Estimate of Opportunistic Prostate Specific Antigen Testing in the Finnish Randomized Study of Screening for Prostate Cancer

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Abbreviations and Acronyms

CA = control arm

ERSPC = European Randomized Study of Screening for Prostate Cancer

PCa = prostate cancer

PLCO = Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial

PSA = prostate specific antigen

SA = screening arm

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Purpose: Screening for prostate cancer remains controversial, although ERSPC (European Randomized Study of Screening for Prostate Cancer) showed a 21% relative reduction in prostate cancer mortality. The Finnish Randomized Study of Screening for Prostate Cancer, which is the largest component of ERSPC, demonstrated a statistically nonsignificant 16% mortality benefit in a separate analysis. The purpose of this study was to estimate the degree of contamination in the control arm of the Finnish trial.

Materials and Methods: Altogether 48,295 and 31,872 men were randomized to the control and screening arms, respectively. The screening period was 1996 to 2007. The extent of prostate specific antigen testing was analyzed retrospectively using laboratory databases. The incidence of T1c prostate cancer (impalpable prostate cancer detected by elevated prostate specific antigen) was determined from the national Finnish Cancer Registry.

Results: Approximately 1.4% of men had undergone prostate specific antigen testing 1 to 3 years before randomization. By the first 4, 8 and 12 years of followup 18.1%, 47.7% and 62.7% of men in the control arm had undergone prostate specific antigen testing at least once and in the screening arm the proportions were 69.8%, 81.1% and 85.2%, respectively. The cumulative incidence of T1c prostate cancer was 6.1% in the screening arm and 4.5% in the control arm (RR 1.21, 95% CI 1.13–1.30).

Conclusions: A large proportion of men in the control arm had undergone a prostate specific antigen test during the 15-year followup. Contamination is likely to dilute differences in prostate cancer mortality between the arms in the Finnish screening trial.

Key Words: prostatic neoplasms, prostate-specific antigen, mortality, mass screening, bias

Population based screening for PCa remains controversial despite the substantial 21% decrease in PCa mortality observed in ERSPC at 13 years of followup.[1] This beneficial mortality effect is counterbalanced by substantial over diagnosis and overtreatment of clinically insignificant PCa.[1,2] Also, quality of life effects and cost-effectiveness require further elucidation.[3,4]

The ERSPC trial involves 8 centers with some differences in the protocol

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in relation to PSA threshold, interval and recruitment method.[1] To our knowledge it is currently the only randomized trial that has shown a mortality benefit from population based screening.[5] The 3 largest centers of the ERSPC trial have reported mortality results separately. The Swedish center with 20,000 men who were 50 to 64 years old at randomization reported a substantial reduction in PCa mortality at 14 years (HR 0.56, 95% CI 0.39–0.82).[6] The Finnish center with 80,000 men who were 55 to 67 years old reported a modest, statistically nonsignificant reduction (HR 0.85, 95% CI 0.69–1.04).[7] Finally, the Dutch center with 35,000 men with a core age of 55 to 69 years reported a significant result (RR 0.68, 95% CI 0.53–0.89).[8]

Another large, randomized PCa screening trial, the PLCO trial in the United States, demonstrated a risk ratio of 1.09 (95% CI 0.87–1.36) for PCa mortality at 13 years of followup.[9] A major shortcoming in the PLCO trial is the substantial frequency of PSA testing before randomization, which was done in 44% of men in both arms and during followup in the control arm with 40% to 52% of controls screened each year.[10,11] A recent report showed that in fact as many as 90% of men in the CA underwent PSA testing before or during the trial.[12]

Contamination in a randomized trial means that nonorganized (ie opportunistic) intervention in the CA dilutes the observed effect of the intervention because the comparator is not the absence of screening but rather less common and less systematic screening. In other words as some men in the CA receive opportunistic PSA testing, the contrast in the procedures received is reduced and, thus, the relative difference (eg in mortality) is decreased.

The purpose of the current study was to estimate the frequency of contamination at the Finnish center using regional laboratory databases and the incidence of T1c PCa (impalpable cancer detected by abnormal PSA) as an indicator of the outcome of PSA testing to determine effective contamination.

