Individual and Mass Screening

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3.1 Introduction

Prostate cancer (PCa) is the second most frequently diagnosed cancer and the sixth leading cause of cancer death among men worldwide, with 914,000 new cases and 258,000 deaths were predicted to occur in 2008 (Ferlay et al. 2010). The lifetime risk of a PCa diagnosis is 15.8% for an individual man in the United States and approximately 9% for a man in Western Europe (Jemal et al. 2010; Collin et al. 2008; Bray et al. 2010). The lifetime risk of dying from PCa is lower, i.e. 2.8% in the United States and 3.1% in Western Europe (Jemal et al. 2010; Collin et al. 2008; Bray et al. 2010). Overall, these incidence and mortality rates give PCa an important public health relevance (Dixon et al. 2009).

The introduction and widespread use of prostate-specific antigen (PSA) testing for the early detection of PCa have led to major changes in PCa incidence (see Chap. 1), the tumour grade and stage at diagnosis, treatment, and the mortality from PCa over the past two decades. This has lead to the diagnosis of cancers that rather should not have been diagnosed, as their detection and subsequent treatment is unlikely to benefit patients, or even might harm them. These cancers are referred to as ‘overdiagnosis’, and their treatment as ‘overtreatment’.

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Table 3.1 The continuum of prostate cancer risk for different PSA ranges

Authors	Methods	Results							Notes
		PSA, ng/ml	PC, any grade			PC, Gleason grade ≥8			
			Sen (%)	Spec (%)	LR	Sen (%)	Spec (%)	LR	
Thompson et al. (2004), PCPT	Among 5,587 men, a PSA determination and a sextant prostate biopsy were performed to assess the sensitivity and specificity of PC detection for all PSA ranges in relation to Gleason grade.	1.1	83.4	38.9	1.4	94.7	35.9	1.5	*N*=1,225 (21.9%) were diagnosed with prostate cancer
		2.1	52.6	72.5	1.9	86.0	65.9	2.5	
		2.6	40.5	81.1	2.1	78.9	75.1	3.2	
		3.1	32.2	86.7	2.4	68.4	81.0	3.6	
		4.1	20.5	93.8	3.3	50.9	89.1	4.7	
		6.1	4.6	98.5	3.1	26.3	97.5	10.5	
		10.1	0.9	99.7	3.0	5.3	99.5	10.6	

PCPT Prostate Cancer Prevention Trial, *PC* prostate cancer, *PSA* prostate-specific antigen, *DRE* digital rectal examination, *TRUS* transrectal ultrasound, *Sen* sensitivity, *Spec* specificity, *LR* likelihood ratio

3.2 Screening Instruments: PSA, DRE, TRUS and the Prostate Biopsy

PSA (prostate-specific antigen), DRE (digital rectal examination), and transrectal ultrasound (TRUS) are the three main modalities for the early detection of PCa, of which serum PSA is the main tool. All serve as an indicator for diagnostic prostatic biopsies. The PSA test seems to be acceptable to the population as a screening procedure since the participation and adherence to mass screening in subsequent screening rounds is overall high (Schroder et al. 2003). PSA is a specific organ marker, but not strictly a tumour marker, since prostatitis and benign prostate hyperplasia (BPH) can also increase the serum PSA (Sindhwani and Wilson 2005; Rao et al. 2008). Due to this, no clear PSA threshold level exists as an indicator for diagnostic prostatic biopsies. The continuum of PCa risk for different PSA ranges is presented as a result of the Prostate Cancer Prevention Trial (PCPT) and the European Randomized Study of Screening for Prostate Cancer (ERSPC) (Thompson et al. 2004; Schroder et al. 2008) (Table 3.1). According to these study results, a physician who would like an 80% confidence in not missing a PCa should apply a PSA cut-off value of 1.1 ng/ml as indication for biopsy (sensitivity), which would result in 60% unnecessary (negative) biopsies (specificity) (Thompson and Ankerst 2007) (sensitivity = those who test positive divided by all those who have cancer, specificity = those who test negative divided by all those who do not have cancer).

