Values	Heijnsdijk et al 2015[3]
PSA screening	35	
Staging	290	
Radical prostatectomy (RP)	17,119	
Radiation therapy (RT)	20,568	

Table 1. The test sensitivity values for the MRI pathway, the utility values and durations of the health states, and the unit costs of interventions. (continued)

Remaining unit costs in Euro used in the model (common for both strategies)		
Variables	Values	Heijnsdijk et al 2015[3]
Active surveillance (AS)	2,303	
Follow up	218	
Advanced disease (Palliative treatment)	17,800	
Utility values and duration of health states used in the model (common for both strategies, except biopsy and mpMRI)		Heijnsdijk et al 2012[18]
Health states	Utility estimates (Favorable, Unfavorable)	Duration
PSA screening attendance	0.99 (1, 0.99)	1 week
mpMRI	0.96[40] -	1 week
TRUSGB	0.90 (0.94, 0.87)	3 weeks
MRIGB ¶	0.95 (0.97, 0.93)	3 weeks
Diagnosis	0.80 (0.85, 0.75)	1 month
RP	0.67 (0.90, 0.56)	2 months
RT	0.73 (0.91, 0.71)	2 months
AS	0.97 (1, 0.85)	7 years
2 months to 1 year RP	0.77 (0.91, 0.70)	10 months
2 months to 1 year RT	0.78 (0.88, 0.61)	10 months
Postrecovery period	0.95 (1, 0.93)	9 years
Palliative therapy	0.60 (0.24, 0.86)	30 months
Terminal illness	0.40 (0.24, 0.56)	6 months

mpMRI = multi parametric magnetic resonance imaging; MRI = magnetic resonance imaging; TRUSGB = transrectal ultrasound-guided biopsy; min = minimum; max = maximum
*HGC= high grade cancer
** assumed as a sensitivity of mpMRI for LGC
#LGC=low grade cancer
† the standard deviations are based on de Rooij et al. 2014[13]
‡ the base value is varied by ±15% for the max and min
¶ Because usually less biopsy complications are associated with MRIGB than TRUSGB, we assumed a 50% lower utility loss due to MRIGB than TRUSGB.

Costs

All the unit costs included in this study were obtained from literature and reported in Euros (Table 1). The number of screening visits, positive biopsies, diagnoses, treatments, and life years were estimated by the model. In order to determine the number of negative biopsies, we calculated the total number of biopsies based on detected cancers and a positive predictive value of a biopsy as described on literature[11,17]. Indirect costs were not included in this study. A 3.5% discounting rate was used for both costs and effects.

Utilities and Quality of life

Most of the utility values and duration of health states were obtained from literature[18], (Table 1). The loss in utility was calculated by subtracting the utility value from 1. The product of the number of men in a given health state with the loss in utility and duration of the health state gives the loss in quality of life[17].

Analysis

For both strategies, the undiscounted LY gained, QALYs gained, and the number of men biopsied were from a single model run. The net effects and costs in each strategy were compared with a no screening strategy. The mean discounted total net costs of screening, diagnosis and treatment, and palliative care, the mean discounted net QALYs gained and the mean total incremental net costs along with 95% CI, the mean incremental cost-effectiveness ratio (ICER), and the mean incremental net monetary benefit (iNMB) were based on probabilistic sensitivity analyses. To estimate the ICER we divided the difference in total net costs between the MRI screening pathway and the classical screening pathway by the difference in net QALYs gained between the two strategies. A willingness to pay threshold (WTP) of €20,000, which is a common Dutch WTP[28], was used to determine the cost-effective of a given strategy. If the ICER of a given strategy is lower than this WTP, it is cost effective. The mean iNMB was calculated by multiplying the incremental net effects (QALYs) with a WTP (€20,000) and subtracting the incremental net costs.

In the probabilistic sensitivity analyses, we performed 1,000 simulations in which selected model parameters were varied (based on distribution) simultaneously. A large sample size (10 million men) was used in each simulation, which eliminated stochastic noise in the model. The parameters included in the probabilistic sensitivity analyses were mainly those parameters which are not common in the two strategies. This includes the test sensitivity values of mpMRI, sensitivity values of MRI-guided biopsy, costs of mpMRI, costs of MRI- guided biopsy, and costs of TRUSGB. The test sensitivity values were varied using their base value and standard deviation. For the costs, we used a Pert distribution with the most likely (base) value and an assumption of ±15% for the minimum and maximum values (Table 1). The uncertainty around utility values and remaining costs were tested only using a one-way sensitivity analysis (because of labour constraints). The baseline utility values were varied using their favourable and unfavourable estimates, obtained from literature[18], and the costs were varied by ±15%.

For post-processing of the outputs, we used R software together with the Bayesian cost-effectiveness analysis (BCEA) and ggplot2 packages to obtain the cost-effec-

tiveness plain with mean ICER and the cost acceptability curves[29]. We used Rmisc package[30] to obtain the mean incremental net costs and effects with their 95% CI based on the 1000 model runs for the probabilistic sensitivity analysis.

RESULTS

Undiscounted effects from the base model

For triennial screening from age 55 to 64, the MRI screening pathway resulted in additional 3.5 life-years gained and 3 additional QALYs gained per 1,000 men invited to screening and followed over their lifetime period. Furthermore, the number of biopsied men reduced by 30% when the MRI screening pathway was used (Table 2).

Table 2. Estimated life time screening outcomes and results of probabilistic sensitivity analysis per 1000 men invited.

	Classical pathway (C)	MRI pathway (M)	Difference (M-C)
Screening outcomes from single run			
Number biopsied	396	278	-118 (30%)
Life years gained*	81.5	85	+3.5 (4%)
Quality adjusted life years gained*	77.2	80.2	+3.0 (4%)
PS-analysis outcome, 3.5% Discounted			
Mean net costs (in €) of *:			
Screening	80,118	156,429	+76,311 (49%)
Diagnosis and treatment	317,999	258,206	-59,793 (19%)
Palliative care	-60,145	-61,250	-1,105 (2%)
Mean total net costs	337,972	353,385	+15,413 (4.4%)
Mean QALY gained*	24.09	25.45	+1.36 (5.3%)
Mean Incremental total net costs with 95% CI in the bracket	-	15,413 (14,556; 16,272)	+15,413 (14,556; 16,272)
Mean Incremental QALYs gained with 95% CI in the bracket	-	1.36 (1.31, 1.40)	+ 1.36 (1.31, 1.40)
Mean ICER	-	11,355	+11,355
Mean incremental net monetary benefit (iNMB)	-	11,735	+11,735

CI= confidence interval, M= MRI pathway, PS-analysis= Probabilistic sensitivity analysis, C= classical pathway
*Compared to no screening

Probabilistic sensitivity analysis

The results show that the mean discounted incremental costs of screening, diagnosis and treatment, and palliative care of the MRI screening pathway versus the classical pathway were €76,300, €-59, 793, and €-1,105 respectively, resulting in a total mean incremental costs of €15,413 (95% confidence interval of €14,556 - €16,272) for 1000 men invited. The associated discounted mean incremental QALYs gained was 1.36, with a 95% confidence interval of 1.31-1.40 (Table 2). The mean ICER of the MRI screening pathway versus classical screening pathway was €11,355 (Table 2 and Figure 1). The cost-effectiveness plane (Figure 1) shows the uncertainty around the mean ICER estimate, and the majority of the incremental net cost-effect pairs gathered in the northeastern part of the plane below the WTP threshold line. In the northeast part of the plane, the MRI strategy is more effective and more expensive. The probabilities that the incremental cost-effect pairs of the MRI pathway, compared to the classical screening pathway, to fall in northeast and southeast quadrants were 85.2% and 11.3% respectively (Supplementary Figure 3).

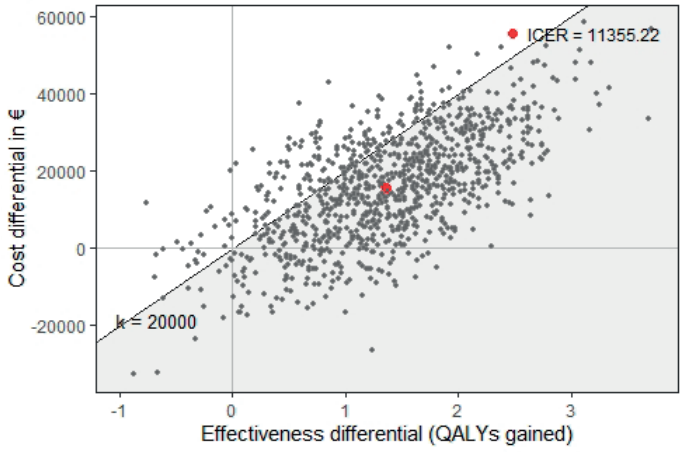

Figure 1. Cost-effectiveness plain of the MRI screening pathway versus the classical pathway at a WTP threshold of €20,000. In the northeast quadrant the MRI screening pathway is more effective and more costly: in the southeast quadrant, it is more effective and less costly (dominant): in the northwest quadrant, it is less effective and more costly (dominated), and in the southwest quadrant, it is less effective and less costly, than the classical screening pathway.

The cost-effectiveness acceptability curves at Figure 2 show that the MRI screening pathway had a high probability of being more cost-effective (84%) compared with the classical screening pathway, using a €20,000 WTP threshold per QALY gained. At this WTP threshold the MRI screening pathway has also a positive mean iNMB of €11,735 compared with the classical screening pathway (Table 2).

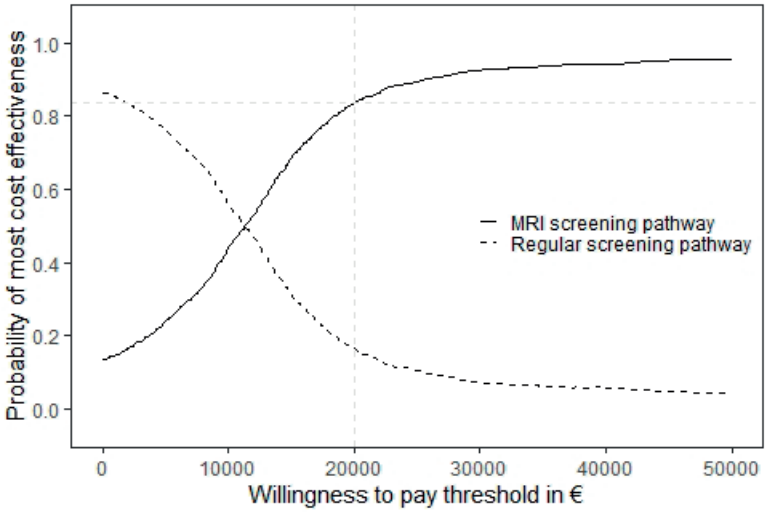

Figure 2. Cost-effectiveness acceptability curves for the MRI screening pathway and classical (regular) pathway

The one-way sensitivity analysis did not change the ICER substantially, ranging only between €10,000 and €13,700 (Supplementary Table 1) Although the change is not substantial, the cost-effectiveness became better for the MRI based screening strategy when the utility estimates for biopsy, diagnosis, treatments, palliative care, and advanced disease were unfavorable. Similarly, the ICER decreased when the costs of staging, treatment, and advanced disease care increased.

DISCUSSION

The results from the model, that accounts for long term prediction of costs and effects, suggest that the use of MRI screening pathway is more cost-effective than the classical prostate cancer screening pathway. The MRI pathway reduced the diagnosis and treatment costs by 19% and that of palliative care by 2% in comparison to the classical pathway. This reduction of diagnosis and treatment costs is mainly due to the lower sensitivity of mpMRI and MRI-guided biopsy for low grade prostate cancer that reduces unnecessary biopsy and treatment. Generally, mpMRI and MRI-guided biopsy have lower sensitivity for low grade cancer and higher sensitivity for clinically significant cancer [31-33] than the traditional random biopsy (TRUSGB)[34]. The latter can explain the reduction in the costs of the palliative care reported in the current study which in turn reduces the occurrence of advanced prostate cancer

(prostate cancer with clinical symptoms). In comparison to the classical screening pathway the MRI pathway also resulted in additional LY gained and QALYs gained. Reduction in biopsy procedure, overlooking of low-grade cancer and better detection of clinically significant cancer [34,35] due to the MRI pathway could explain these findings. Whether the MRI screening strategy is cost-effective than the classical screening pathway depends on the WTP threshold, and according to our results at €20,000 cut-off, the MRI screening pathway is most cost-effective in the majority of the model runs (84%) done for the probabilistic sensitivity analyses. The reduction in biopsy costs due to avoiding unnecessary biopsies, treatment costs due to avoiding overtreatment and the reduction in palliative cares costs due to improved detection of clinically significant cancers, and the modest increment of the QALYs gained in the MRI screening pathway explain how this strategy leads to a high probability to be cost-effective as compared to the regular screening pathway.

