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Epilogue: Different approaches for prostate cancer screening in the EU?

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ABSTRACT

Individual approaches to prostate cancer screening in European countries could occur as a result of individual decision taking, public health policies or the relevance of the prostate cancer problem determined by incidence and mortality in individual countries.

Methods: An attempt is made to analyse current literature with respect to factors that could influence the individual or country-wide preference for or against the use of PSA driven screening.

To obtain background information the incidence and mortality of prostate cancer in the EU countries participating in the ERSPC study, as well as the results of a recent join-point analysis of prostate cancer mortality for the same countries are reviewed. In addition, the question whether geographic differences in incidence and mortality could influence the value of screening tests in the different countries is evaluated.

Results: Our literature review shows large regional differences in incidence and mortality of prostate. Proportions of men testing positive with PSA values $\geqslant$4.0 ng/ml and PPVs do not reflect these regional differences. Also, regional differences are not in line with negative outcomes for any ERSPC center in an exploratory analysis of prostate cancer mortality. In all centers a decrease of prostate cancer mortality at various degrees was seen. Differences in attitude may be visible in the join-point regression analysis which shows differences in mortality trends for some countries. Detection of T1c cancers in the control group is a measure of opportunistic screening (limitations addressed in the text). The differences reported may best reflect regional decision patterns. As far as the validity of PSA driven testing in countries with a different incidence and mortality is concerned, it seems that neither the levels nor the predictive value of PSA is influenced by such differences.

Conclusions: A number of factors are identified which may explain the different individual decisions and different levels of use of opportunistic screening in the different EU countries.

1. Introduction

The title of this epilogue stimulates thinking, not only by the authors but also by potential readers. Do we need individualised approaches to screening for prostate cancer for the different countries of the European Union, provided screening is eventually shown to be effective by matching its up and downsides? Would such differences also relate to the individual man who considers screening?

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In this review the authors attempt to make an inventory of the epidemiology of prostate cancer in the countries which participate in the European Randomized study of Screening for Prostate cancer (ERSPC) and to relate possible differences to the test procedures and to the outcomes of screening. Furthermore, the authors will try to use the available information to evaluate the patterns of decisions taken by men in some of the ERSPC countries towards early detection of prostate cancer by screening. Current evidence coming from the ERSPC study and future perspectives from expected developments will be utilised.

2. Methods

This review considers current literature on epidemiological aspects of prostate cancer in the eight European countries which are participants in ERSPC and data from the ERSPC publications and data base. The term 'screening' in this review addresses screening of populations of men in European countries or in formalised screening studies in which early detection is offered systematically to study populations. Screening upon request is termed either 'opportunistic screening', 'case finding' or 'early detection'.

3. Results and comments

3.1. *Incidence and mortality in ERSPC countries*

In line with the subject of this review the authors explore differences in incidence and mortality of prostate cancer in the ERSPC countries, which can be considered as representatives for northern and southern European countries. The data in Table 1 are extracted from.[1] They indicate incidence and mortality in age specific rates per 100,000 and absolute numbers of prostate cancers and prostate cancer deaths expected in 2008. In addition, the rate ratios of incidence and mortality are presented. Very large differences in incidence and mortality rates are seen. Mortality is lower in southern European countries. The largest difference occurs between Italy and Sweden where prostate cancer mortality is 2.37 times higher. However, differences of mortality between northern European countries such as the Netherlands and Sweden are substantial. Mortality in Sweden is 1.5 times higher than in the Netherlands. Incidence rates and incidence mortality ratios are probably for the largest part driven by the amount of PSA based screening, which differs markedly between ERSPC countries.[2] Still, even in those countries with the lowest incidence mortality rate ratios (the Netherlands, Spain and Sweden) these ratios are more than 2 times higher than the traditional 2:1 ratio which was observed prior to the advent of PSA driven case finding, when on average 2 men were diagnosed with prostate cancer for every one that died of the disease. The absolute numbers, if added up, give an impressive picture of the size of the health care problems, which is encountered in the ERSPC countries. The incidence mortality ratio based on absolute numbers, without age correction, amounts to 5.32 times more cancers diagnosed than those who are at risk of death from the disease.

The relevance of these findings for possible future application of screening or opportunistic screening will be discussed further down in this chapter.

