

PROJECT PROSTATE CANCER 2023



**Prostate cancer and
new European recommendations.**
Strategies to promote access
to early diagnosis.

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Premises

Prostate cancer is the common type of cancer in the male population. Early diagnosis and timely access to dedicated multidisciplinary specialist treatments are crucial for surviving the disease. Intercepting the tumor early when it is still localised within the prostate, allows clinicians to use less invasive therapies, reducing the risk of complications and the impact on patient's quality of life. Early detection is also cost-effective, as it reduces the need for aggressive treatments, as well as possible complications and long-term care.

Europe's Beating Cancer Plan, unveiled in 2021, and the recently published Proposal for a Council Recommendation (CR) on Strengthening Prevention through Early Detection: a New EU Approach to Cancer Screening replacing 2003/878/EC, urge an increased focus on early detection with the goal of reducing mortality and inequalities. The Council focuses on the feasibility of implementing screening programs following the COVID-19 pandemic, which has disrupted health awareness and prevention programs, negatively affecting access to early detection and treatment of cancer. In particular, the new Council Recommendation updates the guidelines for breast, cervical and colorectal cancer screening and calls for the development of organised screening programs to detect other types of cancers.

An organized screening program for the early detection of prostate cancer is not currently active in our country for two main reasons: firstly, a lack of scientific evidence on the new PSA testing, and secondly a lack of awareness. While men generally know about prostate cancer, they are not aware of the importance of early diagnosis and of having regular specialist checkups even in the absence of symptoms.

The European document recommends a specific commitment to this cancer, urging EU countries to consider a stepwise approach, including testing and further research to assess the feasibility and effectiveness of implementing organized programs.

1. Epidemiology of prostate cancer

Over the past decade, prostate cancer has become the most common cancer among men in Western countries. Its incidence has increased over time due to both the progressive aging of the population, and the increased likelihood of early diagnosis. Simultaneously, prostate cancer mortality rates have decreased continuously, demonstrating the crucial role of early diagnosis.

According to the latest report "The Numbers of Cancer in Italy," published in December 2022, there were about 40,500 new prostate cancer cases in 2022, representing 19.8% of all male cancers.

In terms of prevalence, there are 564,000 men that are currently living after a diagnosis of prostate cancer, while in 2021, 7,200 men died of this disease.

2. Risk and protective factors

The aetiology of prostate cancer is multifactorial, as genetic susceptibility and environmental factors both have an impact.

Age is the main risk factor: incidence increases with increasing age, particularly after 50.

Other relevant factors are heritability and the presence of specific genetic mutations (e.g., BRCA2 and BRCA1). It is estimated that the risk of developing prostate cancer doubles if the patient has a close relative with this neoplasm, increasing 5-11 times if there are two or more close relatives with a history of prostate cancer. In addition, the scientific community is now proposing to consider other cancers, such as pancreas, breast, ovary, possibly colon, and melanoma when accessing a patient's familial risk. A person's risk is therefore affected not only by the male hereditary lineage but also the female. This seems particularly true for men that develop prostate cancer early, often presenting an aggressive form of the disease. It is an evolving theory, which highlights the issue of genetic counselling: when and who would benefit the most from genetic testing as part of a screening program aimed at early detection. To date, genetic testing, such as searching for BRCA 1 and 2 mutations, is limited to patients with advanced disease to check their suitability for a new class of drugs, the so-called PARP inhibitors, that have been shown to be effective in "mutated" patients.

Poor lifestyle choices, particularly a diet high in animal fats and characterised by excessive caloric intake, may promote the onset of cancer.

Other minor risk factors, which are considered controversial, include sexually transmitted infections and occupational exposure to certain chemicals such as cadmium and pesticides.

Evidence regarding the potential protective effects of vitamin D, coffee and lycopene-containing foods (e.g., tomatoes), fish and vegetables as well as some hypolipidemic drugs (statins) is low or otherwise very conflicting in the various scientific studies. In contrast, the evidence for the protective role of physical exercise is clear.

3. Role of prevention and early detection

Primary prevention

As with all chronic and oncological diseases, the importance of primary prevention, based on positive lifestyle choices, particularly proper nutrition and regular physical exercise, is recognised.

Secondary prevention - Screening

The goal of conducting an "organized" screening program for prostate cancer among asymptomatic patients (or in a subgroup) is to detect a tumor with a test at an early stage (early detection), and eventually through appropriate treatments, decrease prostate cancer mortality rates.

Early detection allows the tumor to be intercepted at an early stage before symptoms appear, thus offering the possibility to plan ahead, increasing the number of available treatments and the patient's chances of survival. This in turn reduces mortality rates and improves patients' quality of life.

International scientific studies suggest that screening with PSA results in a minimal reduction in prostate cancer mortality rates. However, this reduction is associated with a high rate of overdiagnosis and overtreatment, which can lead to patients undergoing unnecessary treatments with serious side-effects.