Although their screening strategies differed, some published studies showed that the use of mpMRI and MRI-guided biopsy is cost-effective [12,13], which is in agreement with our findings. A cost- effectiveness analysis from the USA reported a higher ICER than the current finding[16], and this could be mainly because of the costs of MRI in the USA are much higher than the costs in Europe that we used in this study. It should be noted that the results may not be directly comparable with the present study due to several reasons (such as screening strategies, model performance, data used, follow-up period), but the general conclusions are consistent. The 30% reduction in biopsy procedure due to the MRI screening pathway in this study is consistent with a recent MRI study [10].

Major strength of the present study is that we determined the cost-effectiveness of the MRI screening pathway at population level which was not reported before, particularly in the European situation. Another strength of the present study is that the MISCAN prostate model, we used in this study, includes the unobservable prostate cancer natural history, and also allows us to estimate effects of screening over life time periods, which is unlikely in trial studies, and most of other modeling cost-effectiveness studies[12,13,15].

This study is also subjected to certain limitations. First, we did not account costs of biopsy complications. There is more risks of complication and subsequent increment of health care costs due to TRUSGB biopsy than MRI guided biopsy [36,37]. Therefore, the cost-effectiveness would be even more in favor of the MRI screening pathway if these costs were included. Second, assumptions were made for certain model parameters when data is not available. Another limitation of the present

study is that treatment options were assumed to be the same and will not change in both strategies. However, how diagniosed cancer should be treated may depend on the MRI outcome, and also treatment behavior may alter in time. More studies are needed to assess whether it is effective to make treatment decisions based on MRI test results.

In conclusion, our study suggests that for triennial screening from age 55 to 64 incorporating mpMRI as a triage test in prostate cancer screening before biopsy with subsequent MRI-guided biopsy has a high probability to be more cost-effective than the classical screening pathway.

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SUPPLEMENTARY MATERIALS

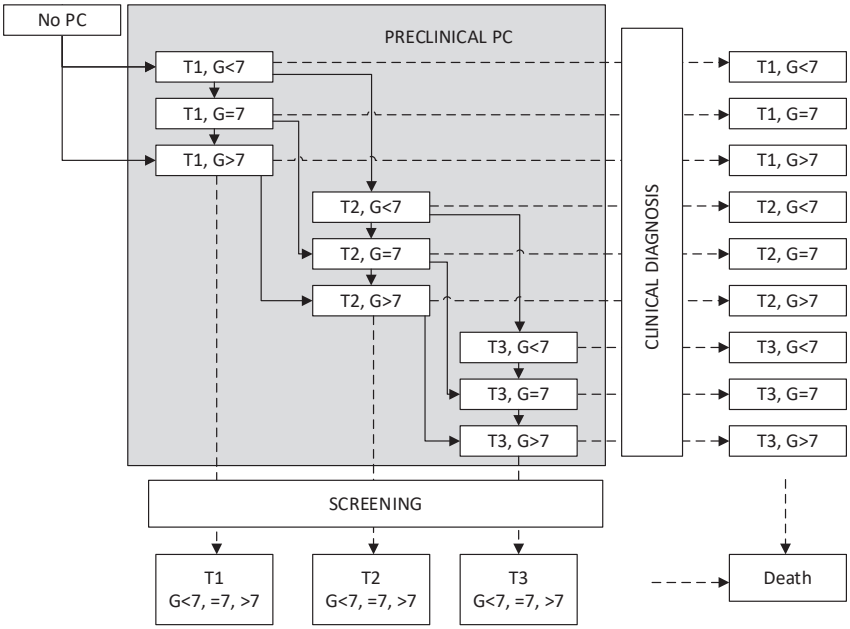
Supplementary Table 1. Results of varying the utility estimates and unit costs using a one way sensitivity analysis (each outcome is based on a single run).

	ICER* in €		
Utilities	**Base case** (=11,135)	**Favorable#**	**Unfavorable#**
utility for screening attendance	Base	11,125	11,135
utility for biopsy	Base	12,970	10,067
utility for diagnosis	Base	11,366	10,914
utility at 2 months after RP treatment	Base	11,870	10,815
utility at 2 months after RT treatment	Base	11,951	11,052
utility at 2 months to 1 year after RP treatment	Base	13721	10,177
utility at 2 months to 1 year after RT treatment	Base	13,741	10,105
utility for AS	Base	12,910	10,490
utility for post recovery period	Base	13,042	10,215
utility for Palliative therapy	Base	12,343	10,664
utility for terminal illness	Base	12,569	10,087
Costs		**+15%**	**-15%**
Costs of PSA test	Base	11,164	11,107
Costs of staging	Base	10,852	11,253
Costs of RP	Base	10,658	11,530
Costs of RT	Base	10,476	11,794
Costs of AS	Base	10,019	12,253
Costs of follow-up	Base	10,016	11,255
Costs of advanced case	Base	11,086	11,267

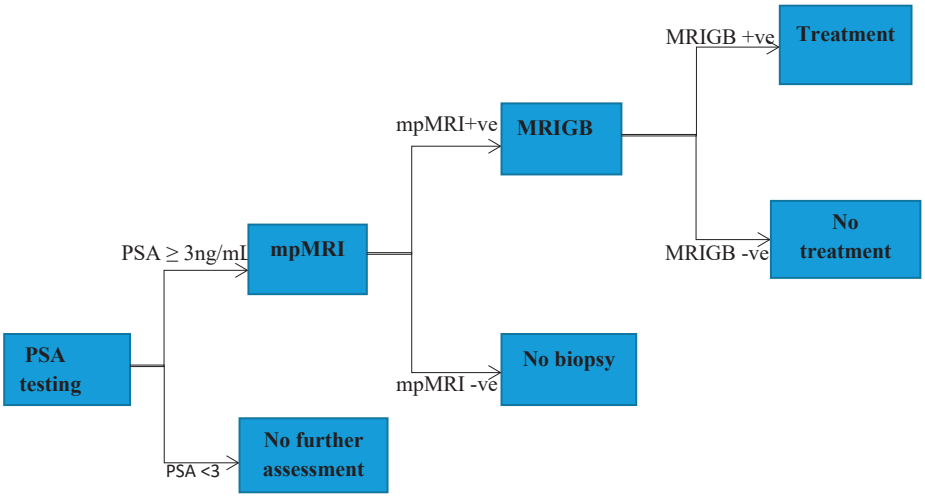
AS = active surveillance, ICER= incremental cost-effectiveness ratio, RP = radical prostatectomy, RT= radiation therapy

the utility estimates are varied using the favorable and unfavorable values based on literature[14]

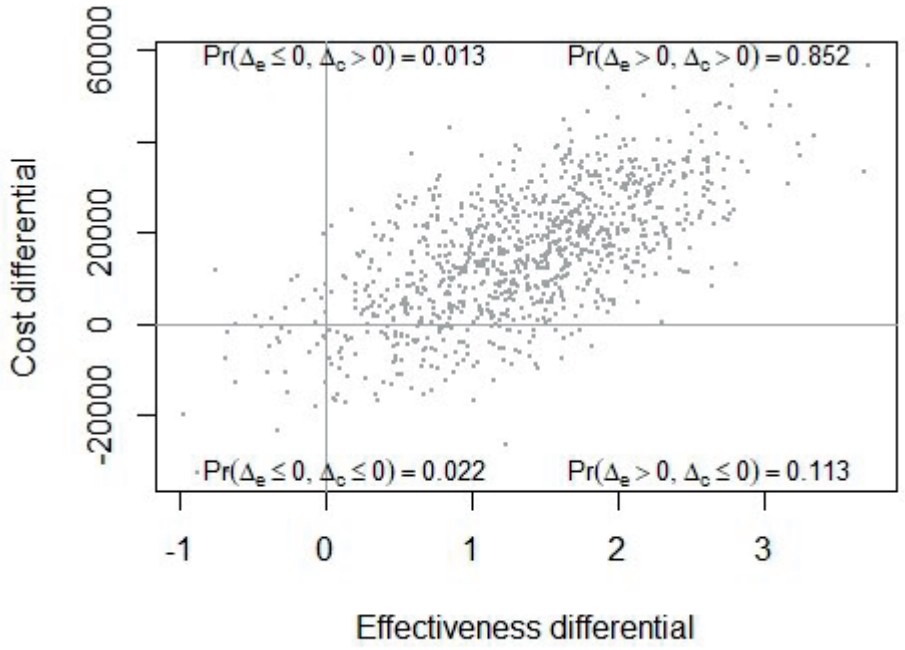
*The incremental cost effectiveness ratio of the MRI screening pathway as compared to the regular pathway



Supplementary Figure 1. Progression/transition of prostate cancer from no prostate cancer to different preclinical and clinical states. Each states in the model can also be local or distant, but for simplicity this is not included in the figure. T stands for tumor stage and G for Gleason score



Supplementary Figure 2. Schematic representation of the MRI pathway.



Supplementary Figure 3. The probabilities that the incremental cost-effect pairs of the MRI screening pathway, relative to the classical screening pathway, to fall in each four quadrants of the cost-effectiveness plain.

Part 3

Decisions Tools

6

A prostate cancer risk calculator that accounts for the long-term harms and benefits of PSA testing: A micro-simulation study

Abraham M. Getaneh, Eveline A.M. Heijnsdijk, and Harry J. de Koning

Manuscript and calculator in preparation.

ABSTRACT

Background: Current prostate cancer guidelines recommend that the decision to undergo early prostate specific antigen (PSA) testing should be shared between patients and their physicians based on information balancing the test's advantages and disadvantages. The aim of this study was to develop a prostate cancer risk calculator using lifetime predictions.

Methods: A Micro-simulation Screening Analysis (MISCAN) model was used for predictions of the different outcomes (risk prostate cancer, prostate cancer mortality, overdiagnosis, and life-years gained) included in our calculator. Age, PSA level, PSA test history, and Gleason scores were used as predictors in the model.

Results: The calibrated model closely predicted the observed prostate cancer incidence and mortality in the Dutch population in all but one age group. The risk of (high grade) prostate cancer increased with PSA measure, whereas overdiagnosis decreased. For a 60 years old man, for instance, the increment was from 3% (at a current PSA measure of 3 ng/mL) to 29% (at a PSA of 10 ng/mL) for prostate cancer in general, and from 0.5% (at a PSA of 3 ng/mL) to 8% (at a PSA of 10 ng/mL) for high grade prostate cancer. The risk of overdiagnosis decreased from 41% for a PSA of 3 ng/mL to 33% for a PSA of 10 ng/mL. The outcomes also varied across age. PSA measures, age, Gleason scores and treatment type determine the life-time risk of dying from prostate cancer and expected life-years gained from screening.

Conclusions: We have developed a prostate cancer risk calculator that incorporates both the long-term harms and benefits of PSA testing in addition to predicting the risk of having prostate cancer and associated death. The calculator can assist patients and their physicians before deciding to undergo a PSA test, a biopsy test, and select treatment.

INTRODUCTION

Although various large-scale studies and secondary analyses have confirmed the benefits of organized prostate specific antigen (PSA) screening,[1-3] a national PSA-based screening program has not yet been introduced in almost any country[4]. However, in many countries there is a high uptake of opportunistic PSA testing.[5-7] This form of PSA testing is likely less efficient and is accompanied by a higher risk of overdiagnosis compared to organized screening,[8,9] which is mainly due to too much screening in older age groups.[5] Current prostate cancer guidelines recommend that the decision to undergo early PSA testing should be shared between patients and their physicians based on information balancing the test's advantages and disadvantages.[10,11] However, the path from PSA testing to treating prostate cancer includes several decision points, and making the right decision at each of these points is not straightforward. This has led to the development of various prostate cancer risk prediction tools aiming to improve a shared decision between patients and their physicians.

Nowadays, various prostate cancer risk calculators are available online.[12-16] However, most of these calculators emphasised on reporting only a probability estimate of having prostate cancer, and this limits their clinical utility. Although the existing calculators have their own strength, they also lack several long-term (lifetime) predictions that could be more informative for patients and their physicians. To the best of our knowledge, there is no prostate cancer risk calculator, so far, that incorporates both the long term harms and benefits of attending a PSA test, or undergoing biopsy test, or select an immediate treatment. Given the natural history of the disease, estimates of the harms and benefits of PSA testing require either longer follow-up trial data, than existing now, or have to be simulated based on such trials.

We aimed to develop a prostate cancer risk calculator, in a Dutch situation, using multiple lifetime projections from a micro-simulation screening analysis (MISCAN) model. These include predictions of the risk of overdiagnosis, lifetime risk of dying from prostate cancer (with and without interventions), and expected life-years gained in addition to presenting a probability estimate of having prostate cancer. Our calculator can be used at three key decision points: decision before taking a PSA test, before undergoing a biopsy test following a positive PSA test result, and before selecting an immediate treatment (radical prostatectomy or radiation therapy) following a positive biopsy result. Such a calculator could supplement other risk assessment tools, in answering key answers, and play a role in reducing unnecessary worrying.

