

# Prostate Cancer Screening

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One ounce of prevention is worth a pound of treatment remains a popular idea in many cultures. It is certainly true that this statement applies to a number of public health threats such as speed control and seat belts to prevent car accidents, smoking cessation programs, and information on lessening the risk of sexually transmitted diseases such as HIV disease. However, prevention of cancer remains controversial and prevention of prostate cancer even more so.

Prostate cancer was somewhat neglected in the previous century for three reasons: it was usually incurable after diagnosis, it was a disease of the elderly, and hormonal treatment brought relief in the great majority of cases. This situation changed drastically with the introduction of Prostate Specific Antigen (PSA), a simple blood test that indicates the risk for having prostate cancer. Simultaneously we saw the development of the biopsy gun, allowing multiple painless biopsies of the prostate gland, and transrectal ultrasound (TRUS) offering accurate positioning of the biopsy needle in the different regions of the prostate. A star technique was born resulting in thousands of publications extolling the virtues of this diagnostic procedure.

## Cancer Screening

The enthusiasm for the hypothesis overcame caution and most people forgot that the U.S. Food and Drug administration took one year to approve the use of PSA in diagnosing progressive disease but needed five years to approve PSA as a diagnostic marker for prostate cancer. No heed was taken to the complex reality that screening results in over detection, increases false positive and false negative results, and can lead to over treatment. A classic case is the neuroblastoma screening in 1996 in Japan with a five-fold increase in incidence, surgery and identical mortality (1). We all know the difficult course in judging the advantages of breast cancer screening in women over 50 and the debate in screening from the age of 40. TRANSBIG, the international translational research network linked to the Breast International Group (BIG), makes it clear that it aims to develop individualized breast cancer treatment and reduce over treatment in breast cancer estimated to range from 10 to 20% of cases (2). Recent results of a failed lung cancer screening test received media interest. In this case, a CT scan detected lung cancer 144 times in 3.246 people. More than 300% of the expected cases and a 1000% increase in surgery resulted from this trial ending up with the same mortality rate achieved without screening (3).

**Table 1: Principles of screening for cancer**

- The disease should be an important health problem
- The disease should have a detectable preclinical phase
- The natural history of the lesions identified by screening should be known
- There should be an effective treatment for such lesions
- The screening test should be acceptable and safe

(Adapted from AB Miller, 1996)

The public health experts and epidemiologists who recognize the danger of simplistic thinking and described the principles of screening which were condensed to five points by Anthony Miller in 1996 (Table 1).

The use of correct definitions is important: screening is the systematic examination of asymptomatic men to detect and hope to cure localised disease in a given population. Screening is not intended to fit the need of the individual patient. Here it is more appropriate to use case finding, cancer testing or early diagnosis.

To be blunt you don't need to be Einstein to use a test that finds more cancer and if you treat all cancers you will save lives. The question is how many lives are saved and at what price of human suffering and health costs? Currently, one needs to operate on 17 to 22 men to save one life leaving half of those treated impotent and a fourth of those patients incontinent (4) which leaves the benefit of such procedures in doubt. Europa Uomo, the European coalition against prostate cancer, believes that quality of life is of utmost importance and that the indication for curative treatment which is aggressive should be limited to younger patients with potentially fatal disease – in reality, only a of the total number of men diagnosed with prostate cancer.

## The Miller Principles applied to Prostate Cancer

### An important health problem

Prostate cancer is the leading cancer in males (20.3%) in Europe. This figure may be influenced by the frequency of use of the PSA test which had a similar effect as mammograms did in breast cancer. Still the number of deaths has risen 16% since 1995 due to the rapid increase in the number of men reaching older age. The figures for incidence (new cases/year) of 237,800, mortality rates of 85,200, and the prevalence of cancer of 2 million men in the EU makes prostate cancer management a priority in public health (5).



### A detectable preclinical phase

Prostate Cancer is characterized by a long (10 to 20 years) subclinical stage. Considered as one of the strong arguments for screening, the long subclinical stage is also an argument to avoid diagnosing prostate cancer without symptoms in men with a life expectancy limited to 10 years. Indeed after the first diagnosis it

takes another 10 to 15 years to die of the disease. With a mean life expectancy of + 77 years in the EU it would seem reasonable from a screening point of view to not screen men over age 70.

