Prostate Cancer Mortality Reduction by Prostate-Specific Antigen–Based Screening Adjusted for Nonattendance and Contamination in the European Randomised Study of Screening for Prostate Cancer (ERSPC)


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Abstract

Background: Prostate-specific antigen (PSA) based screening for prostate cancer (PCa) has been shown to reduce prostate specific mortality by 20% in an intention to screen (ITS) analysis in a randomised trial (European Randomised Study of Screening for Prostate Cancer [ERSPC]). This effect may be diluted by nonattendance in men randomised to the screening arm and contamination in men randomised to the control arm.

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Objective: To assess the magnitude of the PCA-specific mortality reduction after adjustment for nonattendance and contamination.

Design, setting, and participants: We analysed the occurrence of PCA deaths during an average follow-up of 9 yr in 162,243 men 55–69 yr of age randomised in seven participating centres of the ERSPC. Centres were also grouped according to the type of randomisation (ie, before or after informed written consent).

Intervention: Nonattendance was defined as nonattending the initial screening round in ERSPC. The estimate of contamination was based on PSA use in controls in ERSPC Rotterdam.

Measurements: Relative risks (RRs) with 95% confidence intervals (CIs) were compared between an ITS analysis and analyses adjusting for nonattendance and contamination using a statistical method developed for this purpose.

Results and limitations: In the ITS analysis, the RR of PCA death in men allocated to the intervention arm relative to the control arm was 0.80 (95% CI, 0.68–0.96). Adjustment for nonattendance resulted in a RR of 0.73 (95% CI, 0.58–0.93), and additional adjustment for contamination using two different estimates led to estimated reductions of 0.69 (95% CI, 0.51–0.92) to 0.71 (95% CI, 0.55–0.93), respectively. Contamination data were obtained through extrapolation of single-centre data. No heterogeneity was found between the groups of centres.

Conclusions: PSA screening reduces the risk of dying of PCA by up to 31% in men actually screened. This benefit should be weighed against a degree of overdiagnosis and overtreatment inherent in PCA screening.

1. Introduction

Recently the European Randomised Study of Screening for Prostate Cancer (ERSPC) reported a 20% prostate cancer (PCa) mortality reduction in men randomised to screening using an intention-to-screen (ITS) analysis [1]. This type of analysis provides an estimate of the effectiveness of the screening intervention at the population level. This estimate is influenced by two types of noncompliance: nonattendance in men who are randomised to the intervention arm and contamination (ie, the use of prostate-specific antigen [PSA] testing in men randomised to the control arm). To estimate the efficacy of organised PSA testing in a man actually screened, correction for nonattendance and for contamination is necessary. Cuzick et al [2] have described a method that makes such corrections and adjusts for the possibility that non compliers and contaminators may differ in their underlying risk of PCA death. This method was previously applied to breast cancer screening trials [3]. A correction for noncompliance alone within the ERSPC trial was also reported in Schröder et al [1] and resulted in a 27% PCa mortality reduction in men actually screened.

Within the Rotterdam section of ERSPC, PSA usage in the control arm was determined by linkage to the central laboratory of the general practitioners (GPs) and the use of questionnaires (M. Kerkoff et al, unpublished data, 2009) [4,5]. This allowed the identification of asymptomatic and symptomatic PSA use (ie, the request of a PSA test to screen for PCa as opposed to clinical indications). These data, together with the readily available data on noncompliance, were used to assess the effect of PSA-based screening on the occurrence of metastatic PCa. The effect of screening in those who were actually screened was approximately 28% greater than the effect estimated without taking account of contamination and noncompliance [14]; relative risks [RRs] of metastatic cancer without and with adjustments were 0.75 and 0.64, respectively.

Detailed data on PSA use in the control arm were not available in the other centres of the ERSPC, so extrapolation from the Rotterdam data was necessary. This current report has applied two different approaches to estimate the rate of contamination in an analysis correcting for both noncompliance and contamination within the ERSPC cohort as described in Schröder et al [1]. The end point used in these analyses is PCa-specific mortality.