METHODS

Model description

The Micro-simulation Screening Analysis (MISCAN) model was used for predicting the different outcomes included in our calculator[17-19]. It is a stochastic model that simulates individual life histories from birth to death, and each individual in the simulation starts with no prostate cancer. Once an individual develops a prostate tumor, the model simulates the progression of the cancer (Supplementary Figure 1). For each individual it can project life histories without and with screening.

Prostate cancer survival in the absence of screening and localized treatment benefits (baseline survival) was determined at clinical detection based on Surveillance, Epidemiology, and End Results (SEER) data from the pre-PSA era (1983-1986). Other cause of death was modeled using a Dutch life table.[20] The effect of treatment on localized prostate cancer was modeled by assuming a relative risk of dying of 0.56 for radical prostatectomy compared with watchful waiting.[21] A 0.7 relative risk of dying was assumed for radiation therapy.[22] The distributions of treatments were based on age, stage, and Gleason score as described in previous studies.[22,23]

The model was calibrated to ERSPC data, as has been described before.[23] In order to adapt the model to a Dutch population setting and also account for younger age groups (50-54), we calibrated the model to prostate cancer incidence among the Dutch population between 1989 and 2016 by 5-year age categories from age 50 to age 75.[24] We compared prostate cancer mortality predicted by the model with the observed prostate cancer mortality over the same period (1989-2016) to validate the model. A man's PSA growth was modeled as a log-linear with a change-point at disease onset, and the PSA growth parameters were calibrated to SEER incidence data from 1990 to 2002 and to the PSA distribution of the first round of the ERSPC screening trial as described before.[19]

Model parameters were estimated by numerical minimization of the deviance between observed numbers of cases and the corresponding numbers predicted by the model. Deviances were calculated by assuming Poisson likelihood for incidence data and multinomial likelihood for stage distribution data.

Description of the tool

For each age (between 50-70 years), 10 million men were simulated over a lifetime period. Age, prostate specific antigen (PSA) level, PSA test history, and Gleason scores were used as predictors in the model. Based on the model outputs, we developed a

prostate cancer risk calculator to inform men about the harms and benefits of a PSA test, biopsy test and treatment besides predicting their risk of having prostate cancer and associated mortality. The calculator was designed for asymptomatic men between age 50 and 70, and it has three distinct parts. This enables patients and their physicians to use the calculator at three key decision points: decision to take a PSA test, decision to go for a biopsy test, and decision to select a treatment for localized prostate cancer (radical prostatectomy or radiation therapy).

An asymptomatic man (and his physician) who is interested in knowing more about the harms and benefits of attending a PSA test can enter his demographic information (age) and screening history (if any), and the calculator then presents the chance that the current PSA test will be positive (3 ng/mL as a cut-off), that a biopsy will confirm cancer (if biopsy will be done), that the cancer will be high-grade, that the cancer will be overdiagnosed, and lifetime risk of dying from prostate cancer (with and without attending the current PSA test). Gleason score of 7 and above is considered as high-grade cancer. The second part of the calculator was designed for an asymptomatic man who has a positive current PSA test result (cut-off 3 ng/mL) and wants to decide whether he should undergo a biopsy test. He and his physician can enter his age and the current PSA value, and the calculator uses this information to present the chance that the biopsy will find cancer, the cancer will be high-grade, the cancer will be overdiagnosed, and lifetime risk of dying from prostate cancer (with and without undergoing the biopsy test). The third part of the calculator is targeting an asymptomatic man who has a biopsy-confirmed localized cancer and wants to decide whether to select immediate treatment (radical prostatectomy or radiation therapy) or stay untreated. He and his physician can enter his demographic information, current PSA value, Gleason score, and treatment option. Then the calculator uses this information to present the lifetime risk of dying from prostate cancer (with, and without immediate treatment) and the expected life- years gained from immediate treatment (compared with no treatment at screen detection) under each treatment option. If the man decides not to be treated immediately, his disease progresses as if not screen detected.

The calculator was programed on R using package shiny.[25]

RESULTS

The model closely predicted the observed prostate cancer incidence and mortality in the Dutch population in the period 1989-2016, except for the 70-74 age group.

The mortality prediction is taken as validation of the model. (Supplementary Figure 2a and b). Outcomes describing the risk of having prostate cancer, prostate cancer related death, and the harms and benefits of a routine PSA testing/screening varied across the different predictors and decision points included in our calculator.

For men who never had a PSA test before and decide to be screened for the first time, the risk of having a positive PSA test result varied between 2% (age 50) and 29% (age 70). The chance that a biopsy test will find prostate cancer in general (if biopsy will be done) and high grade cancer ranged from 0.14% (age 50) to 6.5% (age 70) and from 0.08% (age 50) to 3% (age 70), respectively. Similarly, the risk of overdiagnosis increased with age: 19% at age 50 and 53% at age 70. The lifetime risk of dying from prostate cancer also differed across age at screening (Table 1). For men who had a PSA test history, the estimates varied both across the men's previous PSA level and age at the current test (Table 1). This part of the calculator is indicated in Figure 1.

The risk of having prostate cancer, high grade prostate cancer, and lifetime risk of dying from prostate cancer increased among screen positive patients as compared to the above category (men who don't know their current PSA measures yet) (Table 2). The risk of prostate cancer and high grade cancer increased with age and current

Table 1. Predictions of the risk of having positive PSA test, having prostate cancer, being overdiagnosed, and dying from prostate cancer for an asymptomatic 60 years old man (example) who is interested in knowing more about the harms and benefits of attending a PSA test.

		% of a positive PSA test[a]	% probability of PC[b]	% probability of HGPC[c]	% PC mortality with screening[d]	% PC mortality without screening[e]	% over-diagnosis[f]
Previous PSA test in last five years	No	11.4	2	0.7	2.7	3.2	34
	Yes :						
If yes, what was the last PSA level ?*	< 3	3	0.7	0.1	2.1	2.3	35
	3-3.9	5	1.3	0.3	2.3	2.4	38
	4-4.9	6	1.5	0.6	2.4	2.5	39
	5-5.9	8	2	1	2.5	2.7	38
	6-6.9	10	2.5	1.3	2.4	2.6	39
	7-7.9	12.5	3	1.4	2.4	2.6	42
	8-8.9	16	4	1.8	2.5	2.8	36
	9-9.9	21	5.2	2	2.7	3	35
	10-10.9	28	7	2.5	2.8	3.4	33

[a] Probability of currently having a positive PSA test; [b] Probability of having prostate cancer; [c] probability of high grade prostate cancer; [d] lifetime risk of dying from prostate cancer with the current PSA test; [e] lifetime risk of dying from prostate cancer without the current PSA test; [f] % of what *Last PSA level must be between 0 and 10.9 ng/mL. If the last PSA doesn't known, it is assumed as not screened before.

Figure 1. The first part of the calculator, designed for an asymptomatic man who is interested in knowing more about the harms and benefits of attending a PSA test. The image was a screenshot picture of the calculator.

Table 2. Predictions of the risk of having prostate cancer, being overdiagnosed, and dying from prostate cancer for an asymptomatic 60 years' old man who has a positive current PSA test result, and want to decides whether to go for a biopsy test.

Current PSA level *	% Cancer[a]	% HGC[b]	PC Mortality with biopsy[c]	PC Mortality without biopsy[d]	% ov.dx[e]
3-4	3	0.5	2.4	2.9	41
4-5	4.6	0.8	2.5	3.3	40
5-6	7	1.4	2.6	3.9	39
6-7	10	2.2	2.8	4.8	38
7-8	14	3.4	2.9	5.9	37
8-9	19	4.6	3.5	7.5	37
9-10	24	6.7	3.9	9.2	35
10-11	30	8.3	4.6	11.7	33

[a] Probability of prostate cancer; [b] probability of high grade prostate cancer; [c] lifetime risk of dying from prostate cancer with biopsy; [d] lifetime risk of dying from prostate cancer without biopsy; [e] risk of overdiagnosis
*Current PSA level must be between 3 and 10.9 ng/mL

PSA measure. For instance, a 60 years' old man with a PSA level of 7 ng/mL has 27% and 11% higher risks to be diagnosed with prostate cancer in general and high grade prostate cancer respectively than a 55 years' old man with the same PSA level. Similarly, the risks rose by PSA level; for the 60 years old man the increment was from 3% (at a PSA of 3 ng/mL) to 29% (at a PSA of 10 ng/mL) for prostate cancer in general, and from 0.5% (at a PSA of 3 ng/mL) to 8% (at a PSA of 10 ng/mL) for high grade prostate cancer. Age and PSA level had an opposite effect on the risk of overdiagnosis. This means that the risk increased with age, whereas it decreased with PSA level (Figure 2). Among men with PSA equals 3 ng/mL, for instance, the risk of overdiagnosis increased from 25% for age 50 to 59% for age 70. For 60 years for example, the risk of overdiagnosis decreased from 41% for PSA 3 ng/mL to 33% for PSA 10 ng/mL.

The lifetime risk of dying from prostate cancer increased with a man's PSA level. For instance, a 60 years old man with a PSA level of 3 ng/mL will have 2.4% and 3% lifetime risk of dying from prostate cancer with and without undergoing the biopsy test respectively, whereas a man with the same age and a PSA level of 6 ng/mL will

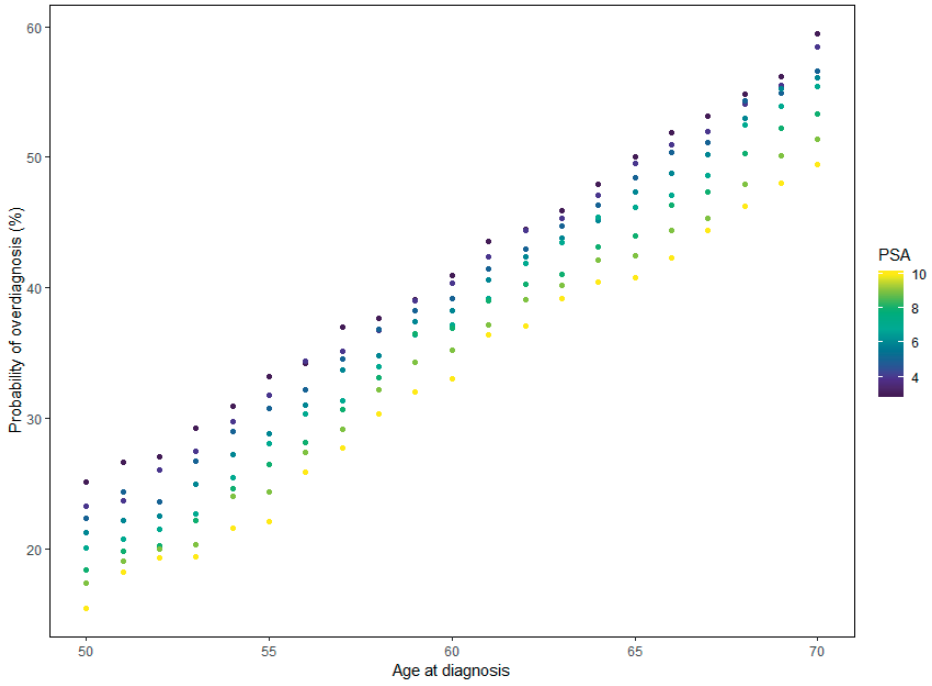


Figure 2. The risk of overdiagnosis across age and prostate specific antigen (PSA) level (between 3 to 10ng/mL)

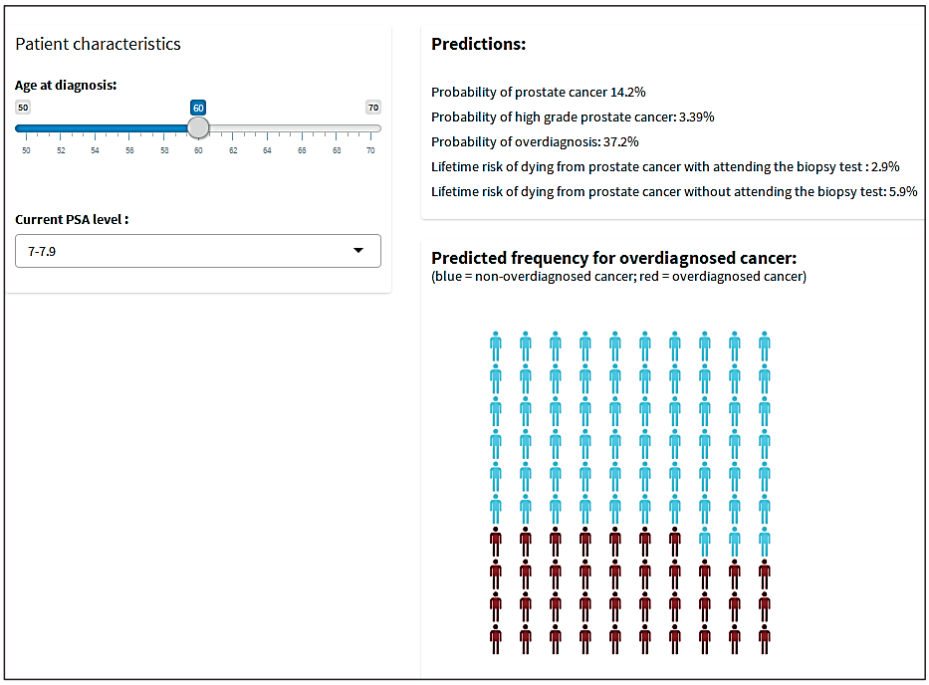


Figure 3. The second part of the calculator, designed for an asymptomatic man who already has a positive PSA test result and wants to decide whether he should undergo a biopsy.

have 3% and 5% lifetime risks respectively (Table 2). The prostate cancer mortality benefit of undergoing the biopsy test increased with PSA level, whereas it decreased with age. This part of the calculator is indicated in Figure 3.