3.2. *Trends of prostate cancer mortality in ERSPC countries and in the United States of America*

Recent studies of time dependent trends using the join-point regression analysis are available for most European countries and specifically for those countries participating in the ERSPC.[3,4] Unfortunately, all available data bases end during the years of 2002–2004. Still, the early trends in mortality reduction, which usually start in 1993 or soon thereafter, are visible in the join-point regression analyses for those countries where a mortality reduction has occurred (Fig. 1) and are likely to reflect the frequency of PSA use indicating the preferences of the corresponding populations. In[4] for two of the Nordic countries (Sweden and Norway) a close statistical relation is revealed between an increase and changes in PSA testing and prostate cancer incidence. Similar observations were made in the USA. Etzioni et al.[5] estimated on the basis of Medicare claims in the United States that between 1995 and 1998 38% of American men above the age of 50 underwent PSA testing. This level increased during later years and in 1996 77–86% of all prostate cancers were diagnosed by PSA driven testing. Other estimates include the National Health Interview Study (NHIS)[6] and the California Men's Health Study[7] which report 29–37% and 75% of PSA testing, respectively. In the Netherlands, the Central Office of Statistics found in an interview study of 2000 men conducted in 2005,

Table 1 – PSA assessment, biopsies and positive predictive values (PPV)* per country. PSA levels ⩾4.0 mg/ml, 1st screen.

	Number screened	PSA ⩾ 4.0 ng/ml N (%)	Biopsied N	PCa N	PPV %
Finland	20.793	1.826 (8.9)	1.720	506	29.4
Sweden	5.855	394 (6.7)	360	106	29.4
The Netherlands	19.970	2.670 (13.5)	2.408	756	31.4
Belgium	4.567	604 (13.2)	268	89	33.2
France	11.648	1.052 (9.0)	314	104	33.1
Switzerland	4.939	430 (8.7)	316	77	24.3
Italy	5.106	567 (11.1)	441	71	16.1
Spain	2.416	167 (6.9)	135	36	26.7

PPV = proportion of men who have a positive biopsy of those who have PSA levels ⩾4.0 ng/ml and are actually biopsied.
Percentage PSA in Sweden and Spain in men aged >54 years is: 9.2% and 9.1%.