2. Materials and methods

Our study cohort and protocol is described in detail in Schröder et al [1]. In the core age group (55–69 yr at time of randomisation), 72,890 men were randomised to the screening arm and 89,353 men to the control arm. Randomisation started in 1991, and follow-up for the current analysis ended December 31, 2006.

Three of the seven centres of ERSPC randomised men before obtaining written informed consent (Finland, Sweden, and Italy). In this setting, men randomised to the control arm of the trial remain uninformed of their participation, and men randomised to the screening arm of the trial are asked for consent at time of invitation. The remaining four centres (The Netherlands, Belgium, Switzerland, and Spain) were legally obliged to obtain written informed consent before randomisation. The differences in the randomisation procedure can affect both nonattendance and contamination rates. Attendance in centres with preconsent randomisation ranged from 61.8% to 68.3%, compared with 88.1–100.0% in those centres with postconsent randomisation. However,
the rate of contamination is likely to be higher in centres with postconsent randomisation because men have agreed to take part but are aware of screening offered within the trial.

Effects of both nonattendance and contamination on PCa mortality reduction are studied in the ERSPC as a whole (including seven centres) and separately in those centres with (YesConsent) and without (NoConsent) written informed consent before randomisation.

2.1. Nonattendance in the screening arm

Nonattendance is defined as failure to attend the initial screening round in men randomised to the intervention arm. These data were available for all seven centres in the study.

2.2. Contamination in the control arm

2.2.1. Extrapolation of prostate-specific antigen use

Prerandomisation written informed consent from all participants included permission to retrieve clinical data, which enabled linkage of the ERSPC study database to that of the general laboratory of the GPs in the Rotterdam region, which covered 77.7% of all men randomised to the control arm [5,6]. Data on PSA testing were available up to January 1, 2005. For the current analyses, PSA contamination is defined as having undergone at least one PSA test after randomisation to the control arm. In addition, linkage of PSA tests to the central pathology laboratory of the Netherlands made it possible to identify all subsequent prostate biopsies and their outcome. PSA testing can be carried out for clinical reasons and for screening purposes. In an additional survey, the indications have been identified and classified as PSA use for clinical reasons (symptomatic testing) and PSA use for screening purposes (true contamination) [4,5]. These data were first extrapolated to all men in the Rotterdam region and subsequently to men randomised to the control arm of the entire ERSPC study cohort. In addition, the clinical stage of the PCa detected both in men who had a clinically indicated PSA test and men who had a PSA test for screening purposes was determined.

2.2.2. Extrapolation of prostate cancer cases detected through prostate-specific antigen contamination according to T stage at time of detection

As mentioned earlier, within the Rotterdam centre, the number, T stage, and related PCa deaths detected as a result of a PSA test for screening purposes were determined. In addition, in the Rotterdam cohort the total number of PCa in the control arm and their T-stage distribution is known. This allows the estimation for each T stage of the proportion of PCa, which are identified as detected by the purpose to screen for PCa (true contamination). This proportion of PCa cases and the related number of PCa deaths per T stage in ERSPC Rotterdam were used to calculate the number of PCa cases and deaths using the T-stage distribution and related PCa deaths in the control arm of ERSPC as a whole.

2.3. Statistical analyses

The mortality reduction in both the ITS analysis and the adjusted analyses were calculated as RRs. For the adjustment for noncompliance and contamination, the method of Cuzick et al [2], displayed in Fig. 1, was applied. Three analytic methods for the adjustments have been described previously, including a binary analysis; a Poisson analysis taking into account the time of noncompliance, contamination, and the event (PCa death); and a semiparametric Cox proportional hazards model assuming that contamination and noncompliance occurred at randomisation. Here we focus on the binary analysis because all three methods when applied in a similar setting gave very similar results (M. Kerkof et al, unpublished data, 2009).

An exploratory analysis of heterogeneity between the different definitions of contamination and the two subcohorts, YesConsent and NoConsent, was carried out and is visualised as a forest plot.