What is PSA?

PSA stands for prostate-specific antigen, a glycoprotein produced primarily by prostate glandular tissues secreted in seminal fluid and normally released into the bloodstream in minute amounts. Alterations in glandular tissues, as in the case of prostate cancer, can result in increased PSA circulating in the blood.

PSA may be elevated for many reasons other than prostate cancer: it rises under physiological conditions (e.g., recent ejaculation and strenuous physical activity), in non-cancerous problems (such as prostatic hypertrophy and prostatitis), and after certain diagnostic tests are performed (e.g., cystoscopy and prostate biopsy). It is therefore an organ-specific and not a tumor-specific marker. In addition to the false-positive rate, one must also consider the false-negative rate, in which PSA values do not rise above the reference threshold despite the presence of cancer.

The usefulness of a national screening program with PSA testing that targets the general population, regardless of risk factors has been much debated. It is hard to draw firm conclusions given the risk of overdiagnosis and overtreatment associated with PSA testing, which can lead to a range of side effects and complications. Many prostate neoplasms are, in fact, clinically insignificant, being indolent small tumors that do not impact the patient's life.

The scientific community has come to the conclusion that the PSA test is useful when offered in accordance to precise guidelines. A patient's individual risk has to be assessed (age, presence of any risk factors, including his hereditary-family history), and patients need to be provided with clear information on the possible benefits, potential risks (overdiagnosis and overtreatment), and diagnostic limitations of the test.

Several guidelines indicate the benefits of 'opportunistic' (non-organised) screening with PSA in men between 50 and 70-75 years of age. Because of age expectancy, the risks involved in screening men over 75 years of age are believed to outweigh the benefits.

In asymptomatic men with hereditary risk factors, the age at which periodic PSA surveillance can be considered may be anticipated to 40-45 years.

Most guidelines agree that PSA tests are only one tool when deciding whether or not to perform a biopsy, and that an elevated PSA value should be confirmed by a second test to be performed after a few weeks.

Although transrectal ultrasounds have in the past been widely used for diagnosing prostate cancer, they have a low diagnostic accuracy, resulting often in false positives and false negatives. Currently they are used during guided biopsies, where clinicians are able to fuse previously taken MRI images with those provided by the ultrasound during the biopsy.

Multiparametric magnetic resonance imaging of the prostate has become the gold standard for diagnosing prostate cancer, displaying soft tissues at a significantly higher resolution. The addition of an internationally validated score (PI-RADS) to interpret these images, has also improved the diagnostic potential of the method, to be performed after the clinical test and before the biopsy.

Symptoms of prostate carcinoma

The more specific symptoms of prostate cancer appear when the tumour mass increases in volume and infiltrates the surrounding structures. The more common symptoms, however, such as decreased urinary output, difficulty in urinating, frequent and/or painful urination, sometimes the presence of blood in the urine or semen, and the sensation of not being able to empty the bladder completely are not specific to prostate cancer. They may instead indicate benign prostate diseases such as prostatic hypertrophy and prostatitis.

The diagnosis of prostate cancer in symptomatic men involves a specialist urological examination as well as additional tests, such as PSA levels and specific diagnostic investigations.

4.Obstacles to early detection

The "Prostate Cancer Awareness" survey conducted by Elma Research and Fondazione Onda in 2021 found that only three out of 10 men consider themselves sufficiently informed about the issue. Most would also like to receive more information and be kept up-to-date, especially by their general practitioner. Although they consider it to be widespread, respondents are quite optimistic, perceiving prostate cancer as a treatable disease that does not drastically impact quality of life and is on the whole little feared compared to other oncological diseases. The survey had also enlisted a group of women in the sample, who reported that they were involved in motivating men to perform preventive check-ups and that they directly arranged them in 57% of cases. According to 54% of respondents, when confronted with genito-urinary symptoms, they didn't feel comfortable sharing them with their doctor, they minimised the problem and waited to seek medical advice.

In general, among male respondents there is a poor attitude to undergo check-ups in the absence of specific problems, especially those that involve sexual and reproductive organs.

Added to this is the fact that prostate cancer remains asymptomatic for a long time and that the information conveyed to the patient on the PSA test is not always univocal and clear.

5. The EU Council Recommendations

On 29 November 2022, the Proposal for a Council Recommendation (CR) on strengthening prevention through early detection: a new approach on cancer screening replacing Recommendation 2003/878/EC was published. The 2003 document was limited to breast, cervical and colorectal cancer, while the most updated version broadened its scope, including lung, prostate and gastric cancer.

The aim, in line with the European Cancer Plan, presented in February 2021, is to offer expanded screening programs to reduce mortality and inequalities. In order to succeed, the programs have to be adequate in quality, and guarantee access to all those who fall within the targeted categories, due to age or risk factors.

