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Predicting prostate cancer many years before diagnosis: how and why?

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Abstract

Evidence of reduced prostate cancer mortality from randomized trials in Europe supports early detection of prostate cancer with prostate-specific antigen (PSA). Yet PSA screening has generated considerable controversy: it is far from clear that the benefits outweigh risks, in terms of overdiagnosis and overtreatment. One way to shift the ratio of benefits to harms is to focus on men at highest risk, who have more to benefit than average. Neither family history nor any of the currently identified genomic markers offer sufficient risk stratification for practical use. However, there is considerable evidence that the levels of PSA in blood are strongly prognostic of the long-term risk of aggressive prostate cancer. Specifically, it is difficult to justify continuing to screen men age 60 or older if they have a PSA less than 1 or 2 ng/ml; for men 45 – 60, intervals between PSA tests can be based on PSA levels, with 2 to 4 year re-testing interval for men with PSA of 1 ng/ml or higher, and tests every 6 to 8 years for men with PSA < 1 ng/ml. Men with the top 10% of PSAs at a young age (PSA ~1.5 ng / ml or higher below 50) are at particularly high risk and should be subject to intensive monitoring.

Keywords

prostatic neoplasms; early detection of cancer; prostate-specific antigen

Early detection of prostate cancer

Despite decades of research, there is no reasonable prospect that prostate cancer can be cured once it has metastasized. The greatest hope of reducing prostate cancer mortality is therefore through early detection and prevention. Moreover, because no important carcinogen or modifiable risk factor has been identified, prevention of prostate cancer is largely a matter of early detection.

In many ways, prostate cancer is an ideal cancer for early detection. The disease is, largely speaking, relatively slow growing, allowing a sufficient lead-time for cancer to be identified before clinical detection of incurable disease, and there is a simple, non-invasive screening test, serum prostate specific-antigen (PSA). But two related factors complicate choices about prostate cancer screening, its ubiquity[1] and the toxicities associated with treatment: the proximity of the prostate to the rectum, bladder, urethra and penis entails that curative treatment is associated with important risks of long term erectile, urinary and bowel dysfunction[2]. These are the twin problems of overdiagnosis and overtreatment. The dilemma for men considering screening is that a cancer may be detected that may never kill

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them, leading at the very least to considerable anxiety, and sometimes also to sexual dysfunction and incontinence following an attempt at curative treatment.

The rationale for risk stratification

Risk stratification is based on the premise that whereas the risk of a disease outcome varies, the risk of harm from treatment is more uniform. As such, some individuals have more to benefit from treatment than others, whereas all are at similar risk of harm. For the purposes of illustration, take the case of a drug that reduces the risk of heart attack by 25%, but which raises the risk of stroke by 1%. Depending on risk factors such as cholesterol, blood pressure and diabetes, risk of heart attack varies between patients. A patient at 10% risk would experience a 2.5% reduction in the risk of heart attack if he took the drug, but an increased risk of stroke of 1%, leading to a net reduction in risk of 1.5%; conversely, a patient at a 1% risk of heart attack who takes the drug has a net increase in risk of 0.75%. It should be obvious that only patients with a heart attack risk above 4% will benefit from the drug.

Similar considerations apply to prostate cancer. A 65 year-old man with a palpable, Gleason 8 tumor is at much higher risk of cancer-specific mortality than a similarly aged man with Gleason 6, T1C disease, and therefore has much more to gain from surgery. Yet the risk of persistent post-operative urinary and erectile dysfunction would not differ markedly between the two men. Given that a PSA test will detect both cancers, we need to design screening programs that preferentially identify aggressive disease.

How to risk stratify: does family history or genetics help?

If screening should be restricted to men at highest risk, we need methods to assess risk. The most obvious would be family history. Indeed, some clinicians who advise against prostate cancer screening do recommend PSA tests to men with a family history. The problem, however, is that family history is too weak a predictor, and a strong family history too rare, to make screening on the basis of family history a feasible strategy.

