Acta Oncologica, 2010; 49: 275–277

informa
healthcare

EDITORIAL

Screening for prostate cancer – will we ever know?

JAN ADOLFSSON

Oncologic Center, Karolinska University Hospital, CLINTEC Department, Karolinska Institutet, Stockholm, Sweden

In this issue of Acta Oncologica, Professor Hans-Olov Adami presents a comprehensive summary of the present knowledge on prostate cancer screening [1]. He concludes that screening with Prostate specific antigen (PSA) as such is questionable and that the use of PSA so far has created an epidemic of prostate cancer with little documented effect but with documented harms. Moreover, he concludes "To date, extensive attempts to identify molecular predictors of outcome have remained unsuccessful, and no ideal screening test is within sight."

However, the same evidence has been judged differently by many decision makers, physicians and patients. Notably screening with PSA has been encouraged by many professional associations but not by any governmental bodies [1]. The bottom line, however, is that we still do not really know if possible benefits from PSA-screening outweigh harms on the population level.

It is true that the use of PSA has increased the incidence of prostate cancer dramatically in the US (see figures in the paper by Adami [1]) and in all Nordic countries [2]. The peak is a typical prevalence peak due to the sifting out of prevalent but not yet detected cases in the population. Interestingly there is a second peak in the US and this is probably due to a decrease in PSA cut-off level again sifting out cases that were not found with the cut-off of 4 ng/ml. However, both in the US and Sweden there is an increase in the pre-PSAera but at a much lower rate. This is most probably real and is driven by changes in risk factors for prostate cancer. Thus, even if the incidence of prostate cancer is decreasing presently we can look forward to an increase in incidence again due to this underlying increase in incidence. This and the present changes in the western world towards a larger and older population will inevitably lead to a dramatic increase in the number of men diagnosed with prostate cancer in the future.

One problem in the debate is that screening as a term is used in different contexts. For prostate cancer it is mostly an opportunistic screening or even case finding among men seeking the health care on their own initiative either because of symptoms or seeking a health check-up. The opposite is service screening where individuals are actively invited to a population-based testing. Screening for breast cancer and cervical cancer in Sweden are examples of such service screening. Contrary to opportunistic screening, service screening is endorsed by the health care officials and governmental bodies. Among many differences between the two settings, of most importance, is that service screening is evaluable.

However, screening is very easy to over sell. It is also very easy to advocate it because of possible benefits (easy to exaggerate) and equally difficult to argue against it on the ground of possible harms to the patients and the population. It is not surprising that the public perception of the actual benefits is higher than what reasonably can be achieved [3,4].

The primary goal for cancer screening is to sift out those with a deadly disease and to try to cure them thus lowering the mortality from the disease. A secondary goal is to reduce morbidity of the disease. Screening does therefore not necessarily have the aim to find all cases with disease as long as some are indolent and not killing the bearer or even not giving any symptoms. Screening should also ideally identify both those with and those without the disease with reasonable precision, i.e. both sensitivity and specificity should be high, a situation which has been shown very difficult to achieve. As pointed out by Adami there are certain criteria that should be fulfilled to make screening acceptable [1]. In the mid 1990s only a few of these criteria could be considered fulfilled for prostate cancer screening with PSA. At that time it was clear that the prostate cancer disease was significant to both the society (large number of patients requiring large resources) and the individual