The key points of the document are: right of access; quality assurance; monitoring inequalities; updating recommendations on screening for breast, cervical and colorectal cancer; extending screening programs to lung, prostate and stomach cancers (in areas where the incidence of gastric cancer is high); and innovation.

The recommendations to member states are divided into seven "areas":

- Implementation of cancer screening programs
- Registration and management of screening data
- Monitoring
- Training
- Participation
- Introduction of new screening tests that take into account the results of international research
- Implementation, report and follow-up

The document highlights the importance of providing information: the benefits and risks of undergoing tests, including the individual risks of overdiagnosis and overtreatment, should be presented in a clear way. Patients need to be able to express informed consent when participating in a screening program.

The Council also recommends ensuring that patients that receive a positive result are offered follow-ups with adequate and timely diagnostic procedures and complementary therapies.

The recommendation pays particular attention to equal access to screening and urges systematic and regular monitoring of screening programmes, to assess disparities.

Given the preliminary evidence and the high prevalence of opportunistic screening, the Commission's senior scientific advisors in regards to prostate cancer suggest a gradual approach. This would involve further research and testing to assess the feasibility and effectiveness of implementing organised programmes with prostate-specific antigen (PSA) testing, in combination with magnetic resonance imaging (MRI) as a follow-up test.

The Commission recommends all Member States to update their screening programs in line with the latest evidence. It urges countries to assess their national and regional governance in regards to cancer screening, to facilitate the timely implementation of possible new or updated European guidelines [...]. These should be implemented in accordance to the incidence of the specific disease, the resources available to the healthcare system, the cost-effectiveness of the screening program, the balance between risks and benefits, as well as evidence gained through new scientific experiments and pilot projects.

This means that we will have to review what we have known until now, as a result of new and growing data regarding the role of genetic and hereditary predispositions in regards to prostate cancer.

6. Intervention strategies to promote correct information and facilitate access to early diagnosis in Italy

Early diagnosis, as already highlighted, represents the most effective strategy for reducing mortality and improving patients' quality of life.

In order to promote it efficiently, it is necessary to invest in several areas of intervention. These are summarised below and require collaboration between all involved stakeholders:

- Promote proper education in sexual and reproductive health among the male population. This should start at a young age, breaking taboos and enhancing the role of consultants in this field.
- Provide more information and increase awareness on prostate cancer, focusing on risk factors and the role of early diagnosis and emphasising the importance of having regular urological check-ups, particularly after the age of 50 (after the age of 40 for those with a positive family history, as mentioned above), even in the absence of symptoms.
- Ensure access to clear and correct information on the benefits and risks of early detection for prostate cancer, as well as on the limitations of current screening techniques.
- Ensuring fair and equal access to early diagnosis throughout the country, targeting those within the at-risk categories, and following the guidelines set by the scientific community.
- Investing in training general practitioners in the promotion of men's health, and specifically in primary and secondary prevention of prostate cancer.
- Promote information and awareness-raising activities on the prevention and early diagnosis of prostate cancer. These should also target women, in light of their role in encouraging active urological prevention to their partners, in intercepting the first alarm bells and in urging timely access to specialist diagnostic and treatment pathways.

The Council Recommendation on Strengthening Prevention through Early Detection: A New EU Approach to Cancer Screening, which replaces Recommendation 2003/878/EC urges countries, as previously mentioned, to focus on prostate cancer, for which no organised screening programme currently exists in our country. The invitation is to invest in scientific trials and research to assess its feasibility and effectiveness, as is currently done in Sweden, for example.

While the focus of this document is on early diagnosis, we ought to emphasise the importance of planning a multi-professional and interdisciplinary approach for effective patient care once prostate cancer is diagnosed. It is therefore necessary to provide correct information to the general public in regards to the existence of dedicated multidisciplinary centres capable of guaranteeing a highly specialised and personalised diagnostic and therapeutic approach.

Appendix

Fondazione Onda

Fondazione Onda has always focused and continues to focus on women's health. The need to overcome an androcentric approach to medicine, as evidenced by demographic, epidemiological, biological and social factors have guided Fondazione Onda over the years.

Recently all specialist medical fields, led by scientific evidence, have gradually moved towards recognising the importance of a gender-specific approach. In light of these developments the Observatory has broadened its scope to include gender-specific medicine, and in 2018 added the word 'gender' in its name.

In 2022, the Foundation launched its first project dedicated to men's health, the Bollino Azzurro (Blue Stamp). These stamps identify centres that guarantee an interdisciplinary approach to the diagnosis and treatment of prostate cancer. The project was followed by the publication of the White Paper 'Prostate Cancer. State of the art and new perspectives'.

This new commitment represents a natural evolution for the Foundation, not only as a response to the rise of gender-specific medicine, but also in consideration of women's active role in protecting the health of their partners.

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