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Prostate cancer screening: the problem of overdiagnosis and lessons to be learned from breast cancer screening

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Abstract

Screening for prostate cancer is a relatively new procedure, still under experimental evaluation within prospective randomised trials. The design of prospective studies has been mainly based on the experience of other cancer screenings, particularly breast cancer, for which data of several controlled studies are available. Unfortunately, breast cancer is very different from prostate cancer, particularly for aspects such as early diagnosis and, thus the screening process, originally modelled on the basis of the lesson taught by breast cancer screening, needs continuous re-evaluation and adjustment, based on data which are now being produced from ongoing screening experiences. In this paper, we will consider the most controversial aspects of prostate cancer screening and compare prostate screening with breast cancer screening in order to promote a better understanding of the current problems and lessons to be learned.

Keywords: Prostate cancer; Screening; Overdiagnosis

1. Rationale of screening

As for breast cancer, the aim of prostate cancer screening is a reduction in mortality obtained through early detection and treatment. The two diseases look similar from many angles:

1. They are both frequent, lethal, socially relevant diseases.
2. They have a similar growth pattern, slow, usually progressing from local disease to distant metastases.
3. They are both curable with locoregional treatment, particularly in the initial stages.
4. They are often hormone-dependent and hormonal treatment may control progression for a long time.

However, they also have major differences:

1. Their incidence is age-dependent but prostate cancer tends to affect older subjects, with a lower life expectancy and a lower potential benefit of screening (life years to be gained).
2. Compared with breast cancer, subjects with prostate cancer, even advanced, have a higher probability of dying 'with' rather than 'of' cancer, from other concurrent causes of death in elderly males, and the potential benefit of palliative treatment is higher compared with breast cancer. This may reduce the importance of early detection.
3. Clinical diagnosis of prostate cancer in the presence of symptoms occurs often at a very advanced stage. Detection in the absence of symptoms implies a potential great diagnostic anticipation. This may allow more effective treatment, but also has negative effects (much earlier awareness of disease and exposure to treatment side-effects), which might possibly outweigh survival benefits.

Although a rationale for prostate cancer screening exists, we still need scientific evidence to support these theories. The benefit in terms of mortality reduction obtained by breast cancer screening is well determined, and its cost/effectiveness has also been established, justifying the current practice of screening on a population basis. The benefits of prostate cancer screening are just theoretical, thus far unknown, and the potential risk of adverse effects much more worrying than for breast cancer: screening as a current practice is unethical, and the practice of screening, at the moment, must be limited to experimental studies.

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2. Screening

The optimal screening modality for prostate cancer (prostate specific antigen (PSA) assay) is substantially different from breast cancer (mammography).

PSA is simple, acceptable and cheap, definitely less operator dependent, compared with mammography: this is a great advantage as implementation of screening, particularly if population-based, is easier, involves less professional skills and needs less training, and population compliance is higher [1]. But, at least in prospective randomised trials, it is also a disadvantage as contamination of the control arm by opportunistic PSA (a simple, cheap blood test, available everywhere) is very easy. PSA is also easier to standardise, whereas wide variability and great subjectivity affect mammography. However, PSA is very unspecific (approximately 90%) compared with mammography (approximately 99%), and unnecessary referrals (causing costs and anxiety) may exceed 10% of the screened subjects.

3. Assessment

In contrast to screening, assessment is complex. Since PSA is unspecific, assessment must be careful and provide reliable diagnoses. Digital rectal examination (DRE) and transrectal ultrasonography (TRUS) are almost regularly followed by invasive assessment, such as directed and random sextant biopsies. For breast cancer, the screening test is often also diagnostic and further assessment is cheaper and less invasive (fine needle aspiration cytology). The cost of assessment in prostate cancer screening is high, and due to the high referral rate, it has a relevant impact on total costs, thus reducing the advantages due to the low cost of the initial screening test.