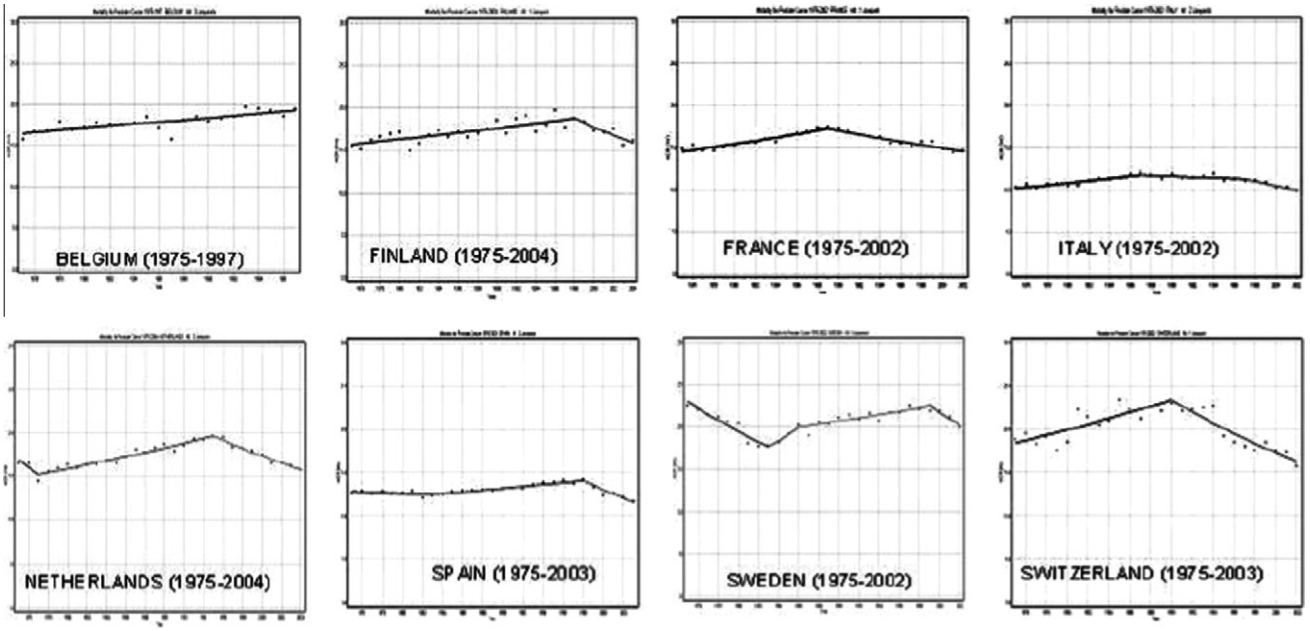

Fig. 1 – Prostate cancer mortality in ERSPC participating countries, join-point analysis 1975–2004 [after 2].

19% and 38% of PSA use in men above 40 and above 70 years of age.[8], respectively. By 2000, a 30% decrease of prostate cancer mortality was observed in the United States, which was preceded by a heavy increase in prostate cancer incidence, which later leveled off. Etzioni and co-workers[9] made use of two different models and estimated that 45–70% of this mortality decrease was due to screening. Other explanations for this decrease include the introduction of the 'anatomic radical prostatectomy',[10] radiotherapy combined with endocrine treatment in locally advanced disease[11] and the frequent use of statins which was shown to influence prostate cancer mortality.[12] It can be concluded that PSA use, which became common after a landmark publication in 1991,[13] has lead to an increase in the incidence of prostate cancer wherever it was applied. In most countries with frequent use of PSA testing also a decrease in prostate cancer mortality was observed[3] (Fig. 1) which often occurred soon after the increase in incidence. Considering the long lead time produced by screening for prostate cancer, it has been suggested that only those cases with a short lead time, the biologically aggressive or locally advanced cancers, might benefit from screening within short periods of time, which may be below 3 years after testing.[14] As mentioned above, other explanations for a decrease in prostate cancer mortality in individual countries are available.

The information presented so far provides the background for an answer to the question asked in the title of this report. Differences in incidence and mortality, as well as the time trends of the use of PSA and its effect observed in the ERSPC participating countries, may impact on the outcomes of screening. In addition, the time trends per country provide information on the attitude towards screening in these European areas. In the following sections an attempt will be made to explore whether the differences in incidence and mortality will impact on the potential application of screening tests and the results, which may be expected. Differences in attitude towards PSA driven testing between the ERSPC countries are likely to be reflected by the different rates of screen detected (T1c) cancers in the control group. For this purpose it is necessary to describe in brief some results of the ERSPC study. However, one must consider that men volunteering for a screening trial are more likely to be screened than other men in the population, even when assigned to the control arm. This may limit inferences regarding PSA testing in the population based on T1c data in the control arm.

3.3. *Screening in ERSPC, summary of results*

The European Randomized study of Screening for Prostate Cancer (ERSPC) is a randomised screening trial addressing as the main end-point prostate cancer mortality.[15] Other end-points, such as the value of the screening tests, prostate cancer morbidity and quality of life were part of the original protocol.

The power of ERSPC in screened men was assessed to be 86% to show a 25% difference in prostate cancer mortality at a p-value of 0.05, based on the data up to December 31, 2008.[16] This is based on a follow-up of 10 years or more for the whole study population. The study was monitored by an independent Data Monitoring Committee which did not report end-point related data to the study group unless predefined conditions, such as reaching a significant difference, were met. Three interim analyses were planned at 2-year intervals after 2002. All results were adjusted to alpha-spending.

162,387 men, age 55–69, were randomised; 72,890 to the screening, 89,353 to the control arm. About 20,437 men tested positive, 17,593 or 85% of these were biopsied resulting in a positive predictive value (PPV) of 24.1%. After an average follow-up of 9 years in the intention to screen analysis, 20% fewer prostate cancer deaths were seen (rate ratio 0.8, 95% CI 0.65–0.98, $p = 0.04$). The absolute risk reduction amounted to