3. Results

3.1. Intention-to-screen analysis of the European Randomised Study of Screening for Prostate Cancer

As reported earlier [1], during a median follow-up of 9 yr the cumulative incidence of PCa was 8.2% in the screening group (5990 PCa cases in 72 890 men) and 4.8% in the control group (4307 PCa cases in 89 353 men). A total of 214 PCa-specific deaths and 326 PCa-specific deaths occurred in the screening group and control group, respectively. The ITS analysis (ie, no correction for nonattendance and contamination) with the binary analysis resulted in a RR for death from PCa in the screening group as compared with the control group of 0.80 (95% confidence interval [CI], 0.68–0.96; p = 0.013).

3.2. Nonattendance

A total of 55 480 men (76.1%) in the intervention arm attended the initial screening round. For the subcohorts NoConsent and YesConsent, these numbers, respectively, were 45 136 and 27 754 men randomised to the screening arm; 29 406 (65.2%) and 26 074 (94.0%) men attended the first screening. Table 1 displays the numbers of PCa deaths in attenders and nonattenders that occurred during the 9 yr of follow-up.

3.3. Contamination rate in the European Randomised Study of Screening for Prostate Cancer based on prostate-specific antigen use in ERSPC Rotterdam

In a total of 17 443 men, 55–69 yr of age, randomised to the control arm of ERSPC section Rotterdam, 5349 men had a PSA test after randomisation, 339 PCa cases were detected, and 27 men died of their disease (adapted to core age group and extrapolated towards 100% coverage from Roemeling et al [5] and Kerkhof et al [4]). A questionnaire survey in a random sample of 345 of men without PC showed that 50.2% of the PSA tests could be classified as asymptomatic PSA testing (true contaminators). Based on a complete assessment of the reasons for screening in all men with PC, we estimate that 39.16% (n = 133) of the 339 PCa cases and 29.6% (n = 8) of the 27 men who died of their disease arose in this group.

Fig. 2 shows the extrapolation of these ERSPC Rotterdam data to the entire study cohort of ERSPC that resulted in 13 579 men estimated to be contaminators, of which 40 men died from PCa. Similar data, applying similar contamination rates, for YesConsent and NoConsent centres were 4215 men with 12 PCa deaths and 9364 men with 28 PCa deaths, respectively.
3.4. Contamination in the European Randomised Study of Screening for Prostate Cancer based on T-stage distribution of the prostate cancer cases detected in true contaminators in ERSPC Rotterdam

Table 2 shows the T stages and the corresponding PCA deaths of the control arm of ERSPC Rotterdam in both the clinically detected and true contaminating PCA cases. Of the 5349 men who were documented to be PSA tested in the control group, 2648 were identified as ‘true contaminators’ in whom 133 PCA cases (a ratio of 19.9:1) and 8 PCA deaths were identified. These data were related to the total number of PCA cases detected in the control arm of ERSPC Rotterdam (N = 903 with 105 PCA deaths) resulting in 23.9% of the T1C

- The method requires the identification of the proportion of non-compliers and the associated endpoint, i.e., prostate cancer mortality, in the screening group (Step 1).
- Similar proportions are assumed to exist in the control arm - the so-called ‘potential’ non-compliers (Step 2).
- To adjust for contamination, we assume that the contaminators and the associated endpoint (Step 3) in the control arm
- exist in the same proportions in the compliers in the intervention arm (Step 4).
- The two hypothetical groups who accept the allocated procedure are then compared. This will result in an estimate of the mortality reduction associated with screening in a man who accepted his random allocation compared to a similar man who was not screened.

Fig. 1 – Flow chart of the Cuzick analysis (numbers are fictitious).
cases, 11.2% of the T2 cases, 12.0% of the T3 cases, and 9% of the T4 cases that were assumed to be detected as a result of true contamination. The corresponding percentages of PCa deaths were 12.5%, 0%, 12.2%, and 5.9%, respectively. In the total study cohort of ERSPC, 4307 PC cases were detected with 326 PC deaths. Applying the percentages just cited to their T-stage distribution and related PC deaths, resulted in 554 PCa cases in 11,025 true contaminators by using the 19.9 to 1 ratio (e.g., 5.03% positivity rate) and 22 PCa deaths for the ERSPC total. Corresponding numbers for the YesConsent and NoConsent subcohorts were 3177 men, 168 PCa cases, 7 PCa deaths, and 7431 men, 393 PCa cases and 16 PCa deaths, respectively.