For men with a biopsy confirmed prostate cancer, their future (lifetime) risk of dying from prostate cancer varied across age at the time of diagnosis, PSA level, Gleason score, and immediate treatment (if the patient decide to be treated immediately) (Table 3). For illustrations, consider a 60 years old man who was recently diagnosed with prostate cancer following routine PSA screening and decided to be treated immediately with radical prostatectomy. His PSA level was 10 ng/ml and biopsy Gleason score was 6 (low grade cancer). Based on these inputs (predictors) combination, the man will have 2.4% of lifetime risk of dying from prostate cancer. If the man decided not to be treated immediately, his lifetime risk of dying from prostate cancer would be 6%. The average life-years gained (from the immediate radical prostatectomy treatment) for this person will be 2.7 years. For a man with the same age and PSA level, but with high grade cancer, the lifetime risk of dying will be 8.3% and 13% with and without immediate radical prostatectomy treatment

Table 3. Lifetime prostate cancer related mortality (with and without immediate treatment) and expected life years gained projections for an asymptomatic 60 years old man who has a biopsy confirmed prostate cancer.

Current PSA level*	Grade	No treatment#	Radical prostatectomy		Radiation therapy	
		PCM in %	PCM in %	LYG	PCM in %	LYG
3-4	6	1.7	1.1	0.23	1.3	0.22
	≥7	3.8	3.5	0.34	3.6	0.32
4-5	6	1.8	1.2	0.36	1.3	0.34
	≥7	4	3.8	0.52	4	0.50
5-6	6	2.2	1.2	0.53	1.33	0.51
	≥7	4.8	4.3	0.74	4.6	0.72
6-7	6	2.6	1.3	0.79	1.4	0.77
	≥7	5.6	4.9	1	5.2	0.97
7-8	6	3	1.4	1.1	1.5	1
	≥7	6.7	5.1	1.4	5.4	1.2
8-9	6	3.7	1.6	1.5	1.8	1.4
	≥7	8.3	6.2	1.7	6.6	1.7
9-10	6	4.6	1.7	1.9	1.9	1.8
	≥7	10.2	7	2.2	7.5	2
10-11	6	6.33	2.4	2.7	2.5	2.7
	≥7	12.7	8.3	2.8	8.8	2.7

[#] In this case the disease progresses as if not screen detected
PCM = prostate cancer related mortality; LYG = life years gained (it is the average life-years gained per patient calculated from all men in the simulation (with the same patient characteristics) who underwent treatment).
Current PSA level must be between 3 and 10.9 ng/mL

respectively. Generally, the risk of dying from prostate cancer is relatively lower among patients treated with radical prostatectomy than radiation therapy (Table 3). Similarly, a slight increment in life-years gained was also seen for men treated with radical prostatectomy than radiation therapy. The third part of the calculator is indicated in Figure 4.

DISCUSSION

We have developed a prostate cancer risk calculator that incorporates the probability estimates of having prostate cancer, high grade prostate cancer, lifetime risk of dying from prostate cancer, overdiagnosis and possible life-years gained from immediate treatment. The calculator enables patients at three different key points to make shared decisions with their physicians.

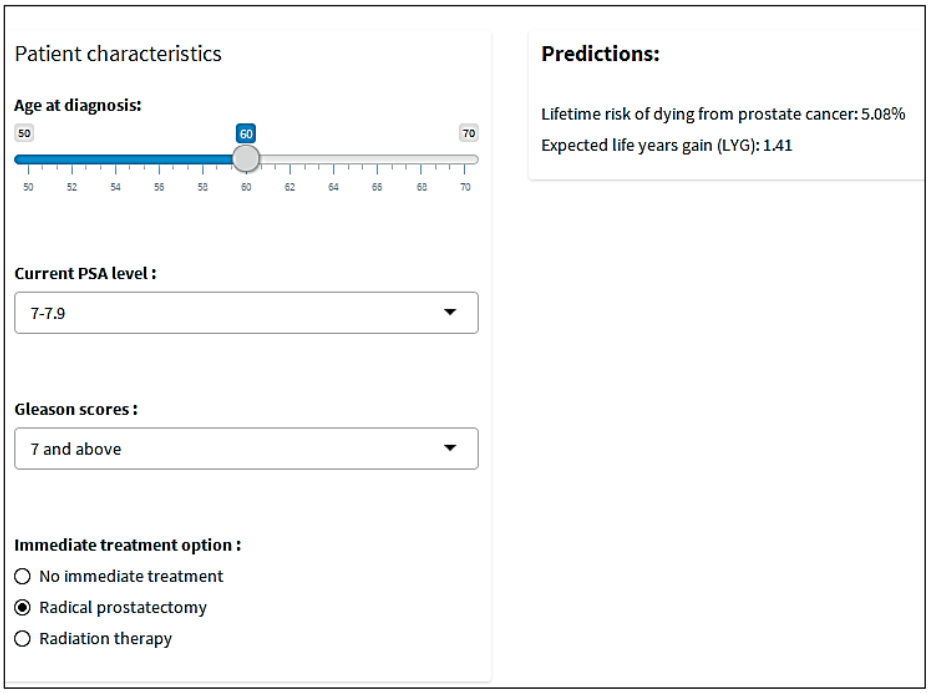


Figure 4. The third part of the calculator, designed for an asymptomatic man who has a biopsy confirmed cancer and wants to decide whether he should select immediate treatment (radical prostatectomy or radiation therapy) or stay untreated.

The importance of the first part of the calculator is to give information for men who are interested in knowing more about the harms and benefits of attending a PSA test. Knowing the long term effects of the test, such as, the prostate cancer mortality benefit and associated risk of overdiagnosis/overtreatment, could help patients to weigh the harm-benefit balance before undergoing the test. This could reduce the unnecessary worrying or anxiety caused by the test result, which might reduce man's quality of life.

Once patients know that they have a positive PSA test result (assumed cutoff 3 ng/mL), together with their physician they can enter their age and current PSA level to evaluate the future risk of dying from prostate cancer, and the harm and benefit of immediate treatment using the second part of the calculator (apart from knowing the chance that biopsy will find prostate cancer). This could help the patients to decide whether to undergo the biopsy. For instance, if a 70 years old man who has a positive PSA test result knows that the chance that the biopsy will confirm cancer is too low, discussing with his physician about additional risks like family history

and race, he might forgo the biopsy. This could avoid biopsy related complications and of course, overtreatment too. Age and current PSA levels are important predictors in our model. A previous study also reported that age is a strong predictor of overdiagnosis.[26] A low PSA level was associated with a substantially higher risk of overdiagnosis and lower risk of dying from prostate cancer as compared to higher PSA level, caused by high grade cancers being associated with higher PSA levels. Similarly, the risk of overdiagnosis and prostate cancer related mortality ranged widely across age at diagnosis. These could have an important clinical implication for decision about pursuing aggressive treatment.

The difference, under each treatment option, seen on the risk of prostate cancer related death and expected life years gained across patient characteristics (Gleason scores, PSA levels, and Age at the time of diagnosis) could influence the decision made by patients and their physicians in managing the disease. For instance, a 70 years old man with a Gleason 6 biopsy confirmed cancer and PSA level of 10 ng/mL has 2 times lower risk of dying from prostate cancer than a man at that same age and PSA level, but with high-grade prostate cancer (1.7% vs 3.4%). This man might decide to participate in active surveillance rather than to be treated immediately with radical treatments. This helps the patient to avoid unnecessary short and long term treatment related complications..

To our knowledge, this the first prostate cancer risk calculator that accounts both the harms and benefits of a PSA test besides predicting the risk of having prostate cancer. Therefore, the main strength of our calculator is that we were capable of incorporating the lifetime risk of dying from prostate cancer (both with and without immediate treatment), the risk of overdiagnosis, and possible life-years gained from a specific treatment. Although previous calculators[12-15] have their own strength (like having more predictors), none of them were able to account these long-term effects of PSA screening, which are, in fact, crucial in weighing the harm-benefit balance of a PSA test. The main reason for this could be the existing trial data, on which the calculators depended on, are not long enough to observe the long term effects of PSA screening, and this is why we necessitated to simulate them. Another strength of our study is that we were able to incorporate treatment options for patients who have a biopsy confirmed cancer. The calculator could provide information about the possible life-years gained and lifetime risk of dying from prostate cancer with and without selecting immediate treatment. A recently published nomogram incorporates life expectancy (chance of 10 years survival) in addition to predicting the risk of having prostate cancer.[12] Based on this life expectancy and the chance of having prostate cancer, the calculator recommends whether to refer a patient to a urologist.

However, it doesn't give further information on which the patient and his urologist could rely on for treatment decision. The patient would benefit more if he knows his Gleason score and associated lifetime risk of dying from prostate cancer (with and without a given treatment choice) before making treatment decisions. For instance, a man with a 10 years survival, low grade (6 and below) prostate cancer, and low risk of dying from prostate cancer would probably benefit more if he chose active surveillance than immediate radical treatment. Lastly, our decision tool can be used at three key points, before taking a PSA test, undergoing a biopsy test, and selecting treatment.

Our study has also some limitations. First, we only account for patients with a PSA level between 0 and 10 ng/mL, and PSA measures are categorized rather than being continuous. Second, because most of the outputs in our model are not observable (lifetime), we couldn't quantify the area under the curve (AUC). Therefore, our predictions depend only on the calibration. Third, in the first part of the calculator the PSA history poorly predicts the risk of overdiagnosis and mortality, so it needs caution in the interpretation. Finally, our calculator misses certain factors that perhaps should be considered when weighing decisions about PSA/biopsy test and treatment, for example, family history, previous biopsy history, prostate volume, PSA velocity, and race. This limits our calculator to men with an average risk of prostate cancer, and doesn't apply to men with additional risks like family history or race. Therefore, users should note that the purpose of this calculator is to supplement and improve other risk prediction tools and improve the patient-physician decisions about a PSA test and selection of immediate treatment for localized prostate cancer.

In conclusion, we have developed a prostate cancer risk calculator that incorporates both the harms and benefits of PSA testing. The calculator assists patients and their physicians before deciding a PSA test, a biopsy test, and select treatment. Together with other risk assessment tools, it could improve the shared decision between patients and physicians about PSA/biopsy test and subsequent interventions.

