Clinical practice guidelines
for use by health professionals

Information for men
requesting screening
for prostate cancer

September 2004
## Synopsis

<table>
<thead>
<tr>
<th>Title</th>
<th>Informing patients about individual screening for prostate cancer</th>
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<tbody>
<tr>
<td>Publication date</td>
<td>September 2004</td>
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<tr>
<td>Requested by</td>
<td>French National Health Executive (DGS)</td>
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<tr>
<td>Produced by</td>
<td>ANAES – French National Agency for Accreditation and Evaluation in Healthcare (Guidelines Dept, Economic Evaluation Dept)</td>
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<tr>
<td>Intended for</td>
<td>Any person who may prescribe a PSA test, particularly GPs and urologists</td>
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<tr>
<td>Objectives</td>
<td>To provide a guide for PSA prescribers on the information to be given to men requesting prostate cancer screening</td>
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</table>
| Assessment method | - Systematic review of the literature (with evidence levels)  
- Discussion among members of an *ad hoc* working group  
- External validation by peer reviewers |
| Literature search | January 1997 – June 2004  
239 references selected among 2940 analysed |
| Economic study | See full report in French:  
[Éléments d'information des hommes envisageant la réalisation d'un dépistage individuel du cancer de la prostate](#) |
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| Collaborations and participants (annex 1) | - Learned societies  
- Steering committee  
- Working group (Chair: Dr Rosemary Ancelle-Park, epidemiologist, InVS, Saint-Maurice)  
- Peer reviewers |
| Internal validation | ANAES Scientific Council (Referees: Dr Michel Delcey, Professor Paul Landais)  
Validated on September 2, 2004. |
| Related ANAES publications | [Opportunité d’un dépistage systématique du cancer de la prostate par le dosage de l’antigène spécifique de la prostate](https://www.anaes.gouv.fr/docs/anaes/cancer/7543/)  
(16/11/2000)  
[Les traitements du cancer localisé de la prostate](https://www.anaes.gouv.fr/docs/anaes/cancer/7542/)  
(31/05/2001) |
Critical appraisal of the literature – Summary

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II. Giving information – How, when and what type

III. How well do prostate cancer screening tests perform?

IV. Epidemiology and natural history of prostate cancer

V. Treatments for localised prostate cancer

VI. Conclusions

30 questions on prostate cancer screening
I. Introduction

• **Epidemiology**
Prostate cancer is the most common cancer in men over 50 in France. Although some forms of prostate cancer can be aggressive, it is usually a relatively symptom-free and slow progressing disease. For the year 2000, 40 000 new cases of prostate cancer and 10 000 disease-related deaths were recorded in France. It is the second most common cause of cancer death in French men, after lung cancer.

• **International recommendations on mass screening**
According to all health technology assessment (HTA) agency reports\(^1\), the total serum prostate specific antigen (PSA) assay cannot be recommended for mass screening (i.e. organised screening programmes, systematic screening). However, conclusions from professional bodies have been contradictory:
  - four felt that the evidence was inadequate and did not recommend PSA testing for mass screening;
  - two\(^2\) recommended individual screening annually for men aged between 50 and 70/75, based on an expert consensus.
Three professional bodies and one HTA agency recommended that patients, particularly at-risk patients, should be told that screening is available. Patients should only take a decision after receiving appropriate information from and after discussion with a health professional.

• **Individual screening**
In France, individual screening by the total serum PSA test is becoming a common practice. The French National Health Executive has asked for guidelines on the appropriateness of such screening in order to update ANAES’ earlier reports on prostate cancer screening and treatment. The assumption is that, for an early diagnosis, a PSA test combined with a digital rectal examination (DRE) could be offered to individuals with statistically and clinically significant risk factors, or who request the PSA test. However, the expected benefits of individual screening are not proven and no conclusive recommendations can be made at the moment. The working group therefore decided to update data on screening and to analyse, define and draft the information needed by someone requesting a screening test. The report is intended as a guide for prescribers of the PSA test and not as an information sheet for the public. Information for the public would need redrafting and pilot testing.

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\(^1\) Including INAHTA (International Network of Agencies for Health Technology Assessment, with 15 members including ANAES in 2000)

\(^2\) The French Urology Association and the American Urological Association
II. Giving information – How, when, and what type

II.1. How and when should information be given?

The patient’s wishes need to be ascertained within a framework of shared information and decision-making. The working group felt that provision of oral information is of paramount importance. It may be completed with written material. Although other media such as video or the internet may be useful, their content and efficacy need to be validated.

The working group reiterated earlier recommendations (ANAES, 2000):
- information should be prioritised;
- the expected benefits of options should be described before their disadvantages and risks;
- serious risks should be mentioned, including very rare risks (i.e. those that threaten life or vital organ function);
- information should be easy to understand.

Information should be tailored to each individual and their ability to understand.

II.2. Factors influencing men’s choices

- **Amount of information**
  
  Published data suggest that the quantity of information directly influences participation in prostate cancer screening. The better informed men are about the pros and cons of screening, the less keen they seem to be (level of evidence 2).