Sensitivity decreases with the increasing PSA level, while specificity increases with the increasing PSA level. Consequently, lowering PSA cut-off levels leads to a higher detection rate of PCa, but also leads to an increase of negative (unnecessary) biopsies and of the overdiagnosis of harmless cancers (Postma et al. 2007). Currently, therefore, the suggested PSA cut-off to biopsy a man for screening differs between 2.6 and 4.0 ng/ml (Gohagan et al. 2000; Krumholtz et al. 2002; Schroder et al. 2003). Future data that include the comparison of the different studies with long follow-up might show the difference in mortality and morbidity outcomes using these different PSA thresholds.

3.2.1 PSA Velocity

The changes of PSA over time were analysed for their predictive value in follow-up rounds of population-based studies with intervals ranging between 1 and 4 years. PSA velocity (the increase of the absolute level of PSA during 1 year) showed in various studies a statistically difference between men with versus without cancer (in the ERSPC 0.62 ng/ml/year for PCa, versus 0.46 ng/ml/year for non-cancer Roobol et al. 2004; Loeb et al. 2007), and also in mean PSA doubling time (5.1 vs. 6.1 years). A threshold of 0.4 ng/ml/year discriminated between significant and insignificant

disease (Loeb et al. 2010). However, the variability of these parameters for individual decisions would be too high for practical application. In a multivariate analysis of a comparable cohort, the odds ratio for the PSA velocity was 0.73 (95% CI: 0.20–2.6; $P=0.64$) (Vickers et al. 2009). In another study, doubling of the PSA concentration within the 4 years, or any other increase of PSA (PSA velocity), did not contribute to the prediction of a detectable cancer (Raaijmakers et al. 2004). PSA velocity as indication for prostate biopsy is, however, included in some US guidelines. An empirical evaluation of the additional value of PSA velocity next to age, PSA, DRE, and family history showed, however, no evidence to support the recommendation that men with high PSA velocity should be biopsied in the absence of other indications (Vickers et al. 2011).

3.2.2 DRE

DRE is the classical method for PCa detection. However, DRE findings are only moderately reproducible, even amongst experienced urologists (Smith and Catalona 1995; Gosselaar et al. 2008). Further, DRE tends to diagnose the tumours when they are pathologically advanced and therefore less likely to be curable by radical prostatectomy (Thompson et al. 1987; Epstein et al. 1994). DRE has a low sensitivity and predictive value in men with low PSA levels (Crawford et al. 1996; Schroder et al. 1998; Yamamoto et al. 2001; Andriole et al. 2005; Bozeman et al. 2005). The positive predictive value of DRE is limited to 4–19% at serum PSA levels below 3.0 ng/ml. Therefore, several researchers suggest that with the use of DRE men will be screened more selectively, as men with a positive DRE are more likely to have high grade PCa than men with non-palpable tumours (Ghavamian et al. 1999; Borden et al. 2007). For this reason, the risk of omitting DRE, and therefore of biopsies at low PSA levels, might be that potentially aggressive tumours remain initially undetected. Still, screening without DRE at low PSA levels (PSA < 3.0 ng/ml) did not lead to the detection of significantly more (poorly differentiated) carcinomas 4 years later in a mass screening program (Gosselaar et al. 2006).

3.2.3 TRUS

TRUS has remained the standard investigation tool for systematic diagnostic prostate needle biopsy since the mid-1980s. TRUS has the advantage of facilitating more accurate measurements of prostate size, which may help interpretation of PSA results (Benson et al. 1992a, b). As serum PSA is closely related to prostatic volume, the PSA density can improve the diagnostic specificity, reducing the number of unnecessary biopsies.

3.2.4 Diagnosis by Biopsy

PCa is diagnosed by histology of prostatic biopsies. For many years, a lateralized sextant biopsy technique was in use (Eskew et al. 1997). An additional biopsy was often performed from any suspicious area on TRUS. Approximately one fifth of biopsy detectable PCas are missed with a sextant biopsy (Schroder et al. 2010). Currently, a volume-adjusted number of biopsy cores is standard (Vashi et al. 1998; Ficarra et al. 2005; Djavan and Margreiter 2007). However, although men with a smaller prostate volume and an initially high PSA level are at greater risk of cancer detection and of an aggressive cancer, this does not mean that in a mass screening program, volume-adjusted biopsy schemes should not be implemented automatically. Relevant cancers will be detected due to regular repeated screening (van Leeuwen et al. 2009). Side effects of biopsy procedures, such as haematuria, haemospermia, infection, and urine retention are well described and have a limited clinical impact even when volume-adjusted biopsy schemes are used (Paul et al. 2004). A recently published Cochrane review of randomized trials on antibiotic prophylaxis for transrectal prostate biopsy showed that antibiotic prophylaxis is effective in preventing infectious complications following prostate biopsy. There were no data to confirm that antibiotics for long-course (3 days) were

superior to short-course treatments (1 day) or that multiple-dose treatment is superior to single-dose (Zani et al. 2011).