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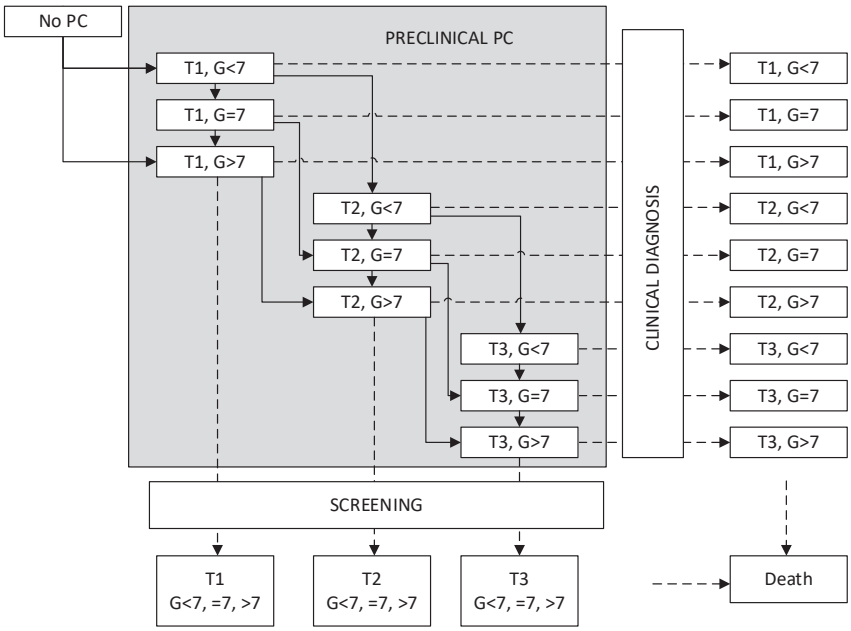
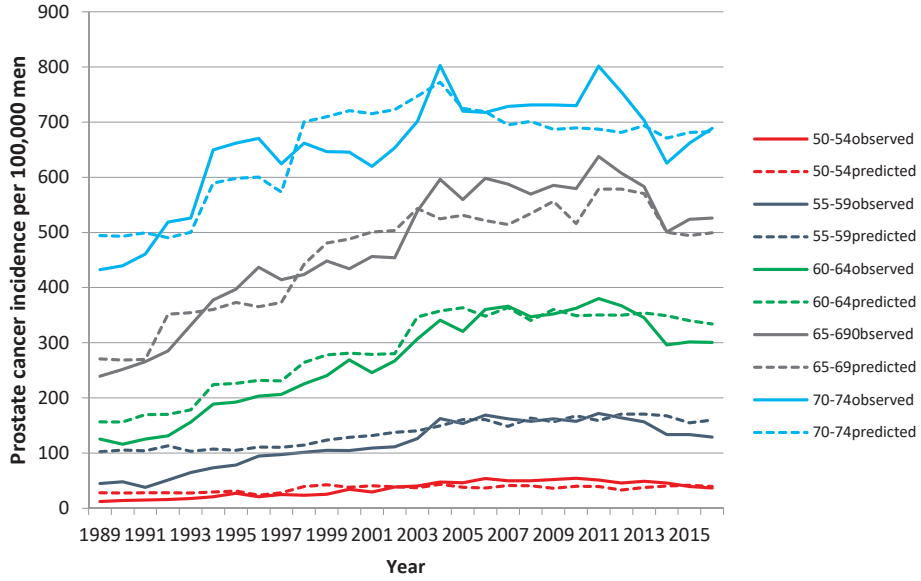
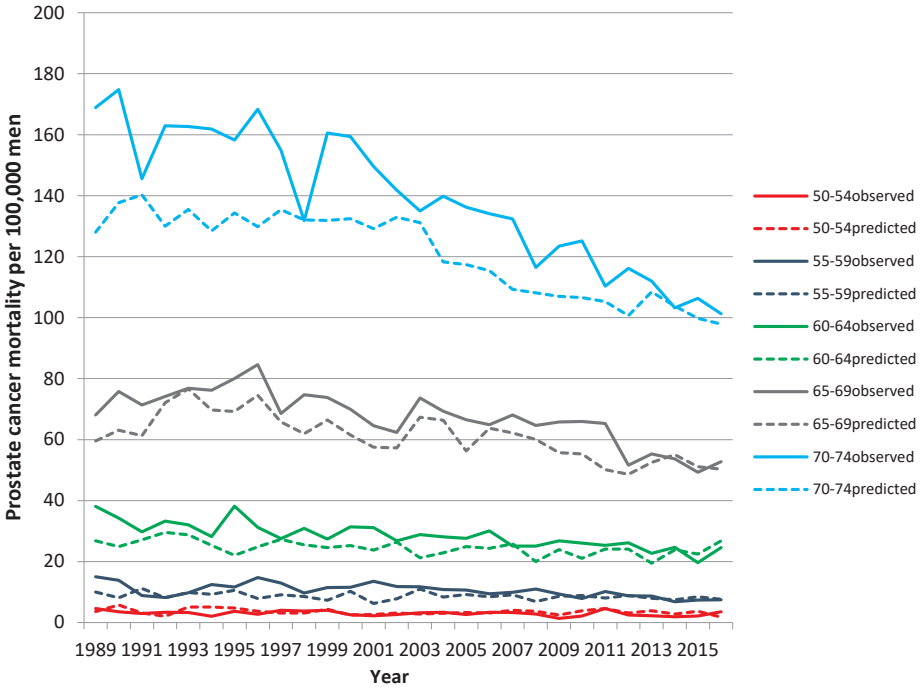
SUPPLEMENTARY MATERIALS



Supplementary Figure 1.The MISCAN prostate cancer model. The model also contains a distinction between local and distant states, but for the sake of simplicity it is not illustrated here. T= T-stage of prostate tumor and G = Gleason score of the tumor.



Supplementary Figure 2a. Observed and predicted prostate cancer incidence rates per 100,000 men across different age categories.



Supplementary Figure 2b. Observed and predicted prostate cancer mortality rates per 100,000 men across different age categories.

7 General Discussion

This thesis contains three main parts with various research questions, and this general discussion begins with descriptions of the answers to the research questions raised in each part of the thesis by summarizing the main findings. This is followed by further discussion and interpretation of the results and indication of future research directions. Finally, the main conclusions of this thesis and recommendations will be given.

7.1 ANSWERS TO THE RESEARCH QUESTIONS

Part 1. PSA Screening for prostate cancer

Research question 1: Can models provide additional information about PSA screening beyond the observed data of randomized controlled trials?

The ERSPC, PLCO and CAP trials were the three large randomized clinical trials aiming to study the effect of prostate cancer screening. However, in general, trials are limited in follow-up time to assesses the long-term effects of screening, especially when the lead time is long like the case of prostate cancer. Furthermore, trials lack alternative screening designs which are essential for finding an optimal screening strategy that can lead to a better balance between the harms and benefits.

In this study using the MISCAN prostate model, that includes quality of life estimates, we indicated that the harm-benefit ratio (overdiagnosis per cancer death averted) of a PSA based screening between the age group 55-63 is better than the broad 55-69 age group (the age group used in the recent USPSTF 'C' recommendation about prostate cancer screening, mainly based on trial data). The ratios were 3.2 and 5.4 respectively. The harm-benefit ratio was worst for the age group 64-69 (7.0).

In the same chapter, we also assessed whether the recently published Cluster Randomized Trial of PSA Testing for Prostate Cancer (CAP) changes the existing evidence for PSA testing by replicating the trial using MISCAN model. After replicating the trial with available data, we predicted a 0.94 prostate cancer mortality ratio over the period of 10 years, the same follow-up period as the trial. The prediction was very close to the observed mortality ratio. To account for the effect of length of follow up period, we also extended the projection to 15 and 20 years, but this did not change the prediction. Based on this we conclude that although the CAP trial did not show statistically significant differences in prostate cancer mortality after 10 years of follow-up, there may still be a mortality benefit.

Research question 2: Can we find an optimal cost-effective prostate cancer screening strategy at population level? If so, what are the associated long-term harms and benefits?

In this study, using the micro-simulation model, we assessed the harms, benefits, and cost-effectiveness of more than 200 alternative PSA based screening strategies, differing by screening start age (50, 51, 52, 53, 54, and 55), stop age (51-69), and intervals (1, 2, 3, 4, 8, and single test), in which efficacy was based on ERSPC trial. We found that the most optimum screening strategy would be screening between ages 55–64 at 3 years intervals, with an incremental cost-effectiveness ratio (ICER) of €19,733 per quality adjusted life-year (QALY). A 27% prostate cancer mortality reduction and 28 life-years gained (LYG) per 1000 men were predicted for this strategy. The associated risk of overdiagnosis for men detected with prostate cancer because of screening was 36% (11/30).

Part 2. Magnetic resonance imaging in prostate cancer screening

Research question 3: does the use of mpMRI as a triage test followed by an MRI-guided biopsy result in a better harm-benefit balance compared to regular PSA screening?

Major concerns with PSA based prostate cancer screening are the associated risk of overdiagnosis and subsequent overtreatment that affect the quality of life of a person. Using mpMR as a reflex test followed by MRI-targeted biopsy has been suggested to decrease the detection of low grade cancer and improved detection of clinically significant prostate cancer. However, its actual effect on the risk of overdiagnosis need to be quantified.

For this study, we found test sensitivity parameters for mpMRI and MRI-guided biopsy from literature, mainly meta-analysis. Since the MRI-guided biopsy has a better classification of graded as compared to TRUSGB, we also included different misclassification rates for the two pathways, based on values from literature. Using the MISCAN model we estimated a reduction of overdiagnosis, harm-benefit ratio, reduction of biopsies, detection of clinically significant and insignificant cancer, prostate cancer death averted, LYs, and QALYs gained for both strategies (the MRI screening pathway and regular screening pathway).

We found that the MRI screening pathway results in a 43% reduction in the risk of overdiagnosis compared to the regular screening pathway. A better harm-benefit ratio (overdiagnosis-per cancer death averted) was also predicted for the MRI pathway. The corresponding biopsy reduction, due to using mpMRI test as a triage before

biopsy, was 30%. A modest increment in prostate cancer mortality reduction, LYs, and QALYs gained was also seen in the MRI pathway compared to the regular screening pathway.

The results show that the use of mpMRI as a reflex test followed by an MRI-guided biopsy can substantially reduce the risk of overdiagnosis and improve the harm-benefit balance as compared to the regular prostate cancer screening-biopsy pathway.

Research question 4: Is the MRI-based prostate cancer screening more cost-effective than the regular screening pathway?

In this study, we assessed whether the MRI screening pathway (increasing cost) could also be more cost-effective than the regular prostate cancer screening pathway. We projected the net costs and effects (compared to no screening) for both screening strategies (triennial screening between the age 55 to 64 without MRI and with MRI). We found that the MRI screening pathway resulted in total discounted mean incremental costs of €15,413 (95% confidence interval (CI) of €14,556 - €16,272) and a corresponding 1.36 (95% CI of 1.31-1.40) discounted mean incremental QALYs gained as compared to the regular screening pathway. The probability that the MRI screening pathway is more cost-effective was around 84% at a WTP threshold of €20,000.

We conclude that when mpMRI is used after a positive PSA test and followed by MRI guided biopsy, it has a high probability to be more cost-effective than performing the regular PSA based screening, and below the suggested CEA cut-off.

Part 3: Online decision tools

Research question 5: Can we develop an online tool, with long term predictions, for patient-physician decision about prostate cancer screening?

Although trials have shown efficacy, and reasonable harm-benefit ratios were indicated using modelling studies, there is no population based PSA screening yet. Existing guidelines on prostate cancer screening recommend individual PSA testing.

In this study, the MIcro-simulation SCreening ANalysis (MISCAN) model was used for predictions of different (long-term) outcomes that are included in a “personalised calculator”. Age, prostate specific antigen (PSA) level, PSA test history, and Gleason scores were used as predictors in the model.

Based on the model prediction, we found that outcomes describing the risk of having (high grade) prostate cancer, prostate cancer related death, overdiagnosis, and expected life-years gained substantially varied across the different predictors included in the model. Using these model outputs, we developed a tool/calculator that can inform patients and their physicians about the harms and benefits of attending PSA test, undergoing biopsy, and taking treatment.

7.2 INTERPRETATION OF THE FINDINGS

PSA Screening for prostate cancer

The implementation of PSA based screening for prostate cancer at a population-level remains debated despite the substantial prostate cancer related mortality reduction observed in the European Randomized Study of Screening for Prostate Cancer (ERSPC)[1,2] . This is mainly because the beneficial mortality effect is counter balanced by the risk of overdiagnosis and subsequent treatment of indolent cancers that eventually affects man's quality of life and can also put the cost-effectiveness in question. However, RCTs in general lack long follow-up and alternative strategies in order to find a better harm-benefit balance that could make PSA screening more effective. Therefore, modeling is probably the only way through which we can find an optimum screening strategy among various competing screening protocols.

In 2018 the USPSTF issued a C-recommendation on screening for prostate cancer for men aged 55-69, urging clinicians to inform men about the potential benefits and harms of prostate-specific antigen (PSA) screening for prostate cancer[3]. The benefits are prostate cancer deaths prevented, life-years gained and prevention of advanced disease, and the harms overdiagnosis, living with a cancer diagnosis, and severe complications of treatment. The USPSTF indicated, based on the ERSPC data, that screening may avert 1 to 2 prostate cancer deaths over 13 years follow-up per 1000 men screened, and estimated a 20% to 50% risk of overdiagnosis. We agree that the balance between benefits and harms of PSA testing is too delicate to support screening men over the entire age range 55-69. But this not because PSA testing is not effective. A modeling study including quality of life estimates showed that it is better not to screen above age 63[4]. In chapter 2, using the same model, we indicated that the ratio between benefits and harms is much better for men screened at ages 55-63 than the broader 55-69 age group. This indicates that there would be an opportunity for USPSTF to give a B recommendation for prostate cancer screening for the narrower age group, 55-63 years. Pashayan etal[5] indicated that the probability of

overdiagnosis increased with age, being highest for the age group 65-69. This report is in agreement with our findings in chapter 2 and chapter 3.