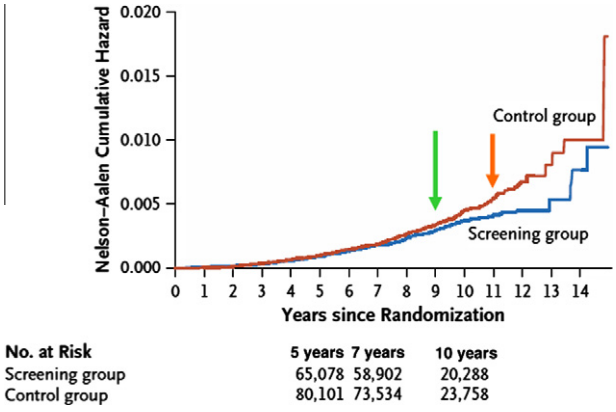

Fig. 2 – Cumulative risk of death from PCa [after 14].

7 per 10,000 screened men. A number needed to screen (NNS) of 1410 and a number needed to treat (NNT) of 48 were seen to avoid one prostate cancer death in access of the control arm. All cause mortality showed a rate ratio of 0.99 (95% CI 0.97–1.02, $p = 0.05$). More details can be found in.[15]

The mortality curves are shown in Fig. 2. It can be seen that the cumulative hazard ratios calculated by the Nelson-Aalen technique start to deviate after 7 years, the blue arrow indicates the 9-year period of the presently reported evaluation. The curves show further deviation after this follow-up period suggesting the possibility of more favourable results on the basis of the planned final analysis based on the mortality data up to December 31, 2008. An analysis of heterogeneity showed that the effect seen could not be attributed to any single center. For the whole of ERSPC a secondary analysis adjusting for non-compliance and contamination, according to the Cuzick technique, was conducted.[17,18] This analysis showed an effect of screening of 31% for men who were in fact screened as compared to men who were not screened at all.

3.4. *How could geographic differences in incidence and mortality influence outcomes of screening?*

A high incidence and mortality in any given country may, with identical screening procedures, lead to the detection of more cancers and more aggressive cancers. On the other hand, it may be that PSA levels vary in line with these unexplained geographic differences. In that case, the positive predictive value of the PSA cut-off value of 3 ng/ml should be similar in countries with a high and low incidence or mortality of prostate cancer. This would apply to the Nordic countries, specifically to Sweden, which has the highest incidence and mortality of the ERSPC countries. The contrary may be true for countries with a low incidence and mortality like Italy. One would expect that in countries with a high incidence more men would be screen-positive than in those with a low incidence. If the test relates to the presence and the stage of prostate cancer, however, the PPV of any given PSA value should be the same in countries with high and low incidence. Is this in line with ERSPC findings? Incidence and mortality rates as well as their change over time in European countries are summarised in the contribution of Bray et al. (this issue).

3.5. *Do geographic differences in incidence and mortality influence the outcomes of testing for prostate cancer?*

In what way, if at all, are the results of testing for prostate cancer influenced by local prostate cancer prevalence? If this were so, one would expect that in countries with a higher prevalence and mortality more men in the same age category would present with higher PSA levels. The distribution of PSA and mortality per age groups are summarised by Otto et al. (this issue) and show differences per country in two screening rounds. In addition to that detailed information an inventory of men who had a PSA > 4.0 ng/ml at the time of the first screen seemed appropriate and shows data per country (Table 1). The figures do not confirm our working hypothesis. The Swedish and Spanish data could be biased by the fact that men in the age group 45–54 are included. After adjustment the percentages were in line with those of the other ERSPC centers. This analysis could be carried out more appropriately by comparing observed/expected PC ratios in biopsied men in different age groups. The next step in our working hypothesis is to consider the PPV per PSA range. In 2005 a comparison between a large screening study in Japan and the Rotterdam section of ERSPC was carried out in men age 55–69 with a PSA < 4.0 ng/ml at the time of the first screen. PSA levels and PSA detection 4 years later were compared. It turned out that Dutch men more frequently had an elevated PSA than Japanese men (5.2% versus 1.6%). Similar PSA levels were associated with identical PPVs in both countries.[19] Looking at the last three columns of Table 2, this working hypothesis seems to be confirmed with the exception of an unexplained outlier: Italy. Potential sources of bias are differences in age distribution, which have a strong influence on PSA levels, incompleteness of data, variations in biopsy techniques and others. The PSA assay as a factor of uncertainty can be excluded, because all centres used the same Beckman Hybritech Access assay and quality control has been carried out within ERSPC.