Compliance to assessment in breast cancer screening is generally high, as women are motivated by the report of some suspicious mammographic abnormality. Most subjects referred for assessment in prostate cancer screening only have a slightly elevated PSA, which their GP at least knows to be poorly predictive of cancer, and are offered a biopsy procedure even with a negative DRE and TRUS. This may cause a lower compliance to complete (including biopsy) assessment.

4. Treatment

Radical treatment may be curative for both diseases, but a big difference is evident as far as side-effects and morbidity are concerned. Radical treatment of breast cancer is obtained by radical mastectomy and often (particularly for screen-detected early cancers) by conservative surgery and breast irradiation. The morbidity is not relevant, usually limited to mild upper arm oedema. The cosmetic impact of surgery has been dramatically reduced since the introduction of conservative treatment. Radical treatment of prostate cancer can be obtained with the same success rate either with radical prostatectomy or radiotherapy, the former being the more diffuse option, also due to the limited availability of high quality radiotherapy facilities in many countries. Unfortunately, the morbidity of radical surgery is relevant, with average figures reporting 0.1–1% perioperatory mortality, 5–10% major urinary incontinence and 80–90% sexual impotence rates.

It is quite evident that the negative implications of overtreatment are maximised for prostate cancer, and the negative impact of screening in terms of quality of life in overdiagnosed subjects may compete with the benefit of reduced mortality.

The problem of the treatment for prostate cancer is also complicated by the fact that the awareness of a high overdiagnosis rate should encourage the identification of latent, slow growing, non-aggressive cancers to avoid overtreatment, but no reliable method is available at the moment and treatment is the standard option in almost all screen-detected cases. It is unclear which is the optimal therapeutic option for early prostate cancer: 'watchful waiting' has been repeatedly suggested as a safe alternative to radical treatment [2]: hormone therapy, though palliative, may control even advanced disease for years and, due to the limited life expectancy of some subjects, compete with radical therapeutic options.

Avoidance of treatment would be in contrast with the rationale of screening which is based on the intention to treat early stage, asymptomatic screen-detected lesions, and particularly in randomised trials it is unclear which threshold for adopting a 'watchful waiting' policy might flaw the whole study.

5. Overdiagnosis and overtreatment

Any attempt to detect cancer early implies some degree of overdiagnosis, that is the identification of cancer which, in absence of screening, would never have reached the clinical threshold, as the subject would have died of other disease before the cancer could become symptomatic. This is more likely with cancer with an average low growth rate, a long preclinical detectable phase, for which very sensitive tests are available, and affecting subjects with a low life expectancy. This is particularly the case for prostate cancer screening.

Cancer is very common in the prostate of males over 50 years of age. Autopsy studies of males over 50 years of age dying of causes other than prostate cancer report a prevalence as high as 30% [3]. If these subjects would have lived to their normal life expectancy, the expected risk of symptomatic prostate cancer would not exceed

Table 1
Estimates of prostate cancer overdiagnosis by screening[a]

Study [Ref.]	Age invited (years)	Screening protocol	Interval considered	Overdiagnosis estimate
Florence, pilot study, Italy [4]	60–74	Every 2 years Bx DRE/TRUS+	14 years after screening	51% (95% CI 44–59)
	65–74	Every 2 years Bx DRE/TRUS+	14 years after screening	93% (95% CI 85–101)
Rotterdam pilot study, The Netherlands [5]	55–74	Only one round Bx PSA > 4	10 years after screening	75–100%
Mettlin study, USA [6]	55–70	Annual Bx PSA > 4	10 years after screening	150–275%

[a] DRE, digital rectal examination; TRUS, transrectal ultrasonography; PSA, prostate specific antigen.

8–10%. Thus, the majority of prostate cancers found at autopsy would never surface as symptomatic: they are currently called 'latent' cancers but can not be identified as such, as they have the same pathological features of 'clinical' cancer. The preclinical detectable phase of latent cancer is, by definition, as long as they live. Latent cancers simply stay there, ready to be detected by screening.

