A Guinea Pig's View on Prostate Cancer Screening Trials

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Many things come to a different view when they become directly personal. This happened to me when I received an invitation to participate in a PSA based prostatic cancer screening trial encompassing 5000 men, 55–67 years of age domiciled in the Espoo area of Finland where I live. I had been publicly critical of the prostatic cancer screening programs in general terms but when it now affected so many of my unsuspecting fellow citizens, the problems involved became suddenly quite concrete.

Finland is traditionally an excellent place for epidemiological intervention studies since the population is quite homogeneous, the people are all identified by their social security numbers and registered regularly for tax and voting purposes. The addresses also tend to be relatively stable since people move around quite little compared with many other nations and they are thus usually available for subsequent follow-up queries and other information. In addition, there is a positive, almost subservient attitude towards studies of this kind which makes it understandable that international funding agencies are quite forthcoming in assigning funds to projects with Finns as 'guinea pigs'. Consistent with these notions, the PSA trial is funded by the European Union as part of a multicenter investigation.

Still, the information distributed with the invitation must obviously be enticing in one way or another in order to be effective. This is the first problem in prostatic cancer screening. What benefits can reasonably be promised to the potential volunteers to make them more likely to participate? In this trial the benefit is described obliquely by stating that the prognosis of prostatic cancer, if detected and treated at an early (intracapsular) phase, is comparable to that of the normal male population of the same age without prostatic cancer. Consequently the aims of the study as given in the invitation are to find out whether screening will lower mortality by earlier diagnosis and to investigate the influence of the whole screening procedure on the quality of life of the study population. Let us examine each of these goals separately.

Prospects for reducing mortality

The treatment of early prostatic cancer is either radical prostatectomy or radiotherapy. In clinical settings there are already quite large series of published material showing that the difference in prognosis between radically treated and conservatively managed (watchful waiting and treatment only at clinical progression—without surgery or radiotherapy) is small and late-appearing (difference apparent only after 10–15 years). Perhaps the most illustrative is the large re-analysis by Chodak et al. (1) of 828 patients from six non-randomized studies comparing the outcome of conservative management of clinically localized prostatic cancer with that of the matched general male population. The curves in Fig. 1, representing a set of trials reproduced from this study are quite striking in demonstrating the minimal effect of early grade I and II prostatic cancer on mortality. The margin for improvement with any radical treatment thus appears very small. This is also clearly shown by the largest so far published clinical series encompassing 59876 patients, 50–79 years of age (2), which compared the effect of radical treatment with watchful waiting and conservative management. The 10-year survival of localized prostatic cancer with grade I tumors was 94% after prostatectomy, 90% after radiotherapy and 93% with conservative management. In grade II the corresponding figures were 87%, 76% and 77%. As these groups, grades I and II, comprise 75–86% of the cases to be identified by in screening exercises, it would really be fair to say to the potential volunteers in PSA screening that the prognosis in the great majority of those with localized prostatic cancer is essentially as good without therapy!

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Another way to look at the potential margin of improvement in prognosis by PSA screening and early intervention is provided by cross-sectional serum-bank materials linked to the subsequent history of the patients by cancer registry data (3, 4). Frozen serum samples from years 1966–1972 were available from 21172 Finnish men aged 55 to 65 years (3). By the end of 1980, 44 new cases of prostatic cancer were diagnosed in this group and their follow-up completed until the end of 1992. The prognosis of cancers either positive (over 4 ng/ml, 24 cases) and negative (20 cases) at the serum-bank samples is shown in Fig. 2. Similar data have also been published from Sweden (4). From these series it can be concluded first that a substantial part of the subsequent fatal cancers arose in the PSA negative population, and secondly, that the positive PSA test advanced the diagnosis by about 10 years. If radical treatment had been instituted immediately after the positive PSA finding became known the prognosis of these cases would presumably have improved. The critical question is how much? The fate of the PSA negative cases would obviously not have been affected. These cases were presumably either cases that never became PSA positive or cases at so early stages that they were still PSA non-detectable. The better survival in this group must then reflect the maximum that is obtainable by the lead-time advantage provided by the screening. This was about 20 percentage points at 10 years and 25 percentage points at 15 years of follow-up in the Finnish material.