3.3 Mass Screening for Prostate Cancer

The objective of screening is to identify a disease at a stage in its natural history where treatment can be applied to prevent death or suffering (Habbema et al. 1982). Screening aims to avoid deaths from cancer by preventing the development of advanced disease. Therefore, effective treatment of early staged disease is essential to attain the aims of screening. Although screening may lead to an earlier diagnosis, screening tests will not always benefit the person being screened; overdetection with the potential result of overtreatment, increased costs, side effects, and complications are potential adverse effects of screening (Habbema et al. 1982; Pienta 2009).

The final endpoint of a cancer screening trial is cancer-specific mortality. However, there are more criteria that have to be fulfilled before screening can be adopted in a public health program. A total of ten WHO criteria for appraising the validity of a screening program were developed by Wilson and Jungner in 1968 (Wilson and Jungner 1968). Medical practice afterwards has resulted in several modifications of the classic criteria, resulting in ten new criteria, Table 3.2. For PCa screening, criteria 3 and 6 are currently not met, while criteria 9 and 10 are at least object of intense discussion.

Table 3.2 The ten updated criteria by Andermann et al. 2008

1. The screening programme should respond to a recognized need.
2. The objectives of screening should be defined at the outset.
3. There should be a defined target population.
4. There should be scientific evidence of screening programme effectiveness.
5. The programme should integrate education, testing, clinical services and programme management.
6. There should be quality assurance, with mechanisms to minimize potential risks of screening.
7. The programme should ensure informed choice, confidentially and respect for autonomy.
8. The programme should promote equity and access to screening for the entire target population.
9. Programme evaluation should be planned from the outset.
10. The overall benefits of screening should overweight the harm.

3.3.1 Randomized Control Trials for Prostate Cancer Screening

A small number of population-based studies have illustrated the grade and stage shift occurring by PSA based early detection of the population, and a significant reduction of prostate cancer mortality compared to geographic or historical controls (Oberaigner et al. 2011). There are, however, five randomized control studies (RCT) that are evaluating the effectives of mass screening, primarily the effect on prostate cancer mortality (Labrie et al. 2004; Sandblom et al. 2004; Andriole et al. 2009a; Kjellman et al. 2009; Schroder et al. 2009). They have been reviewed in the Cochrane systematic review 2010 (Ilic et al. 2011), in which it is stated that only the ERSPC and the PLCO trial provide unbiased data that live up to the Cochrane criteria for meta-analysis. The European Randomized Study of Screening for Prostate Cancer (ERSPC) and the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO trial) were designed to analyse whether population-based screening reduces the mortality from PCa, with an acceptable level of quality-of-life aspects and the associated costs(Gohagan et al. 2000; Schroder et al. 2003). The third randomized trial that reported recently independently on the mortality results after 14-year follow-up is the Swedish study from Gothenburg that participates in the ERSPC (Hugosson et al. 2010).

The ERSPC is conducted in eight European countries (Belgium, Finland, France, Italy, the Netherlands, Spain, Sweden, Switzerland) and enrolled 267,994 men 55–74 years of age. All men with a prior diagnosis of PCa were excluded. In the ERSPC, men were screened in most countries with an interval of 4 years; however, in Sweden, men were screened with an interval of 2 years. The screening algorithm differed among the study centres (Berenguer et al. 2003; Ciatto et al. 2003a; Finne et al. 2003; Hugosson et al.

2003; Kwiatkowski et al. 2003; Roobol and Schroder 2003; Villers et al. 2003).