Some simple mathematics can make this point. Assume, for example, that having a family history doubles a man's risk of death from prostate cancer, exactly the sort of effect size that sounds clinically important. Now assume that 15% of men have a family history, and that the overall risk of prostate cancer death without screening is 3%. It is easily calculated that the risk of prostate cancer with and without a family history is 5.2% and 2.6% respectively ($5.2\% \times 15\% + 2.6\% \times 85\% = 3\%$). The point of risk stratification is to be able to screen some, but not all men. For a policy maker who is in favor of prostate cancer screening, a change in risk of 3% to 2.6% is surely insufficient to exempt from screening men without a family history. Conversely, it is also debatable whether an increase in risk from 3% to 5.2% is enough to convince a policy maker who is against screening to start screening men who do have a family history of prostate cancer.

Table 1 shows the risk separation given for various prevalences and relative risks. The data on family history and genomic risk factors are taken from the literature. For example, although Xu et al. reported that men with 14 or more risk alleles plus a family history had about a 5 times greater risk of prostate cancer, only about 1% of the population met this criterion[3]. There would certainly be a case for screening these men if there was otherwise no policy in favor of screening, but it would be hard to justify giving 100% of men a genetic test to identify just 1% in need of PSA screening.

Given the data in Table 1, it is very difficult to see how family history or genetic testing could be used to determine which men to screen for prostate cancer and which to advise that testing would not be of benefit. Certainly in no case can a negative family history or genetic

screen reassure a man interested in screening that his risk is too low to benefit and is therefore of no benefit at the population level; on the other hand, any time that history or screening would raise risk significantly, this would be only for a small proportion of the population.

Risk stratification using PSA

PSA is often seen as a diagnostic test for prostate cancer in the same way that, say, a throat culture is diagnostic for streptococcal pharyngitis: a culture could be taken every day and would show nothing, until the patient suddenly develops an infection and the test turns positive. Anecdotally, patients with a PSA of 3.8 ng / ml, only a fraction below a typical biopsy threshold, are commonly told that their test is “normal” or “negative” and to come back in a few years’ time. Exactly the same advice is given to men with a PSA of 0.4 ng / ml. It seems reasonable to suppose that a man with a PSA of 3.8 ng / ml is at greater risk for a future diagnosis of prostate cancer than a man with a PSA of 0.4 ng / ml. There is solid empirical evidence that this is indeed the case.

Four classic papers from the mid-1990’s clearly demonstrated that PSA is prognostic as well as diagnostic for prostate cancer. Each of these papers used a nested, case-control design, in which archived bloods taken before the discovery of PSA were retrieved from storage and subject to PSA assay. The pioneering study, albeit small, with 18 cases and 36 controls, was that of Carter et al., who used data from the Baltimore Longitudinal Study of Aging to show that PSA was associated with prostate cancer risk up to 25 years before diagnosis[4]. Carter et al. focused on changes in PSA but did not directly compare the predictive value of PSA velocity or doubling time with absolute PSA level. Such an analysis was conducted by Whittemore et al., who used blood samples taken in 1964 – 1971 as part of a Kaiser Permanente screening study to predict cancers diagnosed to the end of 1987, before PSA testing became available in the clinical practice. Absolute level of PSA was a very strong predictor of subsequent prostate cancer diagnosed within 7 years with an area-under-the-curve (AUC) of 0.92 and outperformed PSA velocity. Of critical importance to the interpretation of the Malmö studies (see below), which included almost exclusively Caucasian patients, is that “there were no important or statistically significant differences in the performance of [PSA] by race”[5], suggesting that data from European populations can be applied to African Americans. The association between PSA and subsequent prostate cancer was then replicated by Stenman et al., using a Finnish cohort with similarly long follow-up: blood samples taken in 1968 – 1973, with follow-up to 1980. The authors reported high sensitivity and specificity of PSA for the detection of cancer within 5 years for men aged <65[6]. The fourth early paper reporting long-term prognostic value to PSA was based on the Physicians’ Health Study, with 366 cases diagnosed within 10 years of the initial blood sample. Using a 4 ng/ml cut-off, specificity was 91% and sensitivity 43%, although the latter increased markedly for more aggressive cancers diagnosed within 4 years (sensitivity of 87%)[7].