Furthermore, modeling plays a crucial role when a trial fails to shows a statistically significant cancer mortality benefit. For instance the PLCO trial didn't show a prostate cancer mortality benefit for PSA screening, unlike the ERSPC trial[2,6]. However, a secondary model based analysis showed that after accounting for differences in implementation and settings between the two trials, the ERSPC and PLCO provide compatible evidence that screening reduces prostate cancer mortality[7]. Similarly CAP is the 2nd of the two trials that are clearly underpowered for statistical significance[8]. In chapter 2 of this thesis, after replicating the trial with our micro-simulation model, we indicated that the insignificant results from the CAP trial, the trial with a single PSA test and low acceptance rate (36%), could not refute PSA screening to be effective. The statistical insignificant result from the CAP trial should be interpreted by taking into consideration the low acceptance rate and the single test applied only at age 50. To see the beneficial effects of PSA screening, factors like sufficient attendance rate and repeated testing (apart from contamination of the control group as seen in the PLCO trial) are very crucial. The French center, one of the centers in the ERSPC trial, was not included in the mortality analyses since acceptance rates below 45% were expected to dilute the power of the trial[9]. Therefore the results in chapter 2 implies that, even when a trial shows no mortality benefit, well-validated modelling can strengthen the evidence on targeted interventions for improved early detection. Although a more detailed analysis with individual data from the CAP-trial may inform the models better, we feel it is imperative to show these results now for future health policy making.

To implement prostate cancer screening at a population level, a cost-effectiveness analysis is one of the key points policy-makers need to consider. In chapter 3, we assessed the harms, benefits, and cost-effectiveness of more than 200 screening scenarios. In this study, we also included the effect of PSA screening in the age group 50 to 55, where limited information is available, unlike several cost-effectiveness studies that start screening from age fifty five[1,4,10,11]. However, our cost-effectiveness analysis doesn't support screening for prostate cancer before age 55. Similarly, screening beyond age 64 is not the preferred strategy according to the analysis. Using the commonly used WTP of €20,000, we found that triennial screening between age 55 to 64 would be the optimal screening strategy. At what age screening should start, at what age it should stop, and what screening interval should be used has been some of the debatable questions in prostate cancer screening, and in this chapter, we tried to answer these important questions. However, these results should be

interpreted carefully as they are projected for a population with average health risk. This means that the results may not be applicable under certain clinical conditions, such as a man with high risks of prostate cancer (for instance with a first degree family history) may benefit from starting screening at an earlier age or extending the screening stop age that was recommended in the study. Additionally, the use of triage tests like mpMRI (chapter 4 and 5) and considering comorbidity status could further reduce the risk of overdiagnosis and/or improve the cost-effectiveness[12-18].

Reducing the harms of PSA screening using MRI

Nowadays, mpMRI is increasingly used to select men before biopsy and to perform targeted biopsy for suspicious lesions on MRI. Studies show that the use of mpMRI before biopsy and MRI-targeted biopsy is superior to the standard TRUSGB, by detecting less clinically insignificant cancers, and more clinical significant cancers[12,13,19]. However, quantifying the actual effects of MRI on overdiagnosis or cancer related mortality requires much longer follow-up time than the existing MRI trials and therefore to be modeled.

In chapter 3, after comparing more than 200 screening strategies, we found that PSA based screening would be optimal when we screen between age 55 to 64 at three-year intervals. Although this age targeted screening relatively reduces the risk of overdiagnosis, the strategy was still associated with about 36% of overdiagnosis (out of screen detected), and there could be a room to further reduce this risk of overdiagnosis. In chapter 4 we incorporated mpMRI as a triage test before biopsy and an MRI-guided biopsy was used instead of the TRUSGB. Our main results show that the screening protocol that includes MRI substantially reduces overdiagnosis (-43%) and biopsy procedures (-30%) and resulted in a better harm-benefit ratio compared to the protocol without MRI. A better approach to improve the harm-benefit ratio of PSA based prostate cancer screening would be to drastically reduce the harm, preferably while improving or maintaining the currently established benefits[20]. Interestingly, our findings are also in line with this concept in which the cancer mortality reduction, LYs, and QALYs gained are slightly increased in the MRI pathway than the regular PSA based screening pathway apart from the substantial reductions in overdiagnosis.

Despite the advantages, still there is a reluctance to include MRI into practice guidelines because it is perceived to be an expensive method[21]. It remains uncertain whether it is cost-effective, especially in a population-based screening setting. In chapter 5, we estimated the cost-effectiveness of the MRI screening pathway compared to the regular pathway, using the same screening strategies used in chapter

3. Our results show that the MRI strategy is more cost-effective (in about 84% of the probabilistic sensitivity analyses) than the regular screening strategy, at a WTP of €20,000. These findings together with the results in chapter 4 show that incorporation of mpMRI after a positive PSA test result followed by MRIGB is a promising method in addition to age targeted screening (chapter 3), and this can inform policy makers better regarding future implementation of prostate cancer screening at a population level.

There are some limitations associated with the findings in Chapter 4 and 5. First, we did not consider the combined approach of TRUGB and MRIGB. Studies show that the MRIGB still misses 10-20% of the clinically significant cancers[12,19,22] and also has more miss-classification of grades than the combined biopsy[23]. Second, the performance of MRIGB may vary in biopsy naïve and previously biopsied men, which has not explicitly been modeled in our studies. But in general, studies show that the performance of MRIGB is superior to that of TRUSGB either in biopsy naïve or previously biopsied men (although the degree may vary)[13,24]. The interpretation of our cost-effectiveness results in chapter 5 also needs caution since the costs of MRI are much lower in Europe than in countries like the United States.

Opportunistic PSA testing

In general, it is clear that opportunistic PSA testing, currently conducted widely, is less effective for reducing prostate cancer related mortality and associated with a higher risk of overdiagnosis as compared to organized population screening. For instance, the Goteborg trial showed that opportunistic screening resulted in a 12% relative prostate cancer mortality reduction as compared to 42% for organized screening[25]. The corresponding numbers of men needed to be diagnosed to avoid one prostate cancer death were 23 vs. 13. Screening at older age is among several reasons that makes opportunistic screening ineffective. For example, in the Netherlands, half of men who receive an initial PSA test is 70 years or older, of whom half are aged ≥80 years[26,27]. Therefore, from chapter 2 through chapter 5, we have tried to indicate possible future directions to implement organized population based prostate cancer screening and also showed how modelling is crucial in policy decision process. However, existing guidelines on prostate cancer screening recommend individual PSA testing and the decision to undergo the test should be shared between patients and their physicians[3,28]. But given the natural history of prostate cancer, it is usually challenging to give comprehensive and balanced information about prostate cancer screening. Web-based tools can be used to inform/support patient-physician decision about prostate cancer screening.

Web based tool to support patient physician decision about prostate cancer screening

Chapter 6 describes the calculator that we have developed. This calculator was designed for asymptomatic men between ages 50 and 70, and it has three distinct parts. This enables patients and their physicians to use the calculator at three key decision points: the decision to take a PSA test, the decision to go for a biopsy, and the decision to select a treatment for localized prostate cancer (radical prostatectomy or radiation therapy). Such predictive information of the calculator at different decision points has considerable value and can provide benefits for the men and physicians by reducing unnecessary worry from the PSA test, unnecessary biopsy, overdiagnosis and moreover unnecessary treatment.

The main strength of the calculator is that we were able of incorporating the lifetime risk of dying from prostate cancer, the risk of overdiagnosis, and possible life-years gained from a specific treatment. Although previous online prostate cancer calculators[29-32] have their own strength (like having more predictors), none of them were able to account these long-term effects of PSA screening, mainly due to the existing trial data, on which the calculators depend on, are not long enough to observe the long term effects of PSA screening.

A main limitation in this study is that the calculator misses certain factors such as family history, previous biopsy history, prostate volume, PSA velocity, race, and comorbidity status. This makes the calculator mainly applicable to men with an average risk of prostate cancer, and doesn't apply to men with additional risks. Furthermore, no specific decision threshold is provided in the calculator, so the final decision to proceed with a PSA test or biopsy or treatment is still left with the patient and physician based on the risk of having the cancer, risk of dying from the cancer, and the long-term harms and benefits of the test provided in the calculator.

7.3 FURTHER RESEARCH DIRECTIONS

Stratifying with comorbidity status and PSA level

As already mentioned elsewhere in this thesis, comorbidity status is not included in our studies. However, it may be important to account for the comorbidity status when analyzing an optimal screening strategy. This is because PSA screening in men with more comorbidity is associated with high risks of overdiagnosis and subsequent overtreatment as these men are more likely to die from other competing diseases/ conditions than prostate cancer. Although a previous study indicated the effect of

comorbidity on the age of screening cessation, the study had major limitations: the comorbidity lifetable used only starts at age 65, and are also not relative to a specific disease but to comorbidity scores[33]. Stratifying by PSA level is another method that can reduce unnecessary test and overdiagnosis. Heijnsdijk et al, reported that compared to biennial screening, PSA stratified screening strategy substantially reduce number of tests and modestly reduce overdiagnosis[34]. However, this study also assumed that 100% of men received biopsy after a positive PSA test regardless of patients comorbidity status, and this could be one reason why the overdiagnosis only reduced modestly. Therefore, more research need to be conducted about the effect of stratifying both by comorbidity and PSA level on the harm-benefit balance of PSA screening.

Combined biopsy (MRI-targeted and Systematic biopsy)

Our studies, in chapter 4 and 5, assess the effects of MRI-targeted biopsy and systematic biopsy separately. However, combined biopsy could result in better detection of clinically significant cancer and has a lower misclassification rate of grade than using either TRUSGB or MRIGB alone[23]. On the other hand, it is also important to know that combined biopsy also increases the detection of clinically insignificant cancer[23,27]. Hence future research should analyze the effects of using combined biopsy, especially in a population based screening setting. Furthermore, there are various ways to use MRI in a screening setting, and it is not clear which one is best. For instance, if an mpMRI does not detect lesions suspicious for prostate cancer, either no biopsy or a standard biopsy can be performed. However, in our studies (chapter 4 and 5) only the no biopsy option was considered, and this caused missing of 11% clinically significant cancer (due to not performing biopsy) as also reported in Pokorny et al[14]. Another point is that we evaluated the effects of MRI only in a single screening strategy (an optimal screening strategy that we found in chapter 3).

Novel molecular tests

Considering novel tests that use biomarkers and genetic polymorphism can result in a better detection of men with clinically significant cancer and also facilitate therapeutic decision. Various novel molecular tests, such as single nucleotide polymorphisms, 4Kscore, PCA3, SelecMDx, and Prostate Health Index, have been proposed to improve the selection of men with clinically significant prostate cancer, reduce unnecessary biopsies and reduce detection of clinically insignificant cancer[35,36]. The aim of using these tests is not to replace the PSA test, but rather to provide complimentary information that can enhance the prediction of high grade cancer. When these novel tests are used together with other diagnostic tools such as mpMRI, they might also reduce unnecessary biopsies without or with minimal risks of miss-

ing clinically significant cancers[37,38]. For instance, in chapter 4 we indicated that the use of mpMRI as a reflex test misses to detect 11% of clinically significant cancer, and integrating such novel tests would reduce this risk of missing clinically relevant cancers. Future research should analyze the exact effects of using such novel molecular tests in the harm-benefit balance of prostate cancer screening under various screening scenarios.

7.4 MAIN CONCLUSIONS

The following conclusions are made, based on the results of this thesis:

- Modeling can play an important role in policy decisions for (prostate) cancer control. This is especially true when it is difficult to get sufficient information, such as long-term effects of a given intervention, from RCTs and other observational studies.
- Compared to the wide 55-69 age range for PSA testing used in the USPSTF's latest "C" recommendation for PSA testing, the 55-63 age range has a better harm-benefit balance
- The result reported from the CAP trial about the insignificant prostate cancer mortality benefit of one PSA screening test (at 36% coverage) cannot refute PSA screening to be effective. The CAP trial rather should be interpreted taking into account the single test offered and its low acceptance rate (36%).
- The optimal age targeted PSA based prostate cancer screening would be screening between age 55-64 at three year intervals. Screening above this age is associated with high risks of overdiagnosis and higher costs. Similarly screening before age 55 is not supported based on the cost-effectiveness analysis.
- Using mpMRI as a triage test after a positive PSA test result followed by an MR-guided biopsy can substantially reduce the risk of overdiagnosis and improve the harm-benefit ratio as compared to the regular PSA screening. This method also significantly reduces the need for biopsy (up to 30%).
- Incorporation of mpMRI in prostate cancer screening with subsequent MRI guided biopsy has also a high probability to be cost-effective compared to the regular PSA screening.
- We developed a prostate cancer risk calculator that incorporates both the long term harms and benefits of a PSA testing. The calculator can assist patients and their physicians before deciding to undergo a PSA test, a biopsy, and select the treatment. Together with other risk calculators, it could improve the shared decision making between patients and physicians.