The PLCO is a trial in the United States that enrolled 155,000 women and men, 55–74 years of age, in ten screening centres. All men with a prior diagnosis of PCa, but not with previous PSA screening, were excluded. In the PLCO, men in the intervention arm received screening once each year by DRE and PSA for a period of 4 years and by PSA alone for 2 years more. A sextant biopsy was recommended for PSA values more than 4.0 ng/ml and/or an abnormal DRE. The regional health-care providers made final decisions on whether to take a biopsy and on the biopsy technique used (Gohagan et al. 2000).

3.3.2 Results of RCTs in Mass Screening

The ERSPC trial reported that PSA screening without digital rectal examination was associated with a 20% relative reduction in the death rate from PCa at a median follow-up of 9 years, the cumulative incidence of PCa was 8.2% and 4.8% for the intervention and control group, respectively (Schroder et al. 2009). The absolute reduction in the screening population was 7 PCa deaths per 10,000 men that were screened. The results were associated with a number of 1,410 men that needed to be screened (NNS) and 48 men that needed treatment (NNT) to save one death from PCa death. The treatment distributions were slightly different between the two groups, however, unlikely to play a major role in interpretation of the final results (Wolters et al. 2010a). Data analysis of the ERSPC with adjustment for the diluting effect of nonattendance and contamination showed that the mortality effect among men was increased to 30% (Roobol et al. 2009; van Leeuwen et al. 2010). In the ERSPC, 82.2% of the men in the screening group were screened at least once, and the average rate of compliance with biopsy recommendations was 85.8% (range, 65.4–90.3). The level of contamination by PSA testing in the control group was estimated in the order of 20–31% (Ciatto et al. 2003b; Otto et al. 2003; Roobol et al. 2009). The ERSPC is constructing their final study report as we write in 2011, demonstrating a relative mortality reduction of 21% in favour of population-based PSA screening after a median follow-up of 11 years in an intention to screen analysis (Schröder et al. 2011). This is only a marginal increase compared to the 2009 figure of 20%, and longer follow-up will be performed as only 19% of participants have reached the mortality endpoint.

The Gothenburg screening trial published their own mortality outcomes independently in 2010 (Hugosson et al. 2010). The Gothenburg trial was initiated as an independent study in 1994 as an effectiveness trial (without upfront informed) but joined the ERSPC trial shortly thereafter. Data up to 2008, after a median follow-up of 14 years, showed a RR for PCa death of 0.56 (95% CI: 0.39–0.82; $P=0.002$). This resulted in a NNS of 234 and NNT of 15. The main differences with the ERSPC as a whole are the type of randomization, younger age, a shorter screen interval, and, most importantly, a longer follow-up due to the simultaneous randomization of all participants in 1994.

The PLCO trial found no mortality benefit from combined screening with PSA testing and DRE during a median follow-up of 7–10 years comparing those screened to those that were not (Andriole et al. 2009b). The incidence of PCa death per 10,000 person-years was 2.0 (50 deaths) in the screening group and 1.7 (44 deaths) in the control group (rate ratio, 1.13; 95% CI: 0.75–1.70) after a median of 7 years follow-up. The data at 10 years were 67% complete and consistent with these overall findings. The treatment distributions were similar in the two groups within each tumour stage. In the PLCO trial, the compliance with the screening protocol overall was 85% for PSA testing and 86% for DRE. The average rate of compliance with the biopsy recommendations was only 40% since the final decision to actually perform the biopsy was left to urologist. The level of contamination is well established, i.e. the rate of PSA testing was 40–52%, and the rate of screening by DRE ranged from 41% to 46% in the control group. Approximately 44% of the men in each study group had undergone one or more PSA tests before randomization, which would have eliminated some cancers detectable on screening from the randomized population, especially in health-conscious men (who tend to be screened more often, a form of selection bias). No

results are available for the effect of screening after the adjustment for the contamination; however, the PCa specific mortality was 25% lower among the men who were screened prior to randomization in the PLCO. Whereas the ERSPC found a statistically significant reduction in PCa mortality with screening, the PLCO trial did not. In the PLCO trial, the contamination in the control group and compliance with the screening protocol in the intervention group is of major influence. This is highlighted in the stage distribution among the men in the control arm of the PLCO study. In comparison to the 96% of men diagnosed with a stage ≤ II tumour in the intervention arm, there were 94.3% of men with a stage ≤ II tumour diagnosed in the control arm of the PLCO. Consequently, the PLCO trial is more a trial comparing two screening strategies of a different intensity and is inadequate in establishing if PCa screening has the potential to reduce the PCa specific mortality. Therefore, we can conclude that systematic PCa screening is not effective in terms of reducing the PCa specific mortality in comparison to widespread opportunistic screening and early detection.