If the expected 50 fatal cases among the participants of the present trial (1% for the estimated 500 screen positive men) by age 77 (10 years follow-up for the oldest screened bracket) were distributed as in the Finnish serum-bank material, one could thus expect 5 deaths saved by this optimistic calculation. If the smaller margin from the Chodak et al. (1) curve is used as a basis the figure would

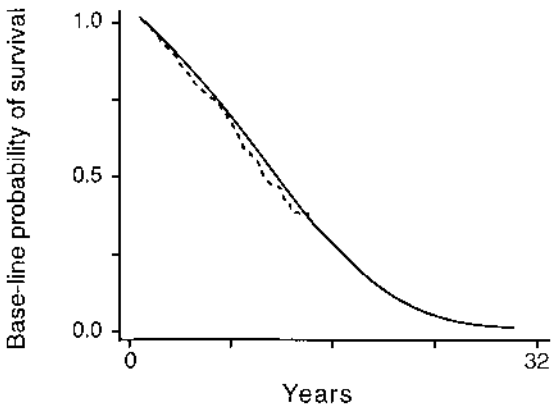

Fig. 1. Life-expectancy of men with prostate cancer of grade I and II treated with watchful waiting and conservative management at the symptomatic phase in the two Swedish cohorts reanalysed by Chodak et al. (1). The survival is compared to normal life-expectancy (––) and adjusted to the age of 70 years by Cox regression of the cancer cases (----).

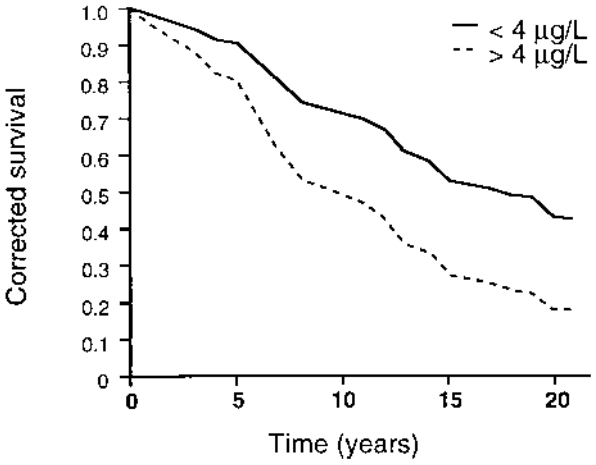

Fig. 2. Prostate cancer-specific survival after time of sampling in 44 subsequently diagnosed cases with PSA levels above (24 cases) or below 4 μg/ml (20 cases) collected from a Finnish serum bank material (Stenman et al. (3)).

be closer to one death saved. It was also notable that among the matched controls of the Swedish series 24% showed false positive PSA values. Only after a follow-up available to 80 years of age the authors felt safe to conclude that the cases represented truly false positives. Such situation in a large-scale screening trial is quite problematic.

Latent prostatic cancer

The data available would thus suggest that the earlier diagnosis has, in fact negligible effect on the total mortality in prostatic cancer. The Danish urologists have been notoriously reluctant to increase their efforts to diagnose latent, non-symptomatic prostatic cancer. This is reflected in the cancer registry data of the Nordic countries shown in Table 1 taken from Tretli et al. (5). As the latent cancers are not specifically searched for, the incidence figures in Denmark are the lowest, 48.9 per 100000, compared with the highest of 85.0 in Iceland. Consequently, the mortality of the incident cases is higher in Denmark, but there is no difference in the total mortality to prostatic cancer in the Nordic countries. Thus, more men in the other Scandinavian countries were treated unnecessarily compared with Denmark, and this was before the PSA era (1983–87). Since then, Tretli et al. (5) report that the increase in prostatic cancer incidence from 1990 to 1992 is 21% in Finland, 18% in Norway, 18% in Iceland and 12% in Sweden. No increase was seen in Denmark! It may thus be truly wise to look to Denmark, as the authors suggest.