- **Information content**
  
  A key factor in the decision to undergo screening is whether an individual perceives a potential personal psychological or therapeutic benefit (level of evidence 4). Screening can also provide reassurance for men with a family history of prostate cancer (level of evidence 4). However, these observations cannot be generalised to all men. Moreover, screening may upset the individual’s state of mind (i.e. cause stress, coping problems, etc.) (agreement among professionals).

II.3. What kind of information should be given?

In general, men know little about the pros and cons of prostate cancer screening. It is difficult to produce a standard list of questions and answers for all patients. However, the following information should be given (level 4 and agreement among professionals):
- what screening is;
- the natural history of prostate cancer and risk factors for prostate cancer;
- a description of diagnostic tests and their power, particularly the possibility of false negatives and false positives;
- the possible negative psychological impact of high PSA levels;
- the lack of evidence on mortality reduction;
- existing treatment options, their benefits and side effects;
- the arguments for and against early treatment;
- the consequences in terms of survival and cure if treatment fails or is not given;
- the cost of testing³.

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³ In 2004, the cost of a total serum PSA test in France was 18.90 € (code 70 B)
III. How well do prostate cancer screening tests perform?

III.1. What is the impact of individual screening on prostate cancer incidence and mortality?

Results of studies of the impact of mass screening on prostate cancer incidence and mortality are not relevant to individual screening. The fall in prostate cancer mortality rates over the last 5-10 years cannot be attributed to screening by the total PSA test because:
- rates also decreased in countries where the PSA test was not implemented;
- the decrease could be due to better - or a greater variety of - treatment options.

Available studies of registries examining the relationship between pressure for screening and prostate cancer mortality have not provided any conclusive evidence in favour of individual screening (level of evidence 4).

III.2. How is prostate cancer diagnosed at an early stage?

The following may contribute to the diagnosis:

<table>
<thead>
<tr>
<th>clinical sign</th>
<th>induration of the prostate on DRE (which may indicate locally advanced disease)</th>
</tr>
</thead>
<tbody>
<tr>
<td>and/or</td>
<td></td>
</tr>
<tr>
<td>lab result</td>
<td>rise in serum PSA</td>
</tr>
</tbody>
</table>

The diagnosis of prostate cancer is then confirmed by ultrasound-guided transrectal prostate biopsy. However, a normal biopsy result does not necessarily eliminate prostate cancer. Endorectal ultrasound is indicated for diagnosis only and is not recommended for screening (mass, targeted or individual screening).

III.3. How useful is DRE in diagnosis?

Studies show that DRE, when used alone, is not an appropriate screening tool as the cancer detection rate is lower than that for the PSA test alone or for both methods combined. DRE completes the PSA test and may enhance detection rate, particularly in patients whose PSA level is lower than the threshold for biopsy. Absence of induration on DRE does not exclude the presence of cancer. DRE is operator dependent and, as previous guidelines have emphasised, should be combined with a PSA test. No studies were found on the power of DRE for early diagnosis of prostate cancer in populations with known risk factors.

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4 There is no evidence that mass screening using the total serum PSA test reduces global mortality. The working group therefore could not conclude to a benefit of a policy of mass screening and decided to await the results of two large multicentre studies - one European (ERSPC) and one American (PLCO) - scheduled for 2005 and 2008 respectively.
III.4. How useful is total serum PSA for early diagnosis?

The total serum PSA test is used for early diagnosis of prostate cancer because blood PSA levels are raised in individuals with prostate cancer. Most guidelines consider the detection threshold to be 4 ng/ml.

The benefit of lowering this threshold before offering a biopsy is still controversial. Lowering the threshold would increase the sensitivity of the test but would reduce its specificity. This would lead to an increased number of cases being diagnosed, but would also increase the number of negative biopsies. The proportion of cancers considered to be clinically non-significant (small volume and low grade) among the additionally diagnosed cancers has not been clearly determined.

At a threshold of 4 ng/ml, the sensitivity of the total serum PSA test for early diagnosis of prostate cancer is about 75%, with specificity about 90%. In an individual screening situation, the positive predictive value (PPV) is about 30%, which means that out of a total population with total PSA > 4 ng/ml, 3 out of 10 men do have prostate cancer and 7 out of 10 do not. Similarly, the negative predictive value (NPV) is about 90%, which means that 9 out of 10 men with a total PSA threshold < 4 ng/ml do not in fact have prostate cancer. Detection rate ranges from 0.9 to 3.4%. About 10% of men aged 50-75 years have a PSA value > 4 ng/ml. There is insufficient published data to estimate specifically the power of the total serum PSA test in populations with risk factors.

When total serum PSA is < 4 ng/ml, the interval between repeat tests depends on the PSA level and should be weighted for the patient's age and any comorbidity.

- **If PSA < 4 ng/ml**: The test should not be repeated for 1 year. In the least favourable case (3-4 ng/ml), the risk of having a cancer after 1 year is about 5%, and the risk of invasive cancer is about 0.5%. When the level is 2-3 ng/ml, these risks are about 1-2% and 0.5% respectively.