The establishment of PSA > 4 ng/ml as the cut-off risk factor (now considered outdated) prompted a tsunami of biopsies resulting in increased incidence. The detection of smaller tumors including indolent cancers, led to a significant shift in the stage of cancer detected and a lower mean age of patients at the time of diagnosis (6).

In simple words, PSA-directed biopsies anticipate the clinical diagnosis by 10 years and the majority of patients in the PSA era present with earlier stages and few with metastatic disease. However, 50% of patients do not need immediate treatment, 30% will probably never need treatment and 25% of those that we treat have locally advanced disease (7).

#### *The natural history of identified cancers*

The facts look easy to understand. Prostate cancer starts at age 30 and half of all men have some type of precancerous lesion (prostate intraepithelial neoplasia - PIN) or microscopic cancer that can only be identified by a meticulous histologic examination on autopsy or surgical specimen by the age of 50. The percentage of these mini-cancers increases with age. At age 80, a man has an 80% chance of having a microscopic cancer. These histologic cancers are called latent since they don't seem to act like cancer.

However some of these cancers controlled by our body defenses do grow very slowly and given enough time can be detected usually at a size of 0,5 cc in up to 30% of men by age 60 in the western world. The detectable number of cancer by biopsy is variable in different parts of the world: there is much less cancer in Asiatic countries and much more in African-Americans which raises the question of genetic determination and/or lifestyle as a possible contributing factor of cancer.

Only one third (10%) of men in the western world develop prostate cancer with symptoms. After a long disease course, metastasis is detected after 7 to 10 years and 2% to 4% of patients die of their cancer after 10 to 15 years.

These figures show that most small cancers remain latent and that screening must lead to over detection and possibly over treatment. There is no guarantee that these mini cancers will never become aggressive over the remaining years of a lifetime. Generally speaking, a relaxed policy is indicated over the age of 65 but extra caution advised in the age range of 50 to 65. It is understandable that this point of uncertainty can be used pro or against screening practice and lies at the base of a continuing controversy between public health experts and clinicians.

**Table 2: Prostate specific problems among Dutch prostate cancer survivors and an age matched norm population in percentages**

	Treated	Norm
Incontinence urine	23 - 48%	4%
Incontinence bowel	5 - 14%	2%
Erectile dysfunction	40 - 74%	18%

(Adapted from TF Mols, 2007)

#### *There should be an effective treatment*

There is no doubt that surgery, radiation (external or internal) and other forms of treatment by cold (cryosurgery) or by heat (high-focused ultrasound) can destroy the prostate and all cancer limited to the gland.

The preferred treatment policy of the last century was seek and destroy. Based on our increased knowledge and experience we now aim treatment to focus and control. Approximately 50% of screen-detected cancers do not need treatment meaning patients could be saved from the side-effects of obliterating the prostate. Treatment side effects are decreasing through improvements in technique both in surgery and radiation therapy but they remain substantial if one observes the reported side effects in a study of 964 patients alive 5 to 10 years after primary treatment based on UCLA-EPIC and SAC questionnaires (Table 2) (8).

#### *The screening test should be acceptable and safe*

There is no dispute that the serum PSA test, used to indicate the risk of having prostate cancer, is acceptable to the patient and safe to perform. It was readily accepted by the medical profession and is now a widespread test used routinely in aging men. However, the PSA is not specific for prostate cancer but for prostate diseases which then produces increasing numbers of false positive and false negative test results causing anxiety for the patients or a false sense of security. The development of a number of derivatives to increase the positive predictive value (PPV) shows that PSA testing is very not reliable (in the clinical accepted ranges from 4 to 10 ng/ml). Free screening with PSA is unreliable as laboratory blood analysis must be performed within 2 to 3 hours of drawing blood samples. More reliable are repeated tests over time to evaluate the kinetics of PSA.

#### **Proving the Advantage of Population Screening for Prostate Cancer**

It is obvious that reflections on the answers to the five requirements to advocate screening for prostate cancer leave room for uncertainty and speculation. To settle the dispute, an evaluation of randomised controlled trials (RCT) may provide evidence of the benefit of screening in lowering cancer mortality in the population with acceptable morbidity (9). The complexity of running and interpreting RCTs on prostate cancer screening, which requires a 10 to 15 year follow up, is one of the reason that only 3 RCTs to evaluate screening benefits were started in the last century.