MATERIALS AND METHODS

The Finnish Randomized Study of Screening for Prostate Cancer is the largest center of the ERSPC trial (http://www.isrctn.com/ISRCTN49127736). Men were identified from the population registry in 1996 to 1999. Each year a random sample of 8,000 men in the Helsinki or Tampere metropolitan area were randomized to the SA. The rest of the age group formed the CA. Men were 55 to 67 years old at study entry. Those in the CA were not contacted.

Men in the SA were invited to undergo serum PSA determination at a local clinic. They were re-invited 4 and 8 years later to subsequent PSA tests. Those men 71 years old or older were no longer invited. Men with a serum PSA 4.0 ng/ml or greater were referred for diagnostic evaluation, ie transrectal prostate biopsies. Men with PSA 3.0 to 3.99 ng/ml were referred for an additional test, ie digital rectal examination in 1996 to 1998 and the free-to-total PSA ratio with a cutoff of less than 16% in 1999 and thereafter. Men with an abnormal result were referred for biopsy. Those who had died or emigrated from the study area or Finland were identified from the population registry.

Information on all PCas were obtained from the Finnish Cancer Registry, which has 99% coverage of solid cancers.[13] Information on opportunistic PSA testing was retrospectively extracted from regional laboratory databases, including HUSLAB in Helsinki, and TamLab and Fimlab in Tampere. These databases have essentially complete coverage on tests administered in public health care, including primary health care, and central and university hospitals. Tests at private clinics were not available for this study. For reference in Finland in 2012 approximately 25% of primary health care contacts were provided by the private sector.[14]

In the SA the data on organized screens were appended to the opportunistic testing. Information on the intent of PSA testing was not available, ie whether the patient was symptomatic or asymptomatic at the time of the test.

Laboratory data from Helsinki covered a study period from January 1996 to July 2012 and data from Tampere covered January 1996 to December 2010. Followup regarding PSA testing ended at 1) the first PSA test (overall PSA testing analyses), 2) the first positive PSA test (positive PSA test analyses), 3) PCa diagnosis, 4) emigration, 5) death or 6) the common study closing date of July 31, 2012 in Helsinki and December 31, 2010 in Tampere, whichever was first. Data on the PCa incidence in all men were available through December 2014.

For screening and contamination tests a positive test was defined as total serum PSA 4.0 ng/ml or greater, or total serum PSA 3.0 to 3.99 and a free-to-total PSA ratio of less than 16%. The total number of PSA tests per person was recorded. Information on PSA testing before randomization was available on men randomized in 1997 (1 previous year—1996), in 1998 (2 previous years—1996 and 1997) and in 1999 (3 previous years—1996 through 1998).

Incidence rate ratios of the first PSA test, the first positive PSA test and the T1c PCa diagnosis were estimated using Poisson regression with person-years as the offset. Center (Helsinki or Tampere) and age at event served as covariates. The Kaplan-Meier failure estimates method was utilized to graphically present the cumulative incidence. STATA®, version 14 was used for all analyses, 95% CIs are shown and all statistical tests were 2-sided.

The study protocol was reviewed by the Helsinki and Tampere University Hospital Ethics committees. Permission to use cancer registry and laboratory data was obtained from STAKES (Research and Development Centre for Welfare and Health), currently named the National Institute for Health and Welfare.

RESULTS

There were 31,872 men in the SA and 48,295 in the CA (fig. 1). Median followup was 15.6 years in both