- **If PSA < 2 ng/ml**: The test should not be repeated for 3 years. In the least favourable case (1-2 ng/ml) the risk of having a cancer within 3 years is about 1%, and the risk of invasive cancer is < 0.2%. When the level is ≤ 1 ng/ml, these risks are about 0.5% and 0.01% respectively after 5-8 years' follow-up.

III.5. How useful are other PSA tests for early diagnosis?

The free serum PSA test and free-to-total serum PSA ratio for patients with a total serum PSA concentration of between 4 and 10 ng/ml could avoid biopsy in patients who do not have prostate cancer, while retaining good sensitivity. However, there are currently standardisation problems. In addition, the optimum threshold has not been established, and no data have been found on the use of this test as a tool for early diagnosis in either the general or the at-risk population. The use of free PSA is not recommended as a first-line test for early diagnosis of prostate cancer (agreement among professionals).

No evidence was found to show that age-adjusted PSA, PSA density and PSA velocity tests are of any value for early diagnosis of prostate cancer. They are therefore not recommended as first-line tests (agreement among professionals) but may help a patient make a decision about prostate biopsy after discussion of the pros and cons with a specialist (agreement among professionals).
III.6. Prostate biopsy

Prostate biopsy is the examination which confirms the diagnosis of prostate cancer. It is ultrasound-guided and performed by the transrectal route. It can cause acute prostatitis, septicaemia, haematuria and major rectal bleeding, and acute urinary retention (approximately 1% for each of these complications). Minor haematuria (15%) and blood in the sperm are common but are not regarded as complications.

A negative biopsy does not eliminate the presence of prostate cancer. Fewer than 1 in 5 patients may nevertheless have prostate cancer. The biopsies may have missed the tumour.

IV. Epidemiology and natural history of prostate cancer

IV.1. What is the natural history of prostate cancer?

The incidence of prostate cancer increases with age. Autopsies on men who died of causes other than prostate cancer show that the proportion with prostate cancer varies between 12% at age 40-49 and 43% after the age of 80. However, the proportion of clinically significant cancers is much lower than the number of cases detected by histology at autopsy.

The outcome and prognosis of prostate cancer are related to tumour volume, PSA level, stage and, above all, to the degree of histological differentiation (grade or Gleason score) at the time of diagnosis. In particular:

- The higher the stage, the faster PSA level rises which could mean more rapid cancer growth: PSA doubling time (median ~ 2 years) is shorter for higher stage tumours and when there is local or regional spread and/or metastases.
- Poorly differentiated tumours progress to the metastatic stage more often and rapidly than well-differentiated tumours.

In studies with 10 years’ follow-up, tumours have been shown to progress to the metastatic stage in fewer than 1 in 5 patients (depending on tumour characteristics). Mean time from diagnosis to onset of metastases ranges from 5 years for Gleason score 8-10 to more than 15 years for Gleason score 2-4. Death occurs a mean of 2-3 years after onset of metastases.

European registries show that for localised prostate cancer (the type most often diagnosed at an early stage):

- the estimated age-standardised 5-year relative survival rate is 65.4% (after pooling all disease stages, all Gleason scores, and both treated and untreated disease). In France, the corresponding estimate is 75.2%.
- the disease-specific survival rate after pooling all Gleason scores is > 90% at 5 years, > 80% at 10 years, approximately 80% at 15 years and approximately 55% at 20 years. The rate decreases as PSA rises and Gleason score decreases. At 15 years it is approximately 90% for the best-differentiated tumours (grade 1/Gleason score 2-4) and < 50% for the most poorly-differentiated tumours (grade 3/Gleason score 8-10). With 20 years’ follow-up, a grade 3 cancer has a 40-50 times higher risk of causing death than a grade 1 cancer.
These data highlight the individual variability in the course of prostate cancer. The possibility that individual screening could identify men with prostate cancer who could thus benefit from treatment is an indirect argument in its favour\(^5\).

### IV.2. What factors affect the risk of prostate cancer?

- **Age**
  The risk of prostate cancer varies with age. Incidence and associated mortality are very low before the age of 50 years, and then increase rapidly (Table 1). Half of all cases of prostate cancer occur after the age of 74. The mortality rate curve is shifted by 10-15 years compared to the incidence rate curve.

<table>
<thead>
<tr>
<th>Age range (yrs)</th>
<th>Estimated incidence</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>30-34</td>
<td>0.1</td>
<td>0.0</td>
</tr>
<tr>
<td>35-39</td>
<td>0.2</td>
<td>0.1</td>
</tr>
<tr>
<td>40-44</td>
<td>0.9</td>
<td>0.2</td>
</tr>
<tr>
<td>45-49</td>
<td>5.3</td>
<td>0.8</td>
</tr>
<tr>
<td>50-54</td>
<td>29.8</td>
<td>3.0</td>
</tr>
<tr>
<td>55-59</td>
<td>117.6</td>
<td>10.4</td>
</tr>
<tr>
<td>60-64</td>
<td>292.0</td>
<td>28.2</td>
</tr>
<tr>
<td>65-69</td>
<td>575.1</td>
<td>65.2</td>
</tr>
<tr>
<td>70-74</td>
<td>869.1</td>
<td>136.8</td>
</tr>
<tr>
<td>75-79</td>
<td>1086.2</td>
<td>260.5</td>
</tr>
<tr>
<td>80-84</td>
<td>1196.4</td>
<td>459.2</td>
</tr>
<tr>
<td>≥ 85</td>
<td>1111.9</td>
<td>900.8</td>
</tr>
<tr>
<td>TOTAL</td>
<td>141.4</td>
<td>35.1</td>
</tr>
</tbody>
</table>