3.5. **Prostate cancer mortality analyses correcting for nonattendance and contamination**

Fig. 3 shows the correction for nonattendance and contamination (based on the extrapolation of asymptomatic PSA testing) according to the method of Cuzick et al for the entire ERSPC study cohort. Table 3 shows the results of the adjustment for noncompliance and for both noncompliance and contamination.

Adjustment only for nonattendance resulted in a relative increase of the estimated mortality reduction of 35% (RR: 0.73; 95% CI, 0.58–0.93). Adjusting for both noncompliance and contamination increased the relative mortality reduction by 50–55% depending on the definition of contamination used in the calculations (RR: 0.69; 95% CI, 0.51–0.92; and RR: 0.71; 95% CI, 0.55–0.93).

The effect of screening on PCa-specific mortality in the different subgroups with and without adjustment for nonattendance and contamination points towards a mortality reduction in favour of screening. There was no statistically significant heterogeneity between the subcohorts (Fig. 4).

4. **Discussion**

PSA-based PCa screening in men 55–69 yr of age was shown to lower the disease-specific mortality by 20% after an average follow-up of 9 yr [1]. This provides an estimate of the effect of PSA-based screening provided that the screening algorithm applied is identical to that of the screening trial described in Schröder et al [1] and nonattendance and contamination are similar to that

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**Table 1 – Nonattendance in those randomised to screening and related number of prostate cancer (PCa) deaths in the European Randomised Study of Screening for Prostate Cancer (ERSPC) and the NoConsent* and YesConsent subcohorts**

<table>
<thead>
<tr>
<th>Noncompliance</th>
<th>A: Men randomised to screening arm, n</th>
<th>B: PCa deaths, n</th>
<th>C: Attenders to initial screening round, n (% of A)</th>
<th>D: PCa deaths in attenders, n (% of B; % of C)</th>
<th>E: Nonattenders to initial screening round, n (% of A)</th>
<th>F: PCa deaths in nonattenders, n (% of B; % of E)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total ERSPC cohort</td>
<td>72,890</td>
<td>214</td>
<td>55,480 (76.1)</td>
<td>146 (68.2; 0.26)</td>
<td>17,410 (23.9)</td>
<td>68 (31.8; 0.39)</td>
</tr>
<tr>
<td>Cohort NoConsent</td>
<td>45,136</td>
<td>137</td>
<td>29,406 (65.2)</td>
<td>74 (54.0; 0.25)</td>
<td>15,730 (34.8)</td>
<td>63 (46.0; 0.40)</td>
</tr>
<tr>
<td>Cohort YesConsent</td>
<td>27,754</td>
<td>77</td>
<td>26,074 (94.0)</td>
<td>73 (94.8; 0.28)</td>
<td>16,80 (6.0)</td>
<td>5 (6.5; 0.30)</td>
</tr>
</tbody>
</table>

* NoConsent: Centres with randomisation before consent (n = 3).
  | YesConsent: Centres with consent before randomisation (n = 4).

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**Fig. 2 – Extrapolation of European Randomised Study of Screening for Prostate Cancer (ERSPC) Rotterdam data on contamination (defined as prostate-specific antigen testing in control arm after randomisation).**
observed here. After correction for both nonattendance and contamination, the mortality reduction increased by 50%, giving a PCa mortality reduction of 31–33% attributable to attending screening. This estimate represents the reduction of the risk of dying from PCa comparing men who accept an invitation to undergo PSA-based screening as carried out in ERSPC as compared with men who were not tested.