3.3.3 Potential Harms of Prostate Cancer Screening: Overdiagnosis, Overtreatment, Quality of Life

Screening increases the PCa incidence. Approximately 50% of PCa diagnosed in population-based studies are overdiagnosed, as they show the pathological features of the incidental cancers found at autopsy (Gosselaar et al. 2005). With repeat screening sessions, this percentage increases even more (Boevee et al. 2010).

This implies that a subset of men diagnosed with PCa do not require any active, invasive treatment during life. In the ERSPC, over 600 men with these clinically and pathologically defined low-risk PCa features were observed without primary treatment over a period of 10 years (Roemeling et al. 2007). Overall survival was 70%, while none died of PCa.

The excess incidence and overtreatment by radiotherapy or surgery are associated with a distinct pattern of change in quality of life (Sanda et al. 2008; White et al. 2008). Quality-of-life (QoL) parameters that are affected are a change pattern in the urinary, bowel, and erectile functions, as well as the emotional distress and anxiety (Korfage et al. 2005; Mols et al. 2009).

Decisions on whether screening for prostate cancer should become a health-care policy require next to a reduction in the mortality from prostate cancer information on health-related quality of life and cost-effectiveness. A framework within both can be assessed was developed during the course of the two randomized trials (Miller et al. 2001). A first cost-effectiveness analysis on the basis of the ERSPC screening results revealed that introduction of PSA screening will double the total health-care costs for prostate cancer, mostly due to costs related to over detection (Heijnsdijk et al. 2009).

One QoL analysis is presented by the ERSPC study group, none by the PLCO. The QoL analysis have estimated the ratio between the benefits (PCa specific mortality reduction, life years gained, and reduction in advanced disease) and the harms (screening, overdiagnosis, overtreatment, and the additional life years that a man will live with cancer) of screening. To estimate the impact of screening in a large group of asymptomatic men, PCa incidence was compared with a non-screening situation using incidence data in the general population in a period in which not much opportunistic screening was taking place. For screening from age 55 to 70 years at 4-year interval, the predicted benefits per 1,000 men of all ages were 7 PCa deaths prevented and 60 life years gained over the lifetime of the population. The harms were overdiagnosis and overtreatment of 28 men and the loss of 716 PCa-free life years. The QALYs gained were 25 which is only 42% of the life years gained (De Koning et al. submitted 2012).

3.3.4 Interval Cancers

Screening does not detect all cancers, and cancers may emerge in between scheduled screening activities. They are called interval cancers. Therefore, interval cancers are either cancers that have developed after the previous screen or

cancers that were "missed" at the last screen. The reported interval cancers in the ERSPC and PLCO trial were infrequent and in general had favourable characteristics. The ERSPC-Rotterdam reported in the first 4 years after initial screening 25 interval cancers. All were classified as stage T1A–C or T2A, none were poorly differentiated or in a metastatic stage (van der Cruijsen-Koeter et al. 2006). In the PLCO, 204 interval cancers were diagnosed. Of these cancers, 96.1% were classified as stage T1A–C or T2A, and 2.0% were classified as stage IV disease (Grubb et al. 2008).

In ERSPC section Gothenburg, men were screened biennially in contrast to the rest of the ERSPC. Although it was reported in 2004 that the number of interval cancers was favourable and 20% of the number of cancers detected in the control group (Hugosson et al. 2003), a comparison of the rate of interval cancers between the Rotterdam and the Gothenburg group in 2007 did not reveal a difference between screening with the 4- and with the 2-year interval, while also the tumour characteristics were similar in both centres (Roobol et al. 2007). A very recent ERSPC study compared the long-term disease-specific survival of interval cancers to cancers in the control arm and concluded that these were similar (Zhu et al. 2011).

So far, no results from randomized controlled trials are reported on cost-effectiveness, cost utility, or cost benefit of screening for PCa.