- **Family history**
  The risk of prostate cancer is multiplied by a factor of approximately 2.0-3.5 if there is a family history of the cancer among first-degree relatives (level of evidence 2). The risk increases with the number of family members affected and seems to be higher if there is a history of prostate cancer among brothers rather than among fathers. The reported excess risk should be related to stratified risk, notably age-stratified risk (Table 1). The risk is multiplied by 10 when the form is said to be hereditary (level of evidence 3). There are several genes, with differing modes of transmission, which could be involved in prostate cancer. No single gene yet identified explains a substantial proportion of the familial forms.

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\(^5\)Although patients with poorly differentiated prostate cancer have a lower life expectancy at diagnosis than others, there is no published evidence that treatment is beneficial. Like elevated PSA, poor histological differentiation is a prognostic factor for higher recurrence, whatever the treatment option. A randomised study against watchful waiting would not be regarded as ethical.
Information for men requesting screening for prostate cancer

Familial forms of prostate cancer have not been shown to occur earlier (level of evidence 3). If they do, the time interval is very small compared to that normally expected for a hereditary cancer. In addition, the familial/hereditary forms of prostate cancer do not appear to be more severe than the so-called sporadic forms (level of evidence 2).

- **Ethnicity**
  There could be a higher risk of prostate cancer in men of African origin compared with the rest of the population but this higher risk could just be due to socioeconomic differences. In contrast, men of Asian origin have a lower level of risk. Mean age at diagnosis seems to be lower, and the proportion of cancers with a Gleason score > 7 significantly higher, in African-Americans than in Caucasians (level of evidence 3).

- **Other risk factors**
  A history of syphilis or gonorrhoea seems to be associated with a higher risk of prostate cancer (level of evidence 2) though the risk remains low. Neither vasectomy or prostatitis, nor sexual behaviour has been shown to increase the risk of prostate cancer (level of evidence 2). A link has been reported between high blood testosterone levels and increased risk of prostate cancer (level of evidence 2) but the mechanism is not known. It has not been shown that tomatoes and tomato derivatives have a protective effect, nor that fat intake has any influence (level of evidence 2).

V. Treatments for localised prostate cancer

V.1. Who should be offered curative treatment?

The aggressiveness of prostate cancer varies and treatment often has adverse effects. The indication for curative treatment should therefore be discussed with each patient on a case by case basis. It is generally accepted that a patient needs a life expectancy of more than 10 years to benefit from curative treatment. According to the most recent INSEE\(^6\) estimates, the mean threshold age for a 10-year life expectancy is 75 but this age should be seen in relation to tumour characteristics (notably grade), concomitant disease, the patient's personal medical history and family history of longevity. In general, early diagnosis - and therefore individual screening - are not recommended in symptom-free patients over 75 (agreement among professionals).

V.2. How effective and safe is treatment?

Ideally, the most relevant efficacy criterion would be increased overall survival. Failing this, estimates of disease-specific and metastasis-free survival at 10 years may give a reasonable indication of the efficacy of treatment for organ-confined cancer.

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\(^6\) French National Institute for Statistics and Economic Studies
Valid curative treatments are total prostatectomy, external beam radiotherapy (EBRT) and brachytherapy. Watchful waiting with postponement of treatment is an option. Treatment with high intensity focused ultrasound (HIFU Ablatherm®) is currently undergoing clinical assessment. The choice of treatment (not addressed in this report) depends on tumour, prostate and patient characteristics, on analysis of prognostic data, and on a decision shared between patient and health professional(s). The patient must be given information about outcomes, adverse effects and, above all, quality of life.

At present, there is insufficient published data on:
- whether immediate treatment at an early disease stage improves individual prognosis;
- whether any one treatment modality (total prostatectomy, EBRT or brachytherapy) is superior to another, particularly after early stage diagnosis. There are no randomised controlled studies other than a study comparing total prostatectomy and watchful waiting in patients with mainly stage T2 tumours (approx. 75%) and Gleason score ≤ 6 (approx. 60%). It found no significant difference in overall mortality after 8 years' follow-up ($p = 0.31$) but a significant difference in favour of total prostatectomy in disease-specific mortality (7.1% vs 13.6%, $p = 0.02$) and in the occurrence of distant metastases (13.4% vs 27.3%, $p = 0.03$).

Current French practice restricts brachytherapy (iodine 125) to tumours with a low risk of progression, i.e. intracapsular stages (T1 or T2a), initial PSA ≤ 10 ng/ml and Gleason score <7, volume < 50 cc and no obstructive symptoms (no history of endoscopic resection). When these criteria are met, recurrence-free survival at 5 years is about 90%. Brachytherapy may also be proposed in combination with EBRT or with hormone therapy for intermediate stages.