The Quebec trial, started in 1988 and included 7,155 screened patients, received short-lived fame claiming a reduction in mortality of 69% after publication in 1999 (10). However, it was quickly established that the analysis did not follow the required intent to screen methodology and formal reanalysis showed an excess of deaths in the study group suggesting a selection bias (11). The PLCO study accrued 74,000 men for digital rectal examination and PSA testing annually starting in 1993 and the results will be available in the next years. The ERSPC trial accrued close to 270,000 men and was officially launched in 1993 (12). Its main endpoint on mortality measures the value of the employed screening test DRE, PSA and TRUS, and further evaluation of quality of life (QoL) and cost-benefit were assessed.

Recently new screening trials compare curative treatment [PROTECT study (13)] or a genetic predisposition [IMPACT trial (14)] or on an evaluation of over detection while eliminating over treatment by selecting indolent prostate cancers for active surveillance (PRIAS study). The latter study constitutes an integral part of the PROCABIO study as the PRIAS patient cohort is the ideal model to complement the prognosis based on histology by the search for biomarkers that indicate the early genetic changes of aggressive cancers ([www.prias-project.org](http://www.prias-project.org)). We expect that the results of this study will provide guidance for tailored, individual prostate cancer management in EU countries.

#### *Preliminary Results of the ERSPC Trial*

End results on mortality by prostate cancer screening are not yet available as these depend on the number of events (deaths) of the

trial participants. However, results confirm that prostate cancer has a long treatment history and the mortality is low. Analysis of secondary endpoints has provided valuable information on the screening tools DRE, PSA and TRUS.

#### Digital Rectal Examination (DRE)

Symptoms are not reliable as screening tools. Difficulty voiding, for example, could be caused by benign prostatic hyperplasia (BPH). Further, urinary symptoms caused by prostate cancer indicate incurable disease.

Some time ago, a national screening program in Germany based on DRE failed completely. Where DRE is a standard examination in any physical examination its use in screening programs in this PSA era is of little or no benefit to the detection of early prostate cancer (15). The performance of a DRE in a screening program can be a barrier to patient participation (16). However we insist that physicians looking for early diagnosis of prostate cancer on an individual basis should perform this simple examination.

#### Transrectal Ultrasound (TRUS)

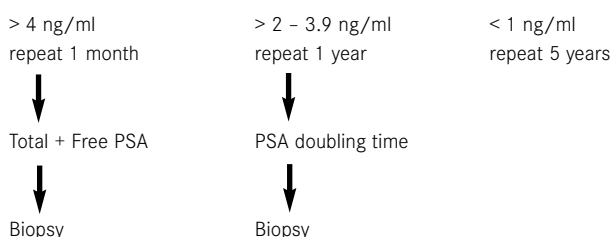
When transrectal ultrasound was introduced in Europa in 1975 we had great hopes to establish a painless, inexpensive, and reliable imaging diagnosis of prostate cancer. The examination has become a standard in the urological evaluation of the lower urinary tract in measuring prostate volume and directing the biopsy needle in specific areas of the prostate, but failed to be reliable in the diagnosis of early cancer (17). Numerous improvements in hard- and software have been introduced without a breakthrough. One of the latest is histoscanning which is performed by extracting and quantifying the statistical features of the reflected ultrasound waves. Other imaging techniques including magnetic resonance imaging (MRI) have not proven effective.

The reliability of TRUS is highly dependent on technique and interpretation: the physician must be skilled at performing TRUS and the radiologist must be skilled at reading the scans. An additional biopsy should be obtained if an area is considered suspicious for cancer.

#### PSA and Derivates

In terms of its volume in clinical use and its qualities in evaluating progression of prostate cancer, PSA and its derivatives remains one of the best and the most popular marker in oncology. Its limitations in diagnosis are due to its specificity for prostate diseases in general rather than prostate cancer in particular and the prevalence of benign prostatic hyperplasia (BPH) in men over 50. Moreover there exists a variability of up to 40% of the reported values in a clinical setting due to biological and methodological variability. It is understandable that sexual activity and bicycle riding increase the PSA and not all clinicians recognize the different results obtained by the different available assays (18). A practical guide to a more reliable use of PSA to determine prostate cancer risk after the age of 50 is presented in Table 3.