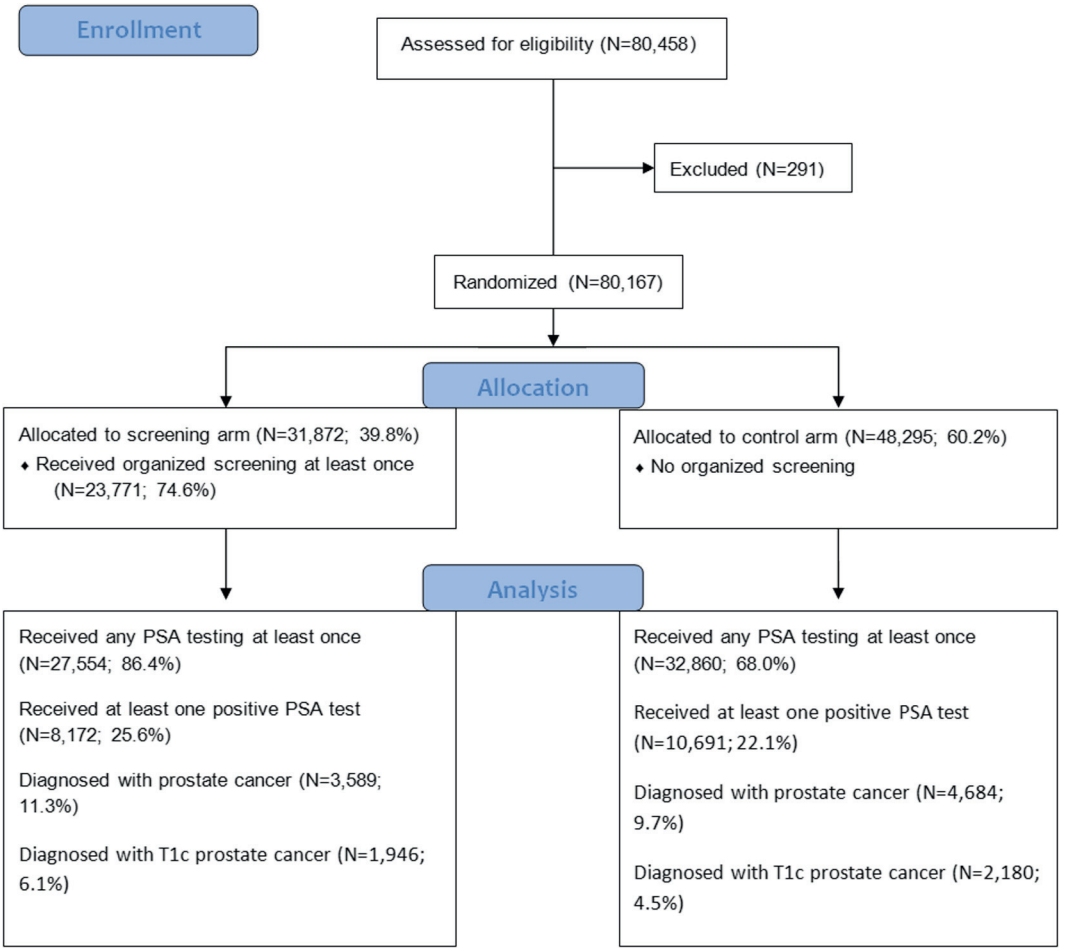

Figure 1. Finnish Randomized Study of Screening for Prostate Cancer flow chart

arms for analyses of the PCa incidence with a maximum of 18.6 years. Median time to the first PSA test in all men was 0.8 years in the SA and 6.9 years in the CA. Median followup in those not tested was 11.8 and 14.0 years in the SA and the CA, respectively. Median age at the first PSA test was 61.3 years in the SA and 66.1 years in the CA.

Prior to randomization 0.7% of men in both arms had undergone a PSA test, ie they were prescreened. Of men with the longest pretrial followup of 3 years before randomization in 1999, 1.7% (137 of 7,957) were prescreened in the SA and 2.1% (258 of 12,441) were prescreened in the CA. By 4 years after randomization 18.1% of men in the CA had been tested at least once (table 1). By 8 years of followup the cumulative incidence of PSA testing was 47.7% in the CA and by 12 years it had reached 62.7%. During the active screening period of 1996 to 2007 in the SA 28,073 men (58.1%) in the CA had been tested at least once. By the end of followup 32,860 men (68.0%) in the CA had been tested (fig. 2).

Men in the CA underwent a mean of 2.9 PSA tests (median 2.0, IQR 0–4). In the SA a mean of 4.3 PSA tests per person were done (median 3.0, IQR 1–6).