The main side effects of curative treatments for localised prostate cancer are summarised in Table 2. These data are operator dependent apart from absence of ejaculation, which always occurs after surgery. Intensity-modulated EBRT reduces the frequency of radiation-related complications (level of evidence 2).

### Table 2. Main side effects of treatments for localised prostate cancer at 1 year (Percent patients)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Urinary incontinence*</th>
<th>Other urinary problems**</th>
<th>Erectile dysfunction¶</th>
<th>No ejaculation</th>
<th>Digestive problems§</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total prostatectomy</td>
<td>4-39</td>
<td>-</td>
<td>20-80</td>
<td>100</td>
<td>-</td>
</tr>
<tr>
<td>EBRT</td>
<td>0-13</td>
<td>3-36</td>
<td>4-55</td>
<td>-</td>
<td>1-36</td>
</tr>
<tr>
<td>Brachytherapy</td>
<td>6-15</td>
<td>0-18</td>
<td>5-70</td>
<td>-</td>
<td>5-19</td>
</tr>
</tbody>
</table>

*: definition depends on age. The severity and circumstances of onset (stress incontinence, regular, occasional, total [0-7%]) vary.
**: late or persistent urinary complications.
¶: definition depends on age at time of treatment.
§: diarrhoea, rectal bleeding.

Few high-quality data were found for post-treatment quality of life (Box 1). Quality of life (urinary irritation, sexual problems and digestive problems) is poorer after brachytherapy than after EBRT (level of evidence 2).
Box 1. Side-effects affecting quality of life

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Side-effects</th>
</tr>
</thead>
</table>
| Surgery   | Urinary incontinence (level of evidence 1)  
Sexual problems (level of evidence 1)  
(approximately three-quarters of these problems occur immediately, but tend to improve over time) |
| EBRT      | Digestive and sexual problems (level of evidence 2)  
(erectile dysfunction appears some time after treatment) |
| Brachytherapy | Urinary irritation, digestive problems, sexual problems and, to a lesser degree, incontinence (level of evidence 2)  
(erectile dysfunction appears some time after treatment) |

VI. General conclusions

It has not been shown that mass screening for prostate cancer by the total serum PSA test reduces mortality. Results of studies on the impact of mass screening on prostate cancer incidence and mortality are not relevant for individual screening.

Notable reported risk factors for prostate cancer are a 1st- or 2nd-degree family history and African-American descent. In addition, risk increases with age. So far, the impact of individual screening has not been assessed as a function of these risks. Nevertheless, basing themselves on indirect evidence, the working group members considered that non-routine individual screening might benefit some patients insofar as:
- there are potential risk factors;
- there is an early diagnostic test;
- if screening is negative, it may reassure men with risk factors;
- curative treatment could increase specific survival and in some cases could improve the individual prognosis.

On the other hand, individual screening does have possible or genuine drawbacks:
- the low positive predictive value of the test and the anxiety it generates;
- the unnecessary tests it may lead to;
- treatment of disease that would not have needed treatment (overdiagnosis);
- side effects of treatment;
- lack of treatment efficacy in some cases.

The decision to carry out individual screening should be taken with the patient. It depends on his point of view, in particular his anxiety level and aversion to risk. The decision should be informed by clear, objective and prioritised information about benefits and risks, notably side effects and quality of life. The working group reaffirmed the paramount importance of oral information and the usefulness of written information. The 30 questions and answers that follow could prove helpful in this regard.

These conclusions should be reassessed in the light of the results of two ongoing studies (European Randomised Study of Screening for Prostate Cancer (ERSPC) and Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening).
30 questions on prostate cancer screening

1. What is the prostate? What does it do?
The prostate is a gland that only exists in men. It consists of glandular cells surrounded by a fibromuscular capsule. It is normally the size of a chestnut and is located under the bladder, in front of the rectum, at the junction of the urinary and genital systems. It secretes seminal fluid and has a role in reproduction.

2. What is prostate cancer?
Prostate cancer is the progressive malignant transformation of glandular cells, which begin to grow without any control. The cells gradually acquire the ability to multiply, so forming one or more tumours. At this stage the cancer is described as localised or organ-confined. These cells may then migrate outside the prostate, mainly into lymph nodes and bones, causing metastases. This is then described as non-localized or extracapsular cancer.

3. What are the warning signs of the disease?
The disease remains occult for a long time. At a very advanced stage, prostate cancer may cause urinary signs and bone pain, particularly in the lumbar spine.

Localised prostate cancer does not cause any urinary signs. The urinary disorders attributed to the prostate are mainly caused by a prostatic adenoma (benign prostate hypertrophy), a very common benign tumour which can coexist with prostate cancer.