**Table 3: Algorithm for risk of prostate cancer diagnosis at age 55-70 based on PSA tests**



(From OCA, 2007)

The final blow to one cut-off value of total PSA (tPSA) resulted from the Prostate Cancer Prevention Trial (PCPT) (19). In this trial, a biopsy was performed in all consenting participants after seven years of follow-up. Up to 40% of cancers were in the low PSA ranges. This finding had been previously recognized and was the reason that the ERSPC lowered its biopsy indication from 4 to 3 ng/ml PSA.

#### Conclusion

Sound clinical evidence is lacking to support a population screening based on the endpoints of mortality and morbidity of prostate cancer. Furthermore there is controversy over the reliability and validity of DRE, TRUS and PSA and its derivatives as screening tools for prostate cancer.

The reality is even worse as we start questioning the basis for cancer diagnosis on histological tissue. The Gleason score was adopted as a fine-tuned grading system but demonstrated shortcomings in clinical practice. There is a trend to return to the classic recording of the amount of high grade cancer present in the biopsy specimen (20). The number and position of the biopsies influence the percentage of diagnosis which as false negative results adds to the overall uncertainty in the diagnosis of prostate cancer.

Waiting for the results of extensive and long-term randomized trials is no consolation to the 80,000 European men dying of prostate cancer each year. We have to do better.

Paradoxically, a way out of this dilemma is the over detection in screening for prostate cancer which reported finding indolent cancers in 50% of screened men which may cause anxiety for the patient and doctor but will not harm the patient in his lifetime (21). These patients are candidates for active surveillance in contrast to the classic radical surgery or radiotherapy. Active surveillance should not be confused with watchful waiting. Primary treatment for localized prostate cancer leaves the options open for cure if against all predictions there is a progression of the indolent cancer. Patients partaking in active surveillance are suitable for undertaking research of new biomarkers that indicate aggression and progression on localized prostate cancer. The PROCABIO (PROstate CAncer BIOMarkers) project intends to do this with the conclusion of the PRIAS (Prostate cancer Research International Active Surveillance) trial to evaluate the active surveillance protocol. This will also include the evaluation of some PSA derivatives such as density, velocity and doubling time.

The right of each man to optimal medical treatment is beyond question and any request by an individual person to be checked for early prostate cancer diagnosis deserves personal attention. Patients should be provided with complete information on all aspects of early prostate cancer diagnosis. There is a trend to lower the ages of patients undergoing PSA evaluation hoping to catch aggressive tumors earlier while avoiding the false positive results of BPH which usually causes problems after the age of 50. The low prevalence of aggressive disease is the cause of a difficult clinical exercise to be used with caution and restraint. The discovery of a new effective biomarker would of course change the total concept.

Last but not least is the potential harm of PSA testing leading to additional testing and treatment, unnecessary side effects and psychological and social distress. As there is more chance to over treat in the senior generation and to under treat in the middle-aged males, special consideration by the physician should be directed to the patient, his (biological) age and his needs.

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## ANNOUNCEMENT

The European Society of Mastology, The European Society of Surgical Oncology, The European School of Oncology and the European Oncology Nursing Society are pleased to announce:

### **“The Training of Specialised Health Professionals dealing with Breast Cancer”**

One month of training in a European Breast Unit  
between January and April 2008

*Prior to the training period the selected candidates will be offered a comprehensive teaching package*

The aim of the programme is to allow young clinicians and nurses dedicated to breast cancer to improve their theoretical knowledge and practical skills in the patient management, in order to create a core team made up of health professionals from various disciplines who have undergone specialist training in breast cancer beyond that given in general training.

#### **Training Fellowship by competitive application**

**Final deadline for application: 31 July 2007**

- ✓ Potential candidates have a maximum age of 40 years for MDs and 45 years for nurses
- ✓ Priority will be given to applicants already working in the field of breast cancer (radiologists, pathologists, surgeons, radiotherapists and medical oncologists, breast care nurses)
- ✓ Candidates from Eastern Europe will be given the priority
- ✓ A good knowledge of the English language is required

Interested candidates should send a copy of their curriculum vitae in English, together with an accompanying letter of recommendation from the Head of the Department that they are working in and a covering letter explaining their motivation. Successful candidates will be notified September 15<sup>th</sup>

For more information or to submit an application,  
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