The four papers described above clearly demonstrate proof-of-principle for PSA as a prognostic factor for prostate cancer. However, it is highly questionable whether they are of practical value for risk stratification. First, the cohorts were heterogeneous with respect to age. The Physicians’ Health Study, for example, included men aged 40 – 84; the Kaiser Permanente cohort included those aged 44 – 81. This is problematic not only because PSA changes with age – making cut-offs derived from these studies somewhat meaningless – but because decisions about screening are highly age dependent. For example, we might consider telling a 70 year-old man with a low PSA that further screening would not be of benefit; it is unlikely that a 40 year-old could be similarly reassured that screening could be avoided. Second, the follow-up in some studies was relatively short, such as 10 years in the

Physicians' health study and 12 in the Finnish cohort. Given that prostate cancer is detectable by PSA several years before clinical diagnosis, very long-term follow-up is required in order to make decisions about screening. Third, measuring PSA in stored blood is not straightforward[8] and questions can be raised about the assays used. Fourth, several studies had relatively few cases, such as 18 in the Baltimore cohort and 44 in Finland. Fifth, in many of the studies, it is not fully clear the degree to which the study cohort is representative of the target population. Finally, the authors of the studies did not choose to present clinically relevant statistics. Sensitivity and specificity have their uses, but cannot help determine which men should be screened and which should be advised against further screening.

The Malmö cohort

The Malmö Preventive Project (MPP) was a study on cardiovascular disease and its prevention that took place in 1974–1986 in Malmö, a city with a population of about a quarter million in southern Sweden. Participants in the MPP can be linked to the Swedish Cancer Registry, which has highly accurate coverage of prostate cancer diagnoses, allowing subsequent retrieval and analysis of stored blood samples.

The Malmö studies on prostate cancer were specifically designed to provide clear answers to questions about PSA for risk stratification.

1. Most men were aged 44 – 50, the ideal age for decisions about subsequent screening.
2. There is long-term follow-up, with all men followed for at least 20 years and some for over 30.
3. Methods for accurate measurement of PSA in the stored samples were developed[8].
4. The study is very large, with over 20,000 men and 1400 prostate cancer cases, and highly representative, with 74% participation.
5. There was very little emigration, and almost all prostate cancers were treated at a single hospital in Malmö, entailing that individual cases could be followed up for ascertainment of outcomes from the clinical record.
6. There were recommendations against the use of PSA testing for screening in Sweden entailing that only few men were subjected to opportunistic PSA testing and few prostate cancers were screen detected until recently. Moreover, the data set was large enough to allow separate analyses on men diagnosed with advanced cancer (stage T3 or T4, or with metastatic disease). As such, the Malmö studies provide a “natural experiment” to examine PSA and long-term prostate cancer outcomes in men who have not been subject to PSA screening.
7. The statistical analyses were specifically designed to allow clinical decision-making. Results were presented in terms of the long-term risk of prostate cancer for a given PSA, and as Lorenz curves, which evaluate risk stratification by calculating the cumulative proportion of cases for different PSA thresholds.

The results of the Malmö studies have been reported in a series of papers. In the most recently published results, a single PSA taken at age 44 – 50 was a very strong predictor of prostate cancer clinically diagnosed up to 30 years subsequently, with an AUC of 0.72. AUC for advanced disease (clinical stage T3 or T4, or metastatic at diagnosis) within 15 years was 0.84. The absolute risk of advanced cancer varied from 1% for men with a PSA at the 25th centile of 0.4 ng / ml, to 6% for men at the 90th centile (~ 1.5 ng / ml), and >10% for men

with a PSA of 3 – 4 ng / ml. Approximately two-thirds of advanced cancer cases occurred in men with PSA in the top quartile (~1 ng / ml)[9]. Even stronger results were reported for a single PSA at age 60. With over 1000 men followed to age 85 or death, the AUC of PSA for predicting prostate cancer death was 0.90. Almost all deaths (90%) occurred in men in the top quartile of PSA (~2 ng / ml or higher). The risk of death for men with PSA below the median (~1 ng / ml) was very low, 0.2% [10]. The risk ratio for high versus low PSA is shown in the final column of Table 1, clearly demonstrating that PSA can provide effective risk stratification.