ISSN 0284-186X print/ISSN 1651-226X online
DOI: 10.3109/02841861003696803

(potentially deadly disease with treatments causing significant morbidity) and that PSA-testing was acceptable and reasonably efficient in finding the disease in a preclinical phase. The efficacy of treatment and particularly after earlier finding with PSA was however not considered to be proven. Since then new knowledge has emerged based on randomized studies. Treatment with radical surgery has in the randomized SPCG-4 trial been found to have at least a moderate beneficial effect in terms of cancer-specific survival [5] and most recently data from the European screening study indicates that treatment in the preclinical phase is efficient in terms of lowering prostate cancer mortality although this could not be confirmed in the American PLCO study [6]. However having to treat 19 patients with clinically detected localized prostate cancer with radical surgery (the SPCG-4 trial [4] or manage (with radical treatment or surveillance) 48 screening-detected cases to save one man from dying of prostate cancer (the ERSPC-trial) [7] has by many observers been considered as not effective enough given the known side effects and possible harms. For the majority of men without prostate cancer the largest risk is false positive PSA tests leading to unnecessary biopsies and worry. For instance, in the PLCO trial the cumulative risk of a false positive finding was 10% after four yearly screenings with PSA [8]. In the Finish part of the ERSPC trial one in eight men were at risk of a false positive test after three tests within a median of 9.4 years [9]. This and the fact that the efficacy of PSA as a screening test in terms of finding a reliable cut-off has had the effect that PSA alone as screening test has been questioned [10,11].

Thus, in the light of all this uncertainty, can we expect to have new data within the near future that will make it possible for us to resolve the remaining questions?

With respect to treatment efficacy the SPCG-4 study is so far the only published study comparing surveillance with active treatment with curative intent. A second randomized study contemporary to the SPCG-4, the PIVOT-trial, is expected to publish soon. The ProtecT study in the UK randomizing PSA-detected cases to active surveillance, radical surgery or radiotherapy has recently completed the recruitment of patients but it will take at least another eight to 10 years before survival results can be expected.

The two screening trials PLCO and ERSPC will hopefully continue to publish follow-ups but it is not likely that any new large studies will be started. The ProtecT- program also has a screening component, the CAP-trial. This trial is randomized on clusters where each cluster is a general practitioner's list and men listed at practices randomized to screening were invited to screening with PSA. Again, it will take a long time before there will be any firm data in this study.

Data on over-diagnosis, over-treatment and side effects will probably emerge from many observational studies but such data will always be subject of different interpretations.

Again, will we ever know? The sad fact is that there will be very few high quality studies in the future that will be able lead us further to a decision on PSA screening for prostate cancer than we have today. We will therefore have to decide on more or less what we presently know. However it is probably better to make an active decision than just passively follow the flow. Unfortunately much of the interpretations and decisions will continue to be in the eye of the beholder and not based on equivocal evidence.

Still many men die an often very unpleasant death of prostate cancer. In Sweden more men with prostate cancer die than women from breast cancer. Thus, there is still a large need to find and cure those and alternative strategies to PSA screening as it is performed today have been proposed. One obvious such strategy would be to prevent men from getting prostate cancer. This would certainly lower the risk of dying of prostate cancer since you have to have a disease before you can die from it. Treatment with finasteride [12] and dutasteride (Andriole AUA, Chicago 2009) has been shown to lower the incidence of prostate cancer of approximately 25% within seven to eight years but the long treatment times make this option less interesting. Moreover, vitamins and other supplements have been a disappointment in three recent large randomized intervention trials [13–15]. Although prevention is intuitively a natural road to try it will take many years before we have population-based programs for this and even longer before we can see any effects.

Another strategy is to try and individualize the risk prediction to develop a lethal prostate cancer [9]. We already know that if a man have a PSA of less than 1 ng/ml at 50 years of age the risk of being diagnosed with prostate cancer within 10 years is very low if any [11,16]. There is also a rapid development in terms of finding genetic alterations that are connected to the development of prostate cancer and just recently the first genetic change coupled to the aggressiveness of prostate cancer was found [17]. Thus, molecular markers combined with other factors such as tumour markers (PSA) and information on family history [18] may give us an opportunity in the future to better predict an individual's risk of both being diagnosed with and to die of prostate cancer. To investigate this we need blood and tumour tissue, clinical information, etc. from large numbers of men with and without prostate cancer

and the effort, which requires large resources must be done in collaboration with preclinical and clinical scientists. One example on such an effort is the CRisP-consortium (www.crispcenter.org).

References

[1] Adami H-O. The prostate cancer pseudo-epidemic. Acta Oncol 2010; 49: 298–304.