The population invited to screening (males 55–70) have a life expectancy of 10–15 years. Detection lead time by screening has been estimated to be as long as 6–7 years [4]. Due to competing causes of death in this particular screened population, the risk of overdiagnosis is high, higher than for breast screening. Moreover, women also have a 10 year longer life expectancy implying this population will have a larger gain from screening. Latent cancers are not necessarily detected from causing PSA elevation, but screening may be detected 'because' the subjects happen to have a spurious PSA elevation and the latent cancer is picked up by chance by a random biopsy, performed routinely in presence of elevated PSA according to the screening protocol.

The fact that most screen-detected prostate cancers are localised but have an aggressive pattern (e.g. capsule involvement, high grade) has been stressed to deny the importance of overdiagnosis, as latent cancers are generally assumed to be minimal in size, and low grade. On the contrary, as (a) prostate cancer may be slow growing even if locally advanced and (b) life expectancy of screened subjects may be limited, we should start to figure out that even an advanced cancer, associated with an average survival of 3–4 years, may actually be 'overdiagnosed'. In fact, the number of screen-detected cancers in some studies (e.g. Rotterdam, including the second round) is higher than the cancers expected in the absence of screening, thus overdiagnosis is, although unpleasant, a reality we should consider when talking about screening, without waiting for any other confirmation of its existence.

Overdiagnosis due to breast cancer screening has been estimated to be as high as 10%, and small non-palpable pT1 and pTis cancers most likely account for the majority of overdiagnosed cases. As these cases are currently treated with conservative treatment (pTis with no axillary dissection, which causes most side-effects of breast surgery) and receive no adjuvant therapy, the load of overtreatment is further minimised. On the contrary, we have estimated in a recent report [4] the magnitude of overdiagnosis, based on the cancer detection rate at first and repeat (when available) screening and the interval cancer rate (when available) in different published screening experiences. Depending on screening aggressivity (frequency of screening and use of random sextant biopsy) overdiagnosis may be as high as 275% (see Table 1).

As prevention through screening is generally based on the intention to treat, overdiagnosis should be automatically associated to overtreatment. In fact, in the presence of minimal cancer with low grade, unapparent at DRE and TRUS, particularly in subjects over 65 years of age and/or with contra-indication to radical surgery, a 'watchful waiting' policy may be adopted. This is reported to occur more frequently in some countries (e.g. Sweden). 'Watchful waiting' may be assumed as a 'treatment option', as treatment prompted at first signs of asymptomatic progression (e.g. PSA elevation) may be still regarded as 'early'. Watchful waiting has been suggested as a possible procedure to avoid or minimise overtreatment even in presence of a relevant overdiagnosis. Nevertheless,

1. No reliable indicator of a latent or non aggressive cancer is available
2. 'Watchful waiting' tends to be adopted in presence of cancers minimal in size and with low grade. But the assumption that most latent cancers have these features is not confirmed by the estimates of overdiagnosis and the stage of screen-detected cancers. Thus, the adoption of 'watchful waiting' might involve only a minority of overdiagnosed cancers and the impact on overtreatment would not be a major one
3. Progression from minimal to more advanced cancer, may be impossible to reveal for a long time. Thus, increasing use of the 'watchful waiting' option might substantially affect screening efficacy, as effective treatment might be postponed, being performed at a more advanced cancer stage.

To conclude, thus far the problem of overtreatment seems unresolved, at least until reliable indicators of cancer aggressivity will allow no treatment of selected cases. In the meantime overtreatment will represent the major adverse effect of screening, the major reason to discourage screening as a current policy. Ongoing controlled studies should provide continuous and careful monitoring of screen-detected cancer rates, stage and treatment and of interval cancer rates, in order to provide a more solid estimate of overdiagnosis and overtreatment.

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