Reanalyses of European Randomized Study of Prostate Cancer Screening (ERSPC)

The ERSPC provides the strongest data available that PSA screening reduces prostate cancer mortality[11,12]. The ERSPC investigators have also conducted a large number of secondary analyses to explore how PSA screening should best be implemented, particularly with respect to risk stratification. One early and highly influential study examined participants with a PSA < 1 ng / ml at initial screening who underwent further testing four and eight years subsequently. The risk of a cancer diagnosis at the intervening visit was 0.23%. The authors concluded that screening every eight years for men with PSA < 1 ng / ml would reduce screening visits with “a minimal risk of missing aggressive cancer at a curable stage”[13].

Bul et al. extended this analysis to mortality data. They focused on men with a PSA < 3 ng / ml at their first screen. The overall risk of prostate cancer death in this group was very low (0.3% at 15 years) and was strongly associated with PSA level: men with a PSA 2 – 3 ng / ml had a 7-fold increased risk of prostate cancer mortality compared to men with a PSA < 1 ng / ml. Risk of prostate cancer in men with PSA < 1 was around 2.5% at 15 years, with a ~0.5% risk of advanced disease [14].

Both of these analyses suggest that risk stratified screening would improve outcome in comparison to screening all men. A direct test of this hypothesis was made by van Leeuwen et al., who compared data from the ERSPC with that from Northern Ireland, where intervention is far less aggressive, with biopsy typically considered only if PSA > 10 ng / ml. The data can be analyzed to examine the effects of a screening program that excluded men from further screening on the basis of PSA. One key finding is that the number of men needing to be screened to prevent one prostate cancer death was 10 times higher amongst men with PSA < 2 ng / ml than amongst those with PSA 2 – 3.99 ng / ml; the number needing to be diagnosed is about 75% higher[15]. Given that the median age in the ERSPC arm was 61 – close to that of the Malmö cohort who were aged 60[10]– this result can be seen an independent replication of the Malmö findings.

Conclusions and clinical implications

A considerable body of data suggests PSA is prognostic, as well as diagnostic, and that there is a steep gradient of risk as PSA increases amongst those with “normal” PSA levels. There is also clear evidence that there is little risk of prostate cancer mortality in men with low PSA, such that continuing to screen these men increases overdiagnosis and overtreatment without a corresponding benefit in reduced prostate cancer mortality. This suggests that PSA screening should take a risk stratification approach, rather than attempting to include all, or nearly all men.

A simple schema for such a risk-stratified approach to screening would be as follows. All men with a reasonable life expectancy should receive a PSA test at age 45. Men with a PSA

of 1 ng / ml or greater should be asked to attend repeat screening every 2 – 4 years until the age of 60. Men with a PSA < 1 ng / ml should be asked to attend repeat screening at 8 year intervals until 60 (i.e. two additional PSA tests). At age 60, only men with a PSA of 1 – 2ng / ml or more should continue to be screened. This would mean that most men could receive only three lifetime PSA tests and would not be screened after 60, when the incidence of benign disease rises sharply, increasing the risk of biopsy and identification of low risk cancer.

In sum, screening depends on a careful balance of benefits and harms. This balance can be dramatically improved by focusing on men at highest risk, as defined by baseline PSA.

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The value of risk stratification as a function of the prevalence of the risk factor and relative risk

Table 1

Data on family history, genetic markers and PSA are taken from published literature[16–18,3,10]. The example of the effects of a very strong family history on risk of prostate cancer mortality is hypothetical.

Risk factor	Family history	Family history	Family history	Strong family history	Very strong family history	Five genetic markers	14 or more risk alleles plus family history	PSA > 2 ng / ml
Endpoint	Prostate cancer	Advanced cancer	Prostate cancer	Prostate cancer	Prostate cancer	Prostate cancer	Prostate cancer	Mortality
Overall risk	10%	5%	10%	3%	10%	10%	10%	3%
Prevalence of the risk factor	15%	15%	5%	1%	3%	3%	1%	25%
Relative risk	2	4	4	25	4.5	5	5	25
Probability of event without risk factor	8.7%	3.4%	8.7%	2.4%	9.0%	9.6%	0.4%	
Probability of event with risk factor	17.4%	13.8%	34.8%	60.5%	40.7%	48.1%	10.7%	