7.5 RECOMMENDATIONS

- The USPSTF has still room to revise its C recommendation for PSA based prostate cancer screening. More specifically, there may be a case for the USPSTF to consider a B-recommendation for PSA testing for the 55–63 age group.
- The implementation of organized population based prostate cancer screening should be considered by policy makers taking into account the current evidence on prostate cancer screening, including modeling studies, being a cost-effective public health intervention.
- mpMRI and subsequent targeted biopsy should be considered in the implementation of prostate cancer screening at a population level because this method substantially reduces overdiagnosis which is one of the main barriers that hinders the introduction of population-based PSA screening.
- More risk stratification like screening by comorbidity status, and using of novel molecular tests could also be considered to make PSA screening more effective by further reducing the risk of overdiagnosis and unnecessary biopsy.
- Use a web-based tool with long-term harms and benefits, like the one included in this thesis; the effect of more predictors could be investigated.

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Summary

Prostate cancer is the second most commonly diagnosed cancer and the 5th leading cause of cancer mortality in men across the world. In Europe the disease has become the second frequent cause of cancer-related death in men behind lung cancer.

The ERSPC, PLCO and CAP trials were the three largest randomized controlled trials that assessed the effect of PSA screening on prostate cancer mortality reduction. Although the PLCO and CAP trials did not show a significant mortality benefit for PSA screening, the ERSPC trial showed after 16 years follow-up a 20% relative prostate cancer mortality reduction for the intervention (screening) arm. There are various differences in the design and implementation among the trials that could explain the discrepancy. A secondary model based analysis showed that after accounting for the differences in implementation and settings between the ERSPC and PLCO, the two trials provide compatible evidence that screening reduces prostate cancer. Whether the insignificant results from the CAP trial change the evidence of PSA testing was addressed in this thesis (**Chapter 2**) by replicating the trial using a simulation model.

Despite prostate cancer remains among the most common causes of cancer-related morbidity and mortality among men, and various studies showed the benefit of PSA screening on prostate cancer mortality reduction, a population-based prostate cancer screening program has not yet been introduced in almost all countries, in contrast with breast, cervical, and colorectal cancers. Important questions, like at what age PSA screening should start, at what age it should stop, and at what interval to screen should be used, remain debatable and need to be explored more. Answering these questions needs comparisons of various alternative screening strategies/scenarios as well as a long follow-up time, which are unlikely or even impossible from trial studies. Similarly, assessing the effects of promising triage tests like MRI on the reduction of the risk of overdiagnosis needs long-term follow-up due to the long lead time of prostate cancer. To answer these questions modeling can play crucial roles, which can help to assess the harms, benefits, and cost-effectiveness of different alternative prostate cancer screening strategies.

Throughout this thesis, the MIcro Simulation SCreening ANalysis (MISCAN) model for prostate cancer was used to assess the effects of prostate cancer screening, particularly at a population level. The first part of this thesis describes how modeling can play a crucial role in policy decision making process regarding (prostate) cancer screening. Furthermore, we assessed an optimal prostate cancer screening strategy at a population level by comparing several alternative screening strategies. The second part of this thesis evaluates the effects of using MRI in prostate cancer

screening and its cost effectiveness in a population screening setting. The third part of the thesis describes the calculator that includes long-term harms and benefits of PSA-based prostate cancer screening.

Chapter 2 indicates how modeling can provide additional information about PSA screening beyond the observed data of randomized controlled trials. In 2018 the USPSTF gave a "C" recommendation for prostate cancer screening between the age 55 to 69, mainly based on the ERSPC trial. However, given the natural history of prostate cancer with on average slow progression, predicting the harm- benefit ratio based on trial data with a relatively short follow-up period is difficult. Using the MISCAN prostate cancer model we showed that the harm-benefit ratio (overdiagnosis/death averted) of PSA screening between the age 55-63 is much better than the 55-69 age group (3.2 vs 5.4), and therefore the USPSTF could consider a B recommendation. Apart from this, in **chapter 2** using the MISCAN prostate model, we indicated that the insignificant results from the CAP trial do not refute the existing evidence about the mortality benefit of PSA screening, rather the results should be interpreted taking into consideration the single test offered at age 50 and its low acceptance rate (36%).

In **chapter 3**, using the MISCAN prostate model, we evaluated more than 200 different PSA screening strategies by considering different starting ages, stopping ages, and intervals of screening. Using a willingness-to-pay threshold of €20,000 per QALY gained, we found that screening between the age 55 to 64 at three years intervals would be the optimal population-based screening strategy. This strategy resulted in a 27% prostate cancer mortality reduction, 28 life- years gained per 1000 men, and a 36% risk of overdiagnosis.

The aim of **chapter 4** was to determine the effects of using mpMRI and MRI-guided biopsy on prostate cancer screening. mpMRI has become an important test to select men with a positive PSA test result before biopsy and perform targeted biopsy. Using the MISCAN prostate model, we added mpMRI to the optimal screening strategy that we found in **chapter 3** and replaced the regular systematic biopsy with MRI-guided biopsy. Based on this, we found that when mpMRI is used after a positive PSA test result and followed by an MRI-guided biopsy, it resulted in a substantial reduction of biopsies and risk of overdiagnosis, and a better harm-benefit balance (overdiagnosis per death averted) compared to the regular PSA screening (all positive PSA test are followed by systematic biopsy).

In **chapter 5**, it was assessed whether the MRI based prostate cancer screening strategy is more cost-effective than the regular PSA-based screening using the same model as used in **chapter 4**. We found that in 84% of the probabilistic sensitivity analyses, the MRI-based screening strategy is more cost-effective than the regular screening pathway.

From **chapter 2** through **chapter 5**, we tried to show possible directions that can help future implementation of prostate cancer screening at a population level. The present guidelines, however, recommend individual PSA screening and the decision to undergo the test should be shared between patients and their physician. Therefore, in **chapter 6**, we developed a calculator aiming to improve patient-physician decision before taking a PSA test, before undergoing biopsy, and before deciding to treat or not. The risk of having (high grade) prostate cancer, prostate cancer related death, overdiagnosis, and expected life-years gained substantially varied across the different predictors included in the model.

Conclusions and recommendations

Based on the results of this thesis the following conclusions are derived:

- Modeling can play an important role in policy decisions for (prostate) cancer control. This is especially true when it is difficult to get sufficient information, such as long-term effects of a given intervention, from RCTs and other observational studies.
- Compared to the wide 55-69 age range for PSA testing used in the USPSTF's latest "C " recommendation for PSA testing, the 55-63 age range (simulated in our model) has a better harm-benefit balance.
- The insignificant result reported from the CAP trial about the mortality benefit of PSA screening cannot refute PSA screening to be effective. The CAP trial rather should be interpreted taking into account the single test offered and its low acceptance rate (36%).
- The optimal age targeted PSA based prostate cancer screening would be screening between age 55-64 at three year intervals. Screening above this age is associated with high risks of overdiagnosis and higher costs. Similarly screening before age 55 is not supported based on the cost-effectiveness analysis.
- Using mpMRI as a triage test after a positive PSA test result followed by an MR-guided biopsy can substantially reduce the risk of overdiagnosis and improve the harm-benefit ratio as compared to the regular PSA screening. This method also significantly reduce the need for biopsy (up to 30%).

- Incorporation of mpMRI in prostate cancer screening with subsequent MRI guided biopsy has also a high probability to be cost-effective compared to the regular PSA screening.
- We developed a prostate cancer risk calculator that incorporates both the long term harms and benefits of a PSA testing. The calculator can assists patients and their physicians before deciding to undergo a PSA test, a biopsy, and select the treatment. Together with other risk calculators, it could improve the shared decision between patients and physicians.

Based on the results and conclusions of this thesis, the following recommendations are given:

- The USPSTF has still room to revise its C recommendation for PSA based prostate cancer screening. More specifically, there may be a case for the USPSTF to consider a B-recommendation for PSA testing for the 55–63 age group.
- The implementation of organized population based prostate cancer screening should be considered by policy makers taking into account the current evidence on prostate cancer screening, including modeling studies.
- mpMRI and subsequent targeted biopsy should be considered in the implementation of prostate cancer screening at a population level because this method substantially reduces overdiagnosis which is one of the main barriers that hinders the introduction of population-based PSA screening.
- More risk stratification like screening by comorbidity status, and using of novel molecular tests could also be considered to make PSA screening more effective by further reducing the risk of overdiagnosis and unnecessary biopsy.
- Build a web based tool with long term harms sand benefit, like the one included in this thesis, but with more predictors.

Samenvatting

Prostaatkanker is de op een na meest gediagnosticeerde kanker en de 5e oorzaak van kankersterfte bij mannen wereldwijd. In Europa is de ziekte de tweede doodsoorzaak bij mannen na longkanker.

De ERSPC-, PLCO- en CAP-trials waren de drie grote gerandomiseerde gecontroleerde onderzoeken die het effect van PSA-screening op de vermindering van de sterfte aan prostaatkanker evalueerden. Hoewel de PLCO- en CAP-onderzoeken geen significante mortaliteitsreductie lieten zien voor PSA-screening, toonde de ERSPC-studie na 16 jaar follow-up een relatieve reductie van de prostaatkankersterfte met 20% voor de interventie (screening) -arm. Er zijn een aantal verschillen in opzet en uitvoering tussen de trials die de discrepantie zouden kunnen verklaren. Een secundaire modelgebaseerde analyse toonde aan dat, als rekening gehouden wordt met de verschillen in opzet en uitvoering tussen de ERSPC en PLCO, de twee trials vergelijkbaar compatibel bewijs leveren dat screening de sterfte aan prostaatkanker vermindert. Of de niet-significante resultaten van de CAP-trial het bewijs van PSA screening veranderen, werd in dit proefschrift (**Hoofdstuk 2**) onderzocht door de studie te repliceren met behulp van een simulatiemodel.

Ondanks dat prostaatkanker nog steeds de meest voorkomende oorzaak is van kankergerelateerde morbiditeit en mortaliteit bij mannen, en verschillende studies het effect van PSA-screening op de vermindering van de sterfte aan prostaatkanker hebben aangetoond, is in bijna geen enkel land een bevolkingsonderzoek naar prostaatkanker geïntroduceerd in tegenstelling tot borst-, baarmoederhals- en colorectale kanker. Belangrijke vragen, zoals de leeftijd waarop PSA-screening zou moeten beginnen, op welke leeftijd het zou moeten stoppen en met welk interval er gescreend moet worden, blijven discutabel en moeten verder worden onderzocht. Om deze vragen te beantwoorden, zijn vergelijkingen nodig van verschillende alternatieve screeningsstrategieën / -scenario's, evenals een lange follow-uptijd die onwaarschijnlijk of zelfs onmogelijk is uit trials. Evenzo vereist het beoordelen van de effecten van veelbelovende triagetests, zoals MRI, op de vermindering van het risico op overdiagnose een langdurige follow-up vanwege het langzame verloop van prostaatkanker. Hier speelt modellering een cruciale rol, wat kan helpen bij het beoordelen van de nadelen, voordelen en kosteneffectiviteit van verschillende alternatieve screeningsstrategieën voor prostaatkanker.

In dit proefschrift werd het MIcro Simulation SCreening ANalysis (MISCAN) -model voor prostaatkanker gebruikt om de effecten van prostaatkankerscreening te beoordelen, met name op populatieniveau. Het eerste deel van dit proefschrift beschrijft hoe modellering een cruciale rol kan spelen in het besluitvormingsproces

van beleid met betrekking tot (prostaat) kankerscreening. Verder hebben we een optimale screeningstrategie voor prostaatkanker op populatieniveau beoordeeld door verschillende alternatieve screeningstrategieën te vergelijken. Het tweede deel van dit proefschrift evalueert de effecten van het gebruik van MRI bij screening op prostaatkanker en de kosteneffectiviteit ervan in een bevolkingsonderzoek. Het derde deel van het proefschrift beschrijft een calculator die de langetermijn nadelen en voordelen van prostaatkankerscreening met PSA omvat.