3.4 Risk Factors in Mass Screening Studies

As a result of the population-based studies or cohorts, also incorporating limited side studies on biological data like family history, serum markers like PSA-isoforms (Bangma et al. 2010), and tissue analysis (genomics, proteomics), a large number of candidate risk factors have been analysed in order to assess diagnostic or prognostic value. The information should be incorporated into the design of prospective population trials that need to answer questions when to start (and stop) screening, how to do this, with which rescreen interval, and how to deal with men diagnosed with cancer. So far, multivariate analysis on ERSPC data has provided the prostate cancer risk calculators that is a decision support at various levels (www.uroweb.org, www.erspc.org, www.prostatecancer-riskcalculator.com), and can be used to stratify men for initial screening and biopsy (Roobol et al. 2010a). Such studies are being initiated in Sweden and the UK. Early initiation of screening at the age of 40 years and beyond has been advocated based on longitudinal serum PSA data (Lilja et al. 2007), in which, amongst other factors, only a PSA value of less than 0.6 ng/ml at the age between 44 and 50 years would predict the near absence of prostate cancer for 25 years. Men between 50 and 74 with a serum PSA < 1.0 ng/ml (36% of all men) or men with PSA < 2.0 ng/ml (67% of all men) can be reassured that even if they harbour a biopsy detectable cancer, it is unlikely to become life-threatening during their lifetime (Roobol et al. 2005). Such risk stratification measures may lead to an increased acceptance of screening among men and might increase the compliance among those at high risk, if they are informed of their risk status and their individualized harm-benefit trade-offs.

'Hereditary' prostate cancer is a term applied to a specific subset of patients with prostate cancer. This form of prostate cancer accounts for an estimated 43% of early onset disease (affecting men less than 55 years of age) but only 9% of all prostate cancer in men up to 85 years of age. A greater number of affected family members and early onset among family members are the most significant predictors of risk (McLellan and Norman 1995). Two meta-analyses, both published in 2003, have shown the association between family history and risk of prostate cancer. Based on 23 studies, the first meta-analysis showed a pooled RR estimate of 1.93 for men with a history of prostate cancer in any relative. A second meta-analysis based on 13 studies showed a pooled relative risk of 2.5 for men with affected first-degree relatives (Bruner et al. 2003; Johns and Houlston 2003).

3.5 Individual Screening

As the public awareness on prostate cancer and early detection by PSA started at the same time as the design for studies on population-based

screening was made, individual screening (or 'wild' screening) took place from around 1990 onwards. This resulted not only in some contamination of the RCTs but especially in a significant increase of overall prostate cancer incidence. The amount of overdiagnosis of indolent cancer started to be quantified after several years from the intermediate results of RCT analyses. Extrapolation of these data was used to improve clinical decisions for individual screening. As it was seen that risk stratification based on baseline PSA appeared an option in order to optimize the harm-benefit trade-off in a PCa screening program [van Leeuwen], this was transferred to risk calculators for individual men that wanted to be screened.

3.5.1 Risk Assessment Strategies

Men with low initial PSA values are unlikely to benefit from early detection. This observation allows making specific individualized risk stratifications after measuring men's PSA baseline. As a result, men at high risk can be informed about their more favourable harm-benefit trade-off in respect to the overall NNS and NNT presented by the randomized controlled trials. Men may present at the outpatient clinic of physicians and urologists at any age and with any previous history of screening. Therefore, relevant risk factors need to be addressed, such as previous PSA and negative biopsies in order to analyse their current risk. Based on their individual and objective assessment, they should obtain an advice and decide how to continue. For example, the relation between concentrations of PSA at age 60 and subsequent diagnosis of clinically relevant PCa in an unscreened population showed that men aged 60 with PSA concentrations below the median (≤1 ng/ml) were unlikely to have clinically relevant PCa (0.5% risk of metastasis by the age 85 and 0.2% risk of death from PCa). The risk of dying from PCa for men with PSA lower than 1.0 ng/ml after 9 years follow-up was 0.1% (Vickers et al. 2010a).

Figure 3.1 shows the various levels of the ERSPC risk calculator, and a screenshot from the free accessible website (www.prostatecancer-riskcalculator.com).