The general notion above has since obtained additional support in the Scandinavian arena. Hans-Olof Adami and his colleagues reported from the Swedish Cancer Registry that the statistical analyses provided compelling evidence that the increasing diagnosis of latent, non-lethal tumors was responsible for the altered trends of prostatic cancer

Table 1

Prostate cancer incidence, relative survival, and mortality in Denmark, Finland, Iceland, Norway, and Sweden 1983–87 (from Tretli et al. (5)).

	Denmark	Finland	Iceland	Norway	Sweden
Incidence per 100 000 person-years[1] 1983–1987	48.9	61.8	85.0	71.8	81.6
Five-year relative survival,[1] 1983–1987[2]	38%	60%	59%	55%	62%
Mortality per 100 000 person-years[2] 1983–1987	29.5	26.7	30.3	33.1	30.5

[1] Age-adjusted. [2] Period of diagnosis.

incidence and survival in Sweden from 1960 to 1988 (6). These latent prostatic tumors, which have the morphological characteristics of invasive cancer but are stationary or slowly progressing and do not cause harm during the patient's life-time, are a particular problem in prostate pathology. They provide an almost inexhaustible reservoir of material to be diagnosed as cancer when normal, healthy males are confronted by the diagnostic facilities provided by the Scandinavian welfare societies and, in particular, by screening programs. Table 2 shows the age-related incidence of such latent prostatic tumors calculated for the Finnish population on the basis of autopsy studies. The incidence is estimated to be about 22% at the young end and about 35% at the older age bracket of the screening trial under discussion. This means that approximately 1000 of the 5000 men invited to the screening are at risk of being diagnosed as a cancer patient. In reality, however, only about 10% of those screened with PSA will have an increased (over 4 ng/ml) value. The truly critical problem is that the biology of this selection into the PSA positive pool is not at all understood. How many of those reacting positive are from the latent cancer group, how many are true cancers, and how many of the true cancers are left undetected? On top of this, there are the false positives. As a screening application with our current level of ignorance the use of the PSA test is a lottery!

Consequences of accepting a screening invitation

The logistics of the screening trial under discussion is approximately as follows: Of the 5000 men invited about 500 will have a PSA value exceeding the cut-off level of 4 ng/ml. All these will be subjected to digital rectal examination, ultrasound and six random biopsies taken from three locations on each lobe. About 100 will eventually be subjected to radical prostatectomy. Those with PSA values between 2.5–4 ng/ml will be followed with repeated tests as well as those with the higher values but in whom no cancer was found in the clinical examinations. The follow-up is clearly a signal to everyone inclined to anxiety that once a positive PSA test is registered a definite exclusion of cancer cannot be achieved. This group of several hundred men will be stigmatized for a long time (for life?).

Radical prostatectomy is not a simple operation. The peroperative mortality is 0.5–1%. The overall median risk to die of prostatic cancer in the screened age groups is 0.2%. Thus, the simple fact that a person happened to be selected in the screening program has more than doubled his immediate risk of death in 'prostatic cancer' compared with the situation where men were allowed to go about their daily chores without the screening intervention. Certainly, once the screening is performed and the PSA positive subpopulation is considered, the life-time risk to die from prostatic cancer is higher. Yet those succumbing to the operation are doing so 10–15 years prematurely since no reduction in mortality is expected earlier even by the proponents of screening programs. An unknown, but sizeable proportion is also dying in vain since their disease would never had become clinically manifest. The apocalyptic term 'prostatic holocaust' has been applied to this unfortunate situation in the USA where commercial exploitation of PSA screening has reached epidemic proportions.

Once the radical prostatectomy has been successfully performed, the problems do not end. There are major complications causing chronic morbidity (reviewed in ref. (9)). The loss of sexual function is the most prevalent of these ranging from 20–85% in different materials. Urinary incontinence requiring daily use of diapers affects over 30% and ureter stricturess cause additional problems in 10–18%. Thromboembolic complications and rectal damage occur in smaller percentages but altogether the list is quite formidable. Radical radiotherapy is not widely used in Finland but the complications of this treatment do not offer better outcome in terms of resulting chronic morbidity (9).