What then can we conclude about the influence of underlying differences in prevalence and mortality of prostate cancer on the outcome of screening? If PSA according to an agreed cut-off value is used as an indication for biopsy, the outcome in terms of the detection of prostate cancer per PSA range seems to be independent of the underlying prevalence. Unfortunately, the large differences in prevalence and mortality between European countries, described above, still remains unexplained. Life style variations rather than genetic factors seem to be most likely explanations.

3.6. *T1c prostate cancer and the attitude towards screening*

In the 1992 version of the TNM system, which is used in the ERSPC study, T1c prostate cancer is defined as 'tumour indentified by needle biopsy because of elevated PSA'. Since no other mechanism leads to the detection of T1c cancers, the prevalence of T1c in the control arm of the ERSPC study per country should reflect opportunistic PSA use and therefore

Table 2 – Detection of T1c (screen detected) prostate cancer in the control arms of 8 ERSPC centers (Spring 2010).

Centre	Men randomized to control arm	Prostate cancers, number (*N*), (%)		
		Total (*N*)	T1c (*N*)	T1c (%)
Belgium	5.171	390	40	10.3
Finland	48.409	3.269	987	30.2
France (Herault)	31.114	821	194	23.6
Italy	7.475	138	15	10.9
The Netherlands	21.162	994	365	35.8
Spain	1.862	33	13	39.4
Sweden	9.954	766	338	44.1
Switzerland	5.151	227	111	48.9
Total	130.298	6.638	2.054	30.9

the attitude towards screening in the participating countries. Various biases may influence these rates. T1c cases may have been misclassified as pT categories because of unavailability of the clinical classification, other biases are conceivable. It may make a big difference whether a participant knows that he has been randomised to a control group and is therefore not offered screening. In four of the participating countries (Belgium, the Netherlands, Spain and Switzerland) due to legal regulations upfront informed consent prior to randomisation had to be applied. Besides the randomisation procedure, obviously different levels of awareness of risks and benefits of testing in the different countries could influence the proportion of PSA use and detection of T1c cancers in each of the participating regions. The total numbers of prostate cancers detected in the control arm and the number and proportion of T1c cases are indicated in Table 2. One of the French centers does not differentiate the T1 group and has therefore been excluded from the table. The incompleteness of data which varies between 3.5% and 55% between the centers may also influence the identification of T1c cases. Belgium and Italy have the lowest rates of T1c in the control group. The fact that in Fig. 1 these are the two countries in which prostate cancer mortality does not show a decrease, may be coincidental but, on the basis of the information presented above, is more likely to be related to the lower opportunistic use of PSA testing.

Our data seem to indicate that there are indeed differences in attitude towards early detection per country. The reasons are unclear just as the reasons for differences in incidence and mortality. Obviously, lower rates of screening in certain areas will lead to lower detection rates and also to lower effects of screening in terms of lowering prostate cancer mortality. Such differences have not been analysed and reported in[14] and are unavailable at present.

4. Conclusions

The present report attempts to identify different patterns of decision taking in relation to opportunistic screening in the ERSPC participating countries by considering the differences in incidence and mortality, by comparing mortality trends over time and by evaluating the levels of T1c screen detected cases in the control groups. Similar mortality trends in countries with high and low rates of T1c disease are suggestive for an effect of differences in the use of screening tests on screening outcomes. It has been pointed out above that changes in treatment and life style are likely to contribute to changes in prostate cancer mortality.

Our data furthermore suggest that if a PSA cut-off level is used the probability of finding prostate cancer above that level is not influenced by the underlying prevalence in a given country. This would obviously change if not a PSA cut-off level but, for example, an age cut-off would be chosen as a biopsy indicator. Other factors such as age, screen interval, findings at rectal examination and biopsy technique may influence the outcomes of screening tests. The downsides of screening so far have insufficiently been described. The methodological approach, which will be utilised in calculating quality of life adjusted life years, has been described in.[20] In the meantime, the message to all men in countries with different epidemiological backgrounds can be considered to be the same: if you have an elevated PSA, the chance of finding prostate cancer will depend on that PSA level and not on the underlying prevalence in your country.

Conflict of interest statement

None declared.

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