4. Is prostate cancer common?
Prostate cancer becomes more common with age. It rarely occurs before age 50, and is the most common cancer in men over 50. Half of all prostate cancers are diagnosed after the age of 74. In 2000, an estimated 40,000 new cases of prostate cancer were diagnosed in France.
5. **Is prostate cancer always fatal?**

In 2000, prostate cancer caused about 10,000 deaths in France. It was the second most common cause of cancer death in men, after lung cancer. Because of the time the disease takes to progress to the metastatic stage, patients with prostate cancer may die of another disease in the meantime. A number of men will die with the disease unaware they have it and unaware of any symptoms: 4 out of 10 men over the age of 80 have prostate cancer without experiencing any problems.

6. **Is prostate cancer hereditary?**

Sometimes. The level of risk depends on the number of members of a family who have had prostate cancer. Prostate cancer is considered hereditary when at least 3 cases have been diagnosed in 1st or 2nd degree relatives, or only 2 cases, but occurring before the age of 55. The risk is then 10 times higher. For the familial form not meeting these criteria (the so-called non-hereditary form), the risk is multiplied by 2 to 3.5. Hereditary forms account for about 5-10% of all prostate cancers and familial forms for 5-25%.

7. **Does the risk of prostate cancer vary with ethnic origin?**

Yes, it does. The incidence of prostate cancer is higher in Europe and the United States than in Asia. In the United States, African-Americans have a 3-fold higher risk than other populations.

8. **Does diet have any effect on getting prostate cancer?**

It has not been shown that tomatoes and tomato derivatives have a protective effect, nor that fats, particularly unsaturated fats, have an aggravating role.

9. **Does sexual behaviour have any effect on getting prostate cancer?**

No. There is no evidence to support any link between sexual behaviour and onset of prostate cancer. However, there does appear to be a link between prostate cancer and previous infection with some sexually transmitted diseases such as syphilis or gonorrhoea.

10. **Can you prevent prostate cancer?**

No methods or medicinal plants have been shown to be effective in preventing prostate cancer. No drugs have received a marketing authorisation from the health authorities for preventing prostate cancer.

11. **What does individual screening involve?**

Individual screening is prescribed to an individual because of personal risk factors such as his age or family history, or at the person's request. Its aim is to allow the earliest possible diagnosis.

The best approach is to use both available tests: digital rectal examination (DRE) and a blood test to measure the PSA level. A hard nodule can sometimes be felt in the prostate during DRE.
When thinking about having a PSA test, it should be clear that a diagnosis of prostate cancer will only be confirmed after prostate biopsy. This involves taking samples of prostate tissue, usually under local anaesthetic. The specimens are then examined under a microscope.

No medical imaging methods can be used to diagnose prostate cancer. Ultrasound is only used to guide the biopsy needle into the prostate.

12. What is PSA?
PSA stands for Prostate Specific Antigen, which is a non-toxic protein produced only by the prostate. It is present in sperm, where it has a role in reproduction. PSA is also present in the blood (normally at a very low level). A high PSA value may indicate prostate cancer. It is not necessary to fast before the blood test.

13. When is a PSA value abnormal?
The PSA value has to be interpreted by a doctor in the light of the clinical situation. A value higher than 4 micrograms per litre (µg/l) (or nanograms per millilitre (ng/ml)) is generally regarded as abnormal. However, this depends on a person's age and the size of his prostate.

14. If the PSA value is above normal, what is the risk of having prostate cancer?
When a PSA value is higher than 4 ng/ml, a prostate biopsy will confirm a diagnosis of prostate cancer in 3 out of 10 cases.

15. What other factors can raise the PSA value?
Certain physiological events (e.g., ejaculation) may cause minor variations in PSA level. They do not usually affect interpretation of the result. DRE does not cause any substantial change in PSA level. A substantial rise in PSA can occur after certain diseases such as urinary infection or acute prostatitis, or following certain surgical procedures such as endoscopic examination of the bladder, prostate biopsy or endoscopic resection of the prostate.

16. Does a normal PSA value mean that there is nothing wrong?
A normal PSA value means 9 times out of 10 that there is no cancer. However, an abnormality might still be detected with a DRE. This is why it is useful to use both PSA and DRE to detect prostate cancer.

17. If PSA is normal, do I have to see my doctor again, and if so, when?
If both PSA and DRE are normal, the patient is considered not to have prostate cancer. There is no point in repeating the test and examination in the short term.
- If a man aged 75 or over has a normal PSA value, he will not need another PSA test in the future.
- If a man aged under 75 has a normal PSA value, the doctor will tell him exactly when he should come back for another test - this might be in 1 year, 2 years, 3 years or even longer, but generally not earlier than 1 year. The interval will in fact depend on the previous PSA value.

18. What are the pros and cons of a PSA test?
19. What is a biopsy? Does it hurt?
Prostate biopsies are usually done on an outpatient basis, with prophylactic antibiotics and under local anaesthesia. Samples of prostate tissue (usually at least 6) are taken with a needle from different parts of the prostate under ultrasound guidance. A biopsy can be painful and may sometimes cause bleeding (in the urine, sperm or rectum). More rarely it may cause infection or inflammation (about 1%).