Quality of life

A recent editorial in the British Medical Journal on the subject of prostatic cancer screening was entitled 'Screening could seriously damage your health' (10). Those 5000 men accepting the invitation to participate in a trial like the one under discussion are truly risking a lot. Several hundred are 'losing their night's sleep' worrying about a positive cancer test, although so far the cancer has not been found, one is dead in operation although he might have been a carrier of latent non-lethal tumor, about fifty have lost a major pleasure of their lives (11) and about fifty are chronic patients regularly visiting their urologists

Table 2

Estimated prevalence of latent prostate cancer in Finland according to age

Age (yrs)	Male population[1)]	Prevalence of latent prostate cancer[2)]	Estimated number of men with latent prostate cancer in Finland
50–59	298 600	22.1	61 570
60–69	217 400	36.1	78 481
70–79	116 800	37.8	44 150
≥80	43 900	53.7	23 574
Total	—	—	207 775

[1)] 1997 population; [2)] References: (7, 8).

for a variety of symptoms. How can one assess the influence of the screening program on the quality of life under these circumstances?

It goes without saying that the quality of life would definitely be better without the problems listed above. Also a considerable number of good-quality life years has been lost by the decade that the PSA advanced the diagnosis. The tragedy of the situation is that most of the subjects are ready to accept their subsequent ailments simply because they believe that this is the price for being saved from death due to prostatic cancer. In fact only 5 among the 100 prostatectomised may, in the most optimistic evaluation, be such winners. Also, the urologists are experiencing continuously improving results of treatment, because an increasing number of the men they are operating on are carriers of non-lethal tumors and are doing fine in any case. Consequently both the patients and the physicians are betrayed. As there are no objective measurements for the quality of life this aspect of the study may be less than meaningful.

Ethics of a screening trial

Perhaps the main argument used for the screening trials is that the PSA test is spreading into wide clinical use anyway. It would thus be important to study, in an epidemiologically sound fashion, the effect of PSA screening on prostatic cancer mortality before the confounding effects of this clinical practice become too invalidating. This is a pharisean argument. Enough is known already to make the sacrifice of the large volunteer populations needed for meaningful results out of all proportion to the minor advance in epidemiological knowledge. We know already, that the treatment of early stage prostatic cancer with the current procedures has only a marginal effect on mortality seen 10–15 years later compared with conservative treatment. We know, that radical prostatectomy and radiotherapy cause serious chronic complications to a large fraction of those treated. We know, that a considerable proportion of those treated belong to the group of latent tumors which would never have become clinically manifest unless detected by the PSA-screening, and would not require any treatment. We know, that simply participating in a PSA screening trial will cause excessive concern and anxiety to a minimum of 10% of the volunteers.

I think that the conclusion is quite clear. Only when methods have been developed to select those cases likely to benefit from treatment, or a treatment modality is available that can be safely administered for early stage prostatic cancer fully knowing that some are treated 'in vain', can screening of healthy subjects be considered ethically justified. The PSA test itself is quite unsatisfactory and much more of its biological background should be known. One can make a reasonable argument that the latent prostatic tumors represent early precancerous stages, comparable to the dysplasias and CIS of the uterine cervix. However, the PSA test does not detect all of the precancerous conditions, as a good Papanicolaou test does in the cervix. Some of those undetected are clearly significant since invasive cancers develop from the PSA negative pool in a considerable proportion of the fatal cases. The funds allotted to futile epidemiological screening trials should thus be used to increase our understanding of the biology of prostatic cancer and in educating the public and the practising physicians in its proper clinical management, including the critical use of the PSA test.

In summary then, one is faced with a situation in which the negative test does not exclude cancer, one does not know which of the detected cases are significant and what should be done once a localized cancer is diagnosed! Many responsible health authorities have concluded that not only general population screening of prostatic cancer with the current medical technology should not be done, but also prospective epidemiological trials should be discouraged (e.g. (12)). The trials are unethical since sizeable populations of unsuspecting volunteers are needed and harmfully effected in order to show, in a statistically significant fashion, the marginal long-term effect that can be expected based on what we already know. Therefore, I refused the invitation to participate and am recommending the same to the fellow citizens of the community.

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