3.5.2 Nomograms

Risk-based strategies for biopsy, as provided by the ERSPC PCa risk calculator (www.uroweb.org; www.prostatecancer-riskcalculator.com), or the PTCP risk calculator (www.ptcp.org) are based on study cohorts that are biased by the upfront selection of men that undergo prostate biopsies. It is likely best to use the set of ERSPC calculators as a whole, in the geographical area in which they have been validated (Northern Europe), while using the PTCP calculator, which also includes information on black Americans, in the USA. Nevertheless, for white Americans, the ERSPC risk calculator performed better in white Americans compared to the PTCP calculator, as the ERSPC instrument includes prostate volume in its calculation of probability (Bergh et al. 2008). Direct head to head comparisons of the two risk calculators have been published recently and show that overall, the ERSPC risk calculator has better discriminatory capability (Cavadas et al. 2010; Trottier et al. 2010; Oliveira et al. 2011). It has to be realized that actors not measured by current models are, for example, baseline quality of life, comorbidity, life expectancy, and treatment preference, and this may form a limitation to (Cooperberg 2008).

The importance of comorbidity for PCa treatment decisions, or even for screening, was recently highlighted by Albertsen et al. (2011), illustrating the influence of the Charlson score (Charlson et al. 1994) on overall and tumour-specific survival. For example, for men aged 66–75 diagnosed with a PCa staged T1c with a Gleason sum of 7 or less, a Charlson score of 2 or more increases overall mortality by approximately threefold over a period of 20 years (10-year mortality rate per 100 from 28.8 to 83.1) compared to a Charlson score of 0. This while the tumour-specific mortality rate remained stable with 4.8–5.3%. Using this comorbidity information for individual predictions is preferable to overall statistics of life expectancy on a population level that provide a robust but only very general impression.

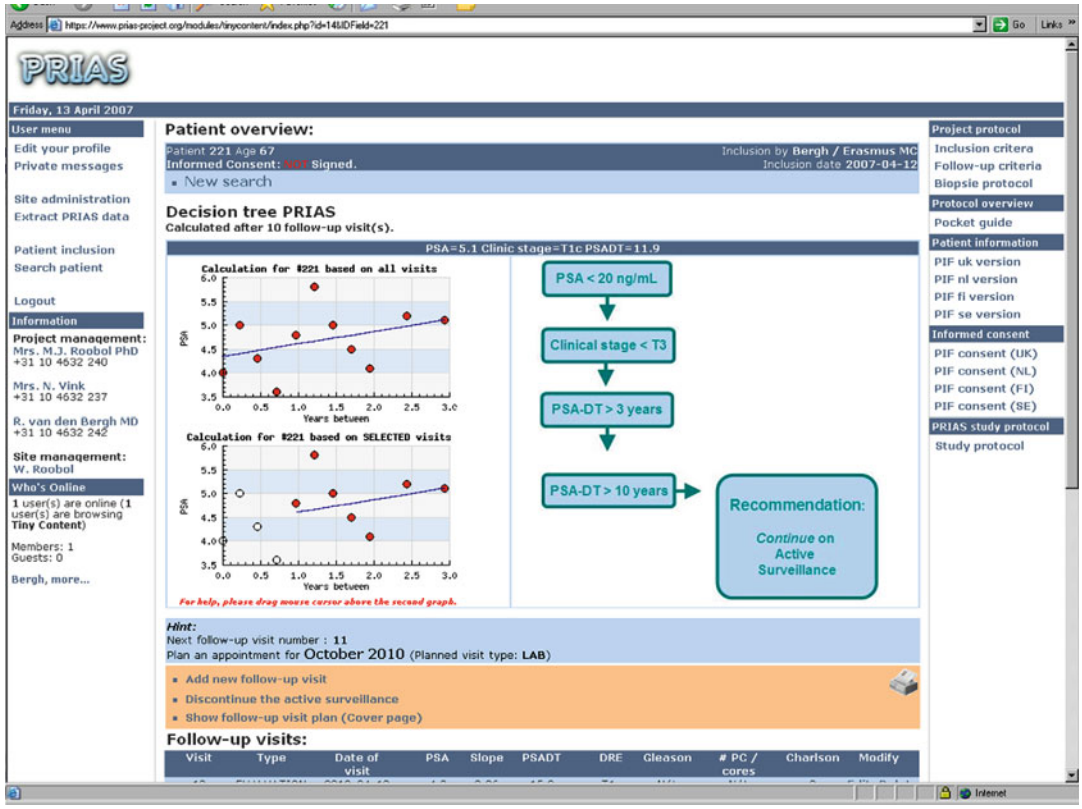

Fig. 3.1 Various levels of the ERSPC risk calculator, and screenshots (From the free accessible website [www.prostate-cancer-riskcalculator.com])