The adjustment for nonattendance alone resulted in a mortality reduction of 27%, an increase of more than a third (from 20%) as compared with the result of the ITS analysis. As expected, adjustment for nonattendance resulted in a larger reduction of the RR (from 0.82 to 0.72) in the NoConsent centres compared with the YesConsent centres (from 0.78 to 0.77) because compliance in the former was lower. The adjustment for both noncompliance and contamination based on extrapolation of the ERSPC Rotterdam data resulted in a slightly larger increase of the effect of screening (RR: 0.69 or 0.71, depending on the definition of contamination), indicating that the effect of the different adjustments for contamination is comparable and are minor. The results of adjustment for nonattendance and contamination in the two groups of centres varied between a RR of 0.64 and a RR of 0.75 and were not significantly different between the two subcohorts.

This reduction in risk of PC death needs to be balanced against the risk of the detection of a potentially indolent PCa, which often leads to overtreatment [7]. This was demonstrated in Schröder et al [1] where after 9 yr of

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Table 2 – Clinical stage and prostate cancer (PCa) deaths in PCa cases detected in men with a symptomatic prostate-specific antigen (PSA) test and men with an asymptomatic PSA test (true contaminators)

<table>
<thead>
<tr>
<th>Clinical stage</th>
<th>n</th>
<th>n</th>
<th>n</th>
<th>n</th>
<th>n</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1A/T1B</td>
<td>72</td>
<td>1</td>
<td>19</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>T1C</td>
<td>322</td>
<td>16</td>
<td>70</td>
<td>3</td>
<td>77 (23.9)</td>
<td>2 (12.5)</td>
</tr>
<tr>
<td>T2</td>
<td>268</td>
<td>29</td>
<td>67</td>
<td>9</td>
<td>30 (11.2)</td>
<td>–</td>
</tr>
<tr>
<td>T3</td>
<td>184</td>
<td>41</td>
<td>39</td>
<td>6</td>
<td>22 (12.0)</td>
<td>5 (12.2)</td>
</tr>
<tr>
<td>T4</td>
<td>33</td>
<td>17</td>
<td>5</td>
<td>1</td>
<td>3 (5.9)</td>
<td>1 (5.9)</td>
</tr>
<tr>
<td>Missing</td>
<td>24</td>
<td>1</td>
<td>6</td>
<td>–</td>
<td>1 (4.0)</td>
<td>–</td>
</tr>
<tr>
<td>Total</td>
<td>903</td>
<td>105</td>
<td>206</td>
<td>19</td>
<td>133</td>
<td>8</td>
</tr>
</tbody>
</table>

ERSPC = European Randomised Study of Screening for Prostate Cancer.
follow-up, 48 cancers needed to be diagnosed and treated for every prevented death from PCa.

Our study may be limited by the fact that the detection of PCa as a result of PSA-driven screening in the control arm is not exclusively initiated by a PSA test requested by a GP. The GP laboratory-based linkage could thus underestimate the true contamination rate. However, these linkages are more realistic estimates as compared with questionnaire-based data that tend to overestimate the rate of PSA testing considerably [8]. In addition, the data on contamination are extrapolated from one single ERSPC centre, which may result in an under- or overestimation of the contamination rate in the total ERSPC study cohort. The level of PSA testing in men randomised to the control arm in the seven ERSPC centres indeed increased differently during the years after initiation of the screening study but was quite similar during the early years, the years having the largest effect on PCa detection and mortality [8].

Next to this, nonattendance in the initial screen was assumed to be identical to nonattendance during the whole trial. This implies that men attending repeat screening(s) (but not the first) were assumed to be nonattenders, and in contrast, men attending first screening, but not the subsequent, are considered attenders. This misclassification results in an underestimate of the real impact of regular screening. The method for adjusting for nonattendance and contamination necessitates certain assumptions [9]. One of these, the assumption that asymptomatic PSA testing in