20. If the biopsy result is normal, can you still have prostate cancer?
Yes., you can. A negative biopsy does not eliminate prostate cancer and does not mean not getting the disease later on. However, if clinical or laboratory findings continue to suggest a risk of prostate cancer, the biopsy can be repeated. If the PSA value remains high while the biopsy is negative, there is a maximum 1 in 4 likelihood that another biopsy would be positive and would diagnose prostate cancer.

21. If prostate cancer is diagnosed, what tests have to be done?
The stage of cancer development is given mainly by clinical examination of the prostate, the PSA value and the results of prostate biopsies. However, a few tests may be proposed to complete the diagnosis. These are abdominal and pelvic CT scan or MRI imaging to judge if and how far the cancer has spread beyond the prostate. Bone scintigraphy may be used to check that there are no bone metastases.

22. What are the treatment options?
Several options may be proposed by the specialist depending on the characteristics of the tumour, the patient’s age and any concomitant disease:
• watchful waiting (postponing treatment)
• surgery (“total prostatectomy”)
• external beam radiotherapy
• brachytherapy.
HIFU (high intensity focused ultrasound, Ablatherm®) is still being assessed. Hormone treatment alone is not normally used to treat localised forms.
23. **How are patients monitored if they decide against treatment? Can they still be treated if they delay treatment?**

Monitoring ("watchful waiting") involves periodic clinical examination and PSA testing. It may be appropriate or possible for certain types of tumour although it is not yet possible to say whether it really compromises outcomes. If the cancer develops further, appropriate treatment is available. It is always possible to change one's mind and discuss with the doctor whether treatment would be appropriate.

24. **How does prostate cancer develop if it is not treated? Can you die from it?**

Progressive forms of prostate cancer are likely to cause problems when urinating, complete urinary retention, or to interfere with kidney function by slowing the flow of urine from the kidneys to the bladder. There is also a possibility that it may spread outside the prostate by direct invasion of tissues and organs close to the prostate. Liver and lung metastases are rare, while bone metastases are more common and painful. Death generally occurs at the metastatic stage, in other words on average about 15 years after diagnosis. Some forms are more aggressive than others.

25. **What are the principles behind each type of treatment?**

- **Curative surgery** involves removing the prostate. The bladder, which is located above the prostate, is then sutured to the urethra, which is underneath the prostate. A urinary catheter is left in place while this heals. This operation is usually performed through an abdominal incision above the pubis. It may also be performed laparoscopically or through an incision in the perineum. The seminal vesicles are removed along with the prostate. Hospital stay for this operation is generally 1-2 weeks.

- **External beam radiotherapy** involves radiographic studies of the prostate, followed by radiation which targets and preferentially kills the abnormal prostatic cells. This method involves a number of short radiotherapy sessions over several weeks (6 to 8 weeks).

- **Brachytherapy** involves permanent implantation of radioactive iodine seeds in the prostate, under ultrasound guidance and under anaesthesia, or temporary implantation of iridium 192 seeds in the prostate. These seeds give off radiation that destroys neighbouring cells. The radiation has a very small range and remains confined to the prostate. Implantation takes about 2 or 3 hours, with a hospital stay of about 2 days.

26. **What are the chances of treatment curing the cancer?**

The key factors affecting the chances of a cure are the stage at which the cancer is discovered and the characteristics of the tumour. When the cancer is localised, 7-9 out of 10 men are still alive 10 years after diagnosis or treatment. In some patients without clinical symptoms of recurrence, serum PSA concentration may rise again after treatment; this is biological recurrence. It may mean a need for further treatment.

27. **Can treatment affect my sex life?**

All treatments for prostate cancer carry a risk of sexual problems, particularly erectile dysfunction that may need medical treatment. However, erectile dysfunction cannot always be treated effectively. In addition, it is not possible to ejaculate after having a total prostatectomy.
28. Can you still have children after treatment?
If the patient wants to father a child, his sperm will need to be frozen before treatment and medically assisted conception techniques will be needed.

29. Can treatment affect urination?
Yes. Total prostatectomy carries a non-negligible risk of urinary incontinence (see table below) but this usually lasts only a few months. However, there may be urine leakage after exertion. External beam radiotherapy and brachytherapy may lead to a frequent need to urinate and/or urgency. These disorders may begin during or after treatment.

30. What are the side effects of the treatments available?
The main potential side effects of total prostatectomy are absence of ejaculation, erectile dysfunction and urinary incontinence. The potential side effects of external beam radiotherapy (EBRT) or brachytherapy are erectile dysfunction, bladder problems and digestive problems. The percentage of patients experiencing these side effects is given in the table below.