Hoofdstuk 2 gaf aan hoe modellering aanvullende informatie kan opleveren over PSA-screening bovenopde geobserveerde gegevens van gerandomiseerde gecontroleerde studies. In 2018 gaf de USPSTF een "C" -aanbeveling voor prostaatkankerscreening tussen de 55 en 69 jaar, voornamelijk gebaseerd op de ERSPC-studie. Gezien de natuurlijk beloopvan prostaatkanker, met een langzame groei, is het echter moeilijk om de balans tussen nadelen en voordelen op basis van onderzoeksgegevens te voorspellen. Daarom hebben we met behulp van het MISCAN-prostaatkankermodel aangetoond dat de nadelen-voordelenverhouding (overdiagnose / vermeden dood) van PSA-screening tussen de 55-63 jaar veel beter is dan die van de leeftijdsgroep 55-69 (3,2 versus 5,4). en de USPSTF zou hiervoor dus een B-aanbeveling kunnen overwegen. Afgezien hiervan hebben we in **hoofdstuk 2** met behulp van het MISCAN--prostaatmodel aangegeven dat de niet significante resultaten van de CAP-studie het bestaande bewijs over de mortaliteitsreductie van PSA-screening niet weerleggen, maar dat de resultaten moeten worden geïnterpreteerd rekening houdend met de enkele test, aangeboden op de leeftijd van 50, en het lage opkomstpercentage (36%).

In **hoofdstuk 3** hebben we met behulp van het MISCAN prostaatmodel meer dan 200 verschillende PSA-screeningsstrategieën met verschillende startleeftijden, stopleeftijden en intervallen van screening geëvalueerd. Met behulp van een WTP--drempel van € 20.000 per gewonnen QALY, ontdekten we dat screening tussen de 55 en 64 jaar met een interval van drie jaar de optimale screeningstrategie voor een bevolkingsonderzoek zou zijn. Deze strategie resulteerde in een reductie van 27% van de prostaatkankersterfte en 28 gewonnen levensjaren per 1000 mannen, en een risico op overdiagnose van 36%.

Het doel van **hoofdstuk 4** was om de effecten te bepalen van het gebruik van mp-MRI en MRI-geleide biopsie op prostaatkankerscreening. mpMRI is een belangrijke test geworden om mannente selecteren met een positief PSA-testresultaat vóór een biopsie, om een gerichte biopsie uit te voeren. Met behulp van het MISCAN-prostaatmodel hebben we mpMRI toegevoegd aan de optimale screeningstrategie die we in **hoofdstuk 3** hebben gevonden en hebben we de reguliere systematische biopsie

vervangen door MRI-geleide biopsie. Op basis hiervan ontdekten we dat wanneer mpMRI wordt gebruikt na een positief PSA-testresultaat gevolgd door een MRI-geleide biopsie, dit resulteerde in een substantiële vermindering van biopsieën en het risico op overdiagnose, en een betere nadelen-voordelenverhouding (overdiagnose per vermeden dood) vergeleken met de reguliere PSA-screening (alle mannen met een positieve PSA-test krijgen een systematische biopsie).

In **hoofdstuk 5** werd onderzocht of de MRI-gebaseerde prostaatkankerscreeningsstrategie kosteneffectiever is dan de reguliere PSA-gebaseerde screening met hetzelfde model als in **hoofdstuk 4**. We vonden dat in 84% van de probabilistische gevoeligheidsanalyses de MRI -gebaseerde screeningsstrategie kosteneffectiever is dan het reguliere screeningstraject.

Van **hoofdstuk 2** tot en met **hoofdstuk 5** hebben we geprobeerd mogelijke richtingen te laten zien die kunnen helpen bij de toekomstige implementatie van prostaatkankerscreening op populatieniveau. De huidige richtlijnen bevelen echter individuele PSA-screening aan en de beslissing om de test te ondergaan moet worden genomen door patiënten en hun arts samen. Daarom hebben we in **Hoofdstuk 6** een calculator ontwikkeld om de beslissing van de patiënt en arts te verbeteren voordat een PSA-test wordt gedaan, voordat een biopsie wordt ondergaan en voordat wordt besloten om al dan niet te behandelen. Het risico op (hooggradige) prostaatkanker, aan prostaatkanker gerelateerde sterfte, overdiagnose en verwachte gewonnen levensjaren varieerde aanzienlijk tussen de verschillende parameters die in het model zijn opgenomen.

Conclusies en Aanbevelingen

Op basis van de resultaten van dit proefschrift worden de volgende conclusies getrokken:

- Modellering kan een belangrijke rol spelen bij beleidsbeslissingen over screening en behandeling van (prostaat) kanker. Dit geldt vooral als het moeilijk is om voldoende informatie, zoals langetermijneffecten van een interventie, uit RCT's en andere observationele studies te halen.
- Vergeleken met de brede leeftijdsrange van 55-69 jaar voor PSA-testen die wordt gebruikt in de nieuwste "C" -aanbeveling van de USPSTF voor PSA-screening, geeft de leeftijdsrange van 55-63 jaar (gesimuleerd in ons model) een betere balans tussen voor- en nadelen.
- Het niet-significante resultaat van de CAP-studie over de mortaliteitsreductie van PSA-screening kan niet weerleggen dat PSA-screening effectief is. De CAP-studie

moet veeleer worden geïnterpreteerd als het aanbieden van één test en het lage acceptatiepercentage (36%).
- Prostaatkanker screening tussen leeftijd 55-64 jaar met intervallen van drie jaar is optimaal. Screening boven deze leeftijd gaat gepaard met een hoog risico op overdiagnose en hogere kosten. Evenzo wordt screening onder de leeftijd van 55 jaar niet ondersteund op basis van de kosteneffectiviteitsanalyse.
- Het gebruik van mpMRI als triagetest na een positief PSA-testresultaat gevolgd door een MR-geleide biopsie kan het risico op overdiagnose aanzienlijk verminderen en de balans tussen voor- en nadelen verbeteren in vergelijking met de reguliere PSA-screening. Deze methode vermindert ook aanzienlijk de behoefte aan biopsie (tot 30%).
- Het uitvoeren van mpMRI in prostaatkankerscreening met daaropvolgende MRI-geleide biopsie is waarschijnlijk ook kosteneffectief in vergelijking met de reguliere PSA-screening.
- We hebben een risicocalculator voor prostaatkanker ontwikkeld die zowel de lange-termijn nadelen en voordelen van een PSA-test omvat. De calculator kan patiënten en hun artsen helpen alvorens te beslissen om een PSA-test of een biopsie te ondergaan en een behandeling te selecteren. Samen met andere risicocalculatoren zou dit de gezamelijke beslissing tussen patiënten en artsen kunnen verbeteren.

Op basis van de resultaten en conclusies van dit proefschrift worden de volgende aanbevelingen gedaan:
- De USPSTF heeft nog ruimte om haar C-aanbeveling voor op PSA-screening op prostaatkanker te herzien in een B-aanbeveling voor PSA-screening voor de leeftijdsgroep 55-63.
- De implementatie van een georganiseerd bevolkingsonderzoek voor prostaatkanker zou door beleidsmakers moeten worden overwogen, rekening houdend met de huidige data over screening op prostaatkanker, met inbegrip van modelstudies.
- mpMRI en daaropvolgende gerichte biopsie moeten worden overwogen bij de implementatie van prostaatkankerscreening op populatieniveau, omdat deze methode overdiagnose substantieel vermindert, wat het belangrijkste probleem is dat de introductie van prostaatkankerscreening belemmert.
- Meer risicostratificatie, zoals screening afhankelijk van co-morbiditeit en het gebruik van nieuwe moleculaire tests, moet ook worden overwogen om PSA--screening effectiever te maken door het risico op overdiagnose en onnodige biopsie verder te verminderen.

- Een internet tool met voordelen en nadelen op lange termijn, zoals de tool die in dit proefschrift is opgenomen, maar met meer voorspellers, moet worden ontwikkeld.

About the author

CURRICULUM VITAE

Abraham Mekibeb Getaneh was born on August 9, 1984, in Holeta, Ethiopia. He completed his secondary school education in Holeta in 2003. In the same year he started studying veterinary medicine at Jimma university and obtained his doctor of veterinary medicine (DVM) degree in 2009. From 2010-2013 he worked as an instructor at Ambo university, Ethiopia. In 2013 he joined Utrecht university, the Netherlands as a Master Student after awarding the Netherlands fellowship program (NFP) scholarship, and he obtained an MSc degree in (Veterinary) Epidemiology and Economics in 2015. Following this he moved to Ethiopia and worked as an instructor until 2017 at Ambo university, Ethiopia. From November 2017 to May 2021 he was appointed as a Junior Researcher at the Department of Public Health, Erasmus Medical center, Rotterdam. During this period, he performed research using the MISCAN-prostate model by predicting the harm, benefits and Cost-effectiveness of various prostate cancer screening strategies, mainly at a population level. He also developed a decision tool for prostate cancer screening that accounts for the long term benefits and harms of PSA screening. The results of his investigations are described in this thesis.

PUBLICATIONS

In this thesis:

1. Getaneh AM, Heijnsdijk E, de Koning HJ. The role of modelling in the policy decision making process for cancer screening: example of prostate specific antigen screening. *Public Health Res Pract*.2019;29(2):2921912.

2. Getaneh AM, Heijnsdijk EAM, Roobol MJ, de Koning HJ. Assessment of harms, benefits, and cost-effectiveness of prostate cancer screening: A micro-simulation study of 230 scenarios. *Cancer Medicine.* 2020.

3. Getaneh AM, Heijnsdijk EAM, de Koning HJ. The comparative effectiveness of mpMRI and MRI-guided biopsy vs regular biopsy in a population-based PSA testing: a modeling study. *Sci Rep.* 2021;11(1):1-8.

4. Getaneh AM, Heijnsdijk EAM, de Koning HJ. Cost-effectiveness of multiparametric magnetic resonance imaging and MRI-guided biopsy in a population-based prostate cancer screening setting using a micro-simulation model. Accepted, *Cancer Medicine*. *Cancer Med. 2021; 10 (12):4046-53*

5. Getaneh AM, Heijnsdijk EAM, de Koning HJ. A prostate cancer risk calculator that accounts for the long-term harms and benefits of PSA testing: A micro-simulation study. In preparation.

Other Publications (unrelated to this thesis):

1. Getaneh AM, Mekonnen SA, Hogeveen H. Stochastic bio-economic modeling of mastitis in Ethiopian dairy farms. Prev Vet Med. 2017 Mar 1;138:94-103.

2. Getaneh AM, Gebremedhin EZ. Meta-analysis of the prevalence of mastitis and associated risk factors in dairy cattle in Ethiopia. Trop Anim Health Prod. 2017 Apr;49(4):697-705.

3. Abraham M, Fulasa TT, Firdessa R, Hailu E. Prevalence study on bovine tuberculosis and molecular characterization of its causative agents in cattle slaughtered at Addis Ababa municipal abattoir, Central Ethiopia. Trop Anim Health Prod. 2013 Mar;45(3):763-9.

PHD PORTFOLIO

Activity	Year	ECTS
Courses taken		
Scientific integrity	2019	0.3
Planning and Evaluation of Screening	2018	1.4
Advanced Topics in Decision-making in Medicine	2018	2.4
Advanced Decision Science Modeling	2018	1.4
Health economics	2019	0.7
Joint Models for Longitudinal and Survival Data	2019	0.7
Survival Analysis for Clinicians	2019	1.9
Advanced Analysis of Prognostic Studies	2020	0.9
Introduction to Bayesian Methods in Clinical Research	2020	1.4
Seminars and Workshops		
Seminars at the Department of Public Health, Erasmus MC Rotterdam	2017-2021	5.3
Methodology Club at Department of Public Health, Erasmus MC Rotterdam	2017-2021	1.8
Health(y) science research day , Rotterdam	2019	0.3
Oral Presentations	2018	
Cancer Intervention and Surveillance Modeling Network meeting, Michigan.	2018	0.3
Cancer Intervention and Surveillance Modeling Network meeting, Rockville, MD.	2018	0.3
Cancer Intervention and Surveillance Modeling Network, Seattle, WA.	2019	0.3
Screen section meeting for MISCAN Education	2019	0.3
Poster presentations		
International Cancer Screening Network Conference, Rotterdam	2019	0.3
35th Annual European Association of Urology (EAU) congress (online)	2020	0.3
International conferences and meetings		
Cancer Intervention and Surveillance Modeling Network meeting, Michigan.	2018	0.6
Cancer Intervention and Surveillance Modeling Network meeting, Rockville, MD.	2018	0.6
International Cancer Screening Network Conference, Rotterdam	2019	0.9
Cancer Intervention and Surveillance Modeling Network, Seattle, WA.	2019	0.6
Cancer Intervention and Surveillance Modeling Network meeting, Rockville, MD.	2019	0.6
35th Annual European Association of Urology (EAU) congress (online)	2020	2.9
Cancer Intervention and Surveillance Modeling Network meeting (Online)	2020	0.6
Other		
MISCAN education and documentation working group, and preparing a manual for MISCAN prostate cancer	2018-2019	5.6
Peer reviewing for BMC cancer	2019	0.9
Peer reviewing for BJU International	2020	0.9
Total	**2017-2021**	**34.5**

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