<table>
<thead>
<tr>
<th>Effect measurement</th>
<th>RR (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intention-to-treat analysis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ERSPC study cohort</td>
<td>0.80 (0.68–0.96)</td>
<td>0.013</td>
</tr>
<tr>
<td>NoConsent* cohort</td>
<td>0.82 (0.67–1.02)</td>
<td>–</td>
</tr>
<tr>
<td>YesConsent</td>
<td>cohort</td>
<td>0.78 (0.58–1.05)</td>
</tr>
<tr>
<td>Adjusted for nonattendance</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ERSPC study cohort</td>
<td>0.73 (0.58–0.93)</td>
<td>0.010</td>
</tr>
<tr>
<td>NoConsent* cohort</td>
<td>0.72 (0.51–1.01)</td>
<td>–</td>
</tr>
<tr>
<td>YesConsent</td>
<td>cohort</td>
<td>0.77 (0.56–1.05)</td>
</tr>
<tr>
<td>Adjusted for nonattendance and contamination based on PSA use</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ERSPC study cohort</td>
<td>0.69 (0.51–0.92)</td>
<td>0.013</td>
</tr>
<tr>
<td>NoConsent* cohort</td>
<td>0.64 (0.40–1.03)</td>
<td>–</td>
</tr>
<tr>
<td>YesConsent</td>
<td>cohort</td>
<td>0.73 (0.50–1.07)</td>
</tr>
<tr>
<td>Adjusted for nonattendance and contamination based on T-stage distribution in true contaminators</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ERSPC study cohort</td>
<td>0.71 (0.55–0.93)</td>
<td>0.011</td>
</tr>
<tr>
<td>NoConsent* cohort</td>
<td>0.68 (0.45–1.02)</td>
<td>–</td>
</tr>
<tr>
<td>YesConsent</td>
<td>cohort</td>
<td>0.75 (0.53–1.06)</td>
</tr>
</tbody>
</table>

* NoConsent: Centres with randomisation before consent (n = 3).
| YesConsent: Centres with consent before randomisation (n = 4).

The analyses are all performed with the binary method. In all scenarios, nonattendance is defined as not attending the first screening round, and contamination is based on data on PSA use and T-stage distribution in true contaminators in ERSPC Rotterdam.

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**Table 3 – Effect of screening on prostate cancer mortality in the intention-to-screen analysis and the analyses adjusted for nonattendance and contamination**

**Fig. 4 – Forest plot of the unadjusted and adjusted relative risks of prostate cancer mortality.**
men in the control arm will have exactly the same effect as protocol-based screening in the screening arm, may not be true. This was shown in a previously conducted study by Otto et al [6]. In this study effective contamination in the control arm, defined as a PSA ≥3.0 ng/ml followed by prostate biopsy, was 7–8%, whereas within the intervention arm of ERSPC this percentage is approximately 85%. Possibly for this reason the adjustment for contamination had a minor effect and may indicate a generally lower effectiveness of spontaneous testing.

A strength of our study is the large sample size, the quality of the data, the very detailed information on PSA use in ERSPC Rotterdam, and the fact that extrapolation of contamination in calculating adjusted PCa mortality reduction was done using two different approaches (direct extrapolation of PSA contamination in ERSPC Rotterdam and the use of the T-stage distribution and related PCa deaths in ERSPC as a whole; both gave very similar results).

5. Conclusions

PSA-based screening lowers the relative risk of dying of PCa in an ITT analysis by 20%. This effect among screened men is increased by a half to approximately 30% after adjusting for the diluting effect of nonattendance and contamination. A risk reduction for PCa mortality of 30% when attending a PSA-based screening programme should be balanced against the considerable risk of overdiagnosis and overtreatment inherent in PCa screening. Future research should focus on reducing the adverse effects of screening for PCa so that the benefits can be achieved with fewer men experiencing harm.

Author contributions: M.J. Roobol had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Acquisition of data: Roobol, Kerkhof, Moss.

Analysis and interpretation of data: Roobol, Kerkhof, Cuzick, Moss, Auvinen.

Drafting of the manuscript: Roobol.

Critical revision of the manuscript for important intellectual content: Roobol, Kerkhof, Schröder, Cuzick, Sasieni, Hakama, Stenman, Ciatto, Nelen, Kwiatkowski, Lujan, Liija, Zappa, Denis, Recker, Berenguer, Ruutu, Kugala, Bangma, Aus, Tammela, Villers, Rebillard, Moss, de Koning, Hugosson, Auvinen.

Statistical analysis: Roobol, Kerkhof, Cuzick, Sasieni.

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