In order to implement nomograms into the daily urological routine, a series of validations needs to be followed after the initial construction phase. Traditionally, a nomogram would be tested on an independent but relevant population set. Next, an evaluation of the implementation should take place to analyse the impact of the instrument as a decision tool on the actions taken by patients and physicians. The compliance with biopsy recommendations provided by the ERSPC prostate cancer risk calculator was evaluated by Van Vugt (Van Vugt et al. *abstract*, *2011 EAU*, *article submitted accepted BJUI*). In a setting in which 291 men with a request for PCa screening agreed to submit themselves to the use of this risk assessment instrument, 84% were compliant with the advice to biopsy or to refrain from it. Remarkably, the most important reason for non-compliance of the 31 of 119 men that were advised not to be biopsied was the reluctance of the physicians due to the PSA level as a single parameter. It showed that the traditional biopsy threshold of PSA over 3 ng/ml overruled the advice given by the nomogram. Analysis of the compliance to a risk calculator on the probability of low-risk, or indolent, PCa with subsequent active surveillance was also performed by Van Vugt and showed similar results (in preparation 2011).

3.5.2.1 Improving Nomograms

Candidate markers at presence are the kallikreins (Vickers et al. 2010b) proPSA (Bangma et al. 2010), PCA3 (Ankerst et al. 2008), or histologic markers (Wolters et al. 2010b). However, readers of manuscripts describing the additional the value of a new biomarker in an existing nomogram should be aware of the fact that this new marker should be judged by its impact on the accuracy of a prognostic model, which is best measured by multiple criteria such as change in concordance index, calibration, impact on predictions, and

decision curve analysis (Nguyen and Kattan 2011). Next to biomarkers, imaging is expected to play a larger role in the initial assessment of risk, as it is to be in the monitoring of men on active surveillance (Sciarra et al. 2011).

3.6 Conclusions and Way to Go

Obviously, two of the most important negative side effects of individual and mass screening for PCa are unnecessary invasive testing (prostate biopsy) and overdiagnosis with the related overtreatment. Individual detection and mass screening protocols differ primarily in their way how information about early detection is presented, whether on an individual way by a personal health professional (nurse practitioner, physician), or by public information generated by the health authorities by the public media. The latter may prevent an individual bias but might also not be efficient to identify men at higher risks. Risk-based strategies might be applied in both situations by means of risk calculators derived from population-based studies. Algorithms will offer possibilities to increase specificity at every decisional step during screening, rescreening, diagnosis, and initial treatment, but studies need to be continued in order to decrease the confidence intervals around every step. Algorithms incorporating other variables next to PSA (from genomic, proteomic, or metabolomic analysis of serum, urine, or tissue biopsies) to make accurate risk assessments and predict the chance of having PCa with the possibility to differentiate between indolent and potentially aggressive disease are warranted.

It is obvious that future mass screening protocols have to be adjusted to the currently available information. Mass screening becomes more individualized, while the methods for individualized screening will be closely related to screening protocols of the population. For example, if population-based screening is considered not to be a reasonable option to reduce a 0.2% risk of cancer-specific death after 25 years, systematic repeated screening should not be applied to men with low baseline serum PSA values. Screening algorithms have already been developed and validated (Ankerst et al. 2008; Chun et al. 2009; Roobol et al. 2010b). Nevertheless, future studies must further develop an accurate individualized screening algorithm.

Harm-benefit trade-offs are likely to differ between populations in Europe. The PCa deaths rates in the Nordic European countries (Norway, Sweden, Denmark, Iceland, and Estonia) are five times higher than those seen in several Central and Eastern European countries. National authorities will have to link up with regional study results in order to decide on their national screening policies and the design of guidelines.

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