[2] Bray F, Klint Å, Gislum M, Hakulinen T, Engholm G, Tryggvadottir L, et al. Trends in survival of patients diagnosed with male genital cancers in the Nordic countries 1964–2003 followed up until the end of 2006. Acta Oncol 2010. in press.

[3] Gigerenzer G, Mata J, Frank R. Public knowledge of benefits of breast and prostate cancer screening in Europe. J Natl Cancer Inst 2009;101:1216–20.

[4] Woloshin S, Schwartz L. Numbers needed to decide. J Natl Cancer Inst 2009;101:1163–5.

[5] Bill-Axelson A, Holmberg L, Filén F, Ruutu M, Garmo H, Busch C, et al. Radical prostatectomy versus watchful waiting in localized prostate cancer: The Scandinavian Prostate Cancer Group-4 Randomized Trial. J Natl Cancer Inst 2008;100:1144–54.

[6] Andriole G, Grubb III R, Buys S, Chia D, Church T, Fouad M, et al. Mortality results from a randomized prostate cancer screening trial. New Engl J Med 2009; 360:1310–9.

[7] Schröder FH, Hugosson J, Roobol M, Tammela LJ, Ciatto S, Nelen V, et al. Screening and prostate – cancer mortality in a randomized European study. New Engl J Med 2009;360:1320–8.

[8] Miller Croswell J, Kramer B, Kreimer A, Prorok P, Xu J-L, Baker S, et al. Cumulative incidence of false-positive results in repeated, multimodal cancer screening. Ann Fam Med 2009;7:212–22.

[9] Kilpeläinen T, Tammela T, Määttänen L, Kujala P, Stenman U-H, Ala-Opas M, et al. False positive screening results in the Finnish prostate cancer screening trial. Br J Cancer 2010;Epub, Jan 5.

[10] Esserman L, Shieh Y, Thompson IM. Rethinking screening for breast cancer and prostate cancer. JAMA 2009;302:1685–92.

[11] Holmström B, Johansson M, Bergh A, Stenman U-H, Hallmans G, Stattin P. Prostate specific antigen for early detection of prostate cancer: Longitudinal study. BMJ 2009; 339:b3537.

[12] Thompson IM, Goodman PJ, Tangen CM, Lucia SM, Miller GJ, Ford LG, et al. The influence of finasteride on the development of prostate cancer. New Engl J Med 2003;349:215–24.

[13] Gaziano J, Glynn R, Christen W, Kurth T, Belanger C, MacFadyen J, et al. Vitamins E and C in the prevention of prostate and total cancer in men; The Physicians' Health Study II Randomized Controlled Trial. JAMA 2009;301:52–62.

[14] Lin J, Cook N, Albert C, Zaharris E, Gaziano M, Van Denburgh M, et al. Vitamins C and E and beta carotene supplementation and cancer risk: A randomized controlled trial. J Natl Cancer Inst 2009;101:14–23.

[15] Lippman S, Klein E, Goodman P, Lucia M, Thompson I, Ford L, et al. Effect of selenium and Vitamin E on risk of prostate cancer and other cancers: The Selenium and Vitamin E Cancer Prevention Trial (SELECT). JAMA 2009;301:39–51.

[16] Lilja H, Ulmert D, Björk T, Becker C, Serio A, Nilsson J, et al. Long-term prediction in prostate cancer up to 25 years before diagnosis of prostate cancer using prostate kallikreins measured at age 44 to 50 years. J Clin Oncol 2007;25:431–6.

[17] Xu J, Zheng S, Isaacs S, Wiley K, Wiklund F, Sun J, et al. Inherited genetic variant predisposes to aggressive but not indolent prostate cancer. PNAS 2010;Epub Jan 18.

[18] Zheng A, Sun J, Wiklund F, Gao, Z, Stattin P, Purcell L, et al. Genetic variants and family history predict prostate cancer similar to prostate-specific antigen. Clin Cancer Res 2009;15:1105–11.