### Main side effects of treatments for localised prostate cancer at 1 year (Percent patients)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Urinary incontinence*</th>
<th>Other urinary problems**</th>
<th>Erectile dysfunction¶</th>
<th>No ejaculation</th>
<th>Digestive problems§</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total prostatectomy</td>
<td>4-39</td>
<td>-</td>
<td>20-80</td>
<td>100</td>
<td>-</td>
</tr>
<tr>
<td>EBRT</td>
<td>0-13</td>
<td>3-36</td>
<td>4-55</td>
<td>-</td>
<td>1-36</td>
</tr>
<tr>
<td>Brachytherapy</td>
<td>6-15</td>
<td>0-18</td>
<td>5-70</td>
<td>-</td>
<td>5-19</td>
</tr>
</tbody>
</table>

* definition depends on age. The severity and circumstances of onset (stress incontinence, regular, occasional, total [0-7%]) vary.
** late or persistent urinary complications.
¶ definition depends on age at time of treatment.
§ diarrhoea, rectal bleeding.
Annex 1 – Participants

Agencies, learned societies and patient associations consulted

Association française d'urologie
Société française du cancer
Société française de cancérologie privée
Société française de radiologie et d'imagerie médicale
Société française de radiothérapie oncologie
Société française de santé publique
Société française de documentation et de recherche en médecine générale

Société de formation thérapeutique du généraliste
Collège national des généralistes enseignants
Société française de médecine générale
Société française de biologie clinique
Institut de veille sanitaire (InVS)
Agence française de sécurité sanitaire des produits de santé (AFSSAPS)
Ligue nationale contre le cancer.

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Annex 2 – Assessment method

The ANAES method for producing these clinical practice guidelines\(^7\) comprised the following steps:

**Defining the scope of the guidelines (Steering committee).** ANAES invited representatives from agencies, learned societies and patient associations concerned by the topic to take part in a steering committee whose job was to define the scope of the guidelines, to review previous work on the subject and to nominate professionals to take part in a working group or act as peer reviewers.

**Literature search (Documentation Department of ANAES):** See below

**Drafting the guidelines (Working group).** The ANAES project managers formed a working group of 19 professionals from a number of disciplines, working in public or private practice, from all over the country. The chair of the working group coordinated the production of the guidelines with the help of the project managers whose job was to ensure conformity with the methodological principles of guideline production. Three members of the working group identified, selected, and analysed relevant studies (from a literature search performed by the ANAES Documentation Department) and wrote a draft report. This draft report was discussed by the working group over 5 meetings and amended in the light of comments from other members of the working group and from peer reviewers.

**External validation (Peer reviewers).** Peer reviewers were appointed according to the same criteria as working group members. They were consulted by post after the fourth working group meeting, primarily with regard to the readability and applicability of the guidelines (scores from 1 to 9). One of the ANAES project managers summarized their comments and submitted them to the working group prior to the third meeting. Peer reviewers were asked to sign the final document.

**Internal validation (Evaluation Section of the ANAES Scientific Council).** Two members of the Council acted as referees reporting to the Council, together with the ANAES project managers. The working group finalized the guidelines with due regard to the Council's suggestions.

- **Literature search and analysis (general procedure)**

The scope of the literature search was defined by the steering committee and the project managers. The search was carried out by the ANAES Documentation Department and focused on searching:

- medical and scientific databases over an appropriate period, with special emphasis on retrieving clinical practice guidelines, consensus conferences, articles on medical decision-making, systematic reviews, meta-analyses and

\(^7\) Full details are given in “Recommandations pour la pratique clinique – base méthodologique pour leur réalisation en France – 1999” (Anaes)
other assessments already published nationally or internationally (articles in French or English)
- specific and/or financial/economic databases, if necessary
- all relevant websites (government agencies, professional societies, etc.)
- the grey literature (documents not identified through the usual information distribution circuits)
- legislative and regulatory texts

Further references were obtained from citations in the articles retrieved above and from working group members' and peer reviewers' own reference sources. The search was updated until the project was completed.

The articles selected were analysed according to the principles of a critical appraisal of the literature, using a checklist, to allocate a level of scientific evidence to each study. Whenever possible, the working group based their guidelines on this review of the literature. Guidelines were graded from A to C as shown in Table 1 depending on the level of the evidence of the supporting studies. If no grading is given, they are based on agreement among professionals.

<table>
<thead>
<tr>
<th>Level of published scientific evidence</th>
<th>Grade</th>
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<tbody>
<tr>
<td><strong>Level 1</strong></td>
<td></td>
</tr>
<tr>
<td>Randomised controlled trials of high power</td>
<td><strong>A:</strong> Established scientific evidence</td>
</tr>
<tr>
<td>Meta-analyses of randomised controlled trials</td>
<td></td>
</tr>
<tr>
<td>Decision analyses based on properly conducted studies</td>
<td></td>
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<tr>
<td><strong>Level 2</strong></td>
<td></td>
</tr>
<tr>
<td>Randomised controlled trials of low power</td>
<td><strong>B:</strong> Presumption of scientific foundation</td>
</tr>
<tr>
<td>Properly conducted non-randomised controlled trials</td>
<td></td>
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<tr>
<td>Cohort studies</td>
<td></td>
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<tr>
<td><strong>Level 3</strong></td>
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<tr>
<td>Case-control studies</td>
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<tr>
<td><strong>Level 4</strong></td>
<td></td>
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<tr>
<td>Comparative studies with major bias</td>
<td></td>
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<tr>
<td>Retrospective studies</td>
<td></td>
</tr>
<tr>
<td>Case series</td>
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</tbody>
</table>

Table 1. Grading of guidelines