Of men in the CA 10,691 (22.1%) tested positive at least once whereas in the SA 8,172 (25.6%) tested positive (table 1 and fig. 3). The RR of the incidence of a positive PSA test in the SA vs the CA was 1.20 (95% CI 1.16–1.23).

When analyzed by calendar year, during the first 4 years of the trial (1996 to 1999) only 7.8% of men in the CA underwent opportunistic testing during the first screening round. However, nonorganized PSA testing became common during the second screening round (2000 to 2003). During this period 37.1% of men in the CA were tested at least once. In the third round (2004 to 2007) more than half of the men in the CA underwent PSA testing (table 2).

Each year the proportion of positive PSA tests of all tests was clearly higher in the CA than in the SA. However, after organized screening ceased in 2008, the proportion of positive tests was similar in the 2 arms (table 2).

Table 1. *Incidence of PSA testing, positive tests, T1c cancers by screening interval and followup since randomization*

Incidence	No. Pts	No. at Least 1 PSA Test (%)	No. Pos Test (%)*	No. T1c (%†)
		Screening arm		
Per screening interval:				
1996—1999	31,872	26,732 (83.9)	1,284 (4.8‡)	297 (0.9)
2000—2003	30,062	24,941 (83.0)	3,751 (15.0‡)	557 (1.9)
2004—2007	27,130	21,016 (77.5)	5,178 (24.6‡)	690 (2.5)
Cumulative followup (yrs):				
Less than 4	31,872	22,242 (69.8)	2,475 (7.8†)	383 (1.2)
4—Less than 8	—	25,858 (81.1)	5,078 (15.9†)	1,001 (3.1)
8—Less than 12	—	27,155 (85.2)	7,224 (22.7†)	1,651 (5.2)
12 or Greater	—	27,554 (86.4)	8,172 (25.6†)	1,948 (6.1)
		Control arm		
Per screening interval:				
1996—1999	48,295	3,779 (7.8)	913 (24.2‡)	120 (0.3)
2000—2003	46,173	17,122 (37.1)	4,904 (28.6‡)	427 (0.9)
2004—2007	42,161	21,935 (52.0)	8,652 (39.4‡)	769 (1.8)
Cumulative followup (yrs):				
Less than 4	48,295	8,749 (18.1)	1,793 (3.7†)	262 (0.5)
4—Less than 8	—	23,051 (47.7)	5,494 (11.4†)	856 (1.8)
8—Less than 12	—	30,265 (62.7)	8,843 (18.3†)	1,560 (3.2)
12 or Greater	—	32,860 (68.0)	10,691 (22.1†)	2,180 (4.5)

* Total serum PSA 4.0 ng/ml or greater, or 3.0 to 3.99 ng/ml and free-to-total PSA ratio less than 16%.
† Divided by number of tests.
‡ Divided by number of patients.

Altogether 4,684 PCa cases (cumulative incidence 9.7%) were detected in the CA and 3,589 were found in the SA (11.3%, RR 1.12, 95% CI 1.07−1.18). Of all PCas 2,180 (4.5%) and 1,946 (6.1%) were classified as T1c in the CA and the SA, respectively (T1c incidence RR 1.21, 95% CI 1.13−1.30, fig. 4).

DISCUSSION

Our findings demonstrate considerable frequency of nonorganized PSA testing (ie contamination) in the CA of the Finnish Randomized Study of Screening for Prostate Cancer. However, pretrial PSA testing was rare in both arms at 1.4%. Contamination remained at a moderate level in the first 4 years of the trial since fewer than 20% of men in the CA were tested compared to 70% in the SA. Median time to the first PSA test was 0.8 years in the SA vs 6.9 years in the CA. However, 50% of men in the CA had been tested at least once by year 8. This is also reflected in the high 4.5% cumulative incidence of T1c cancers (impalpable cancers detected by abnormal PSA) in the CA, although the T1c incidence was 1.2-fold in the SA.

The effect of screening can be diminished if the trial population is screened prior to baseline as the risk of disease and mortality from it is lower in a previously screened population. In the PLCO trial the prevalence of prerandomization PSA testing was estimated to be as high as 45% in both arms.[10] The Swedish branch of ERSPC reported that approximately 3% of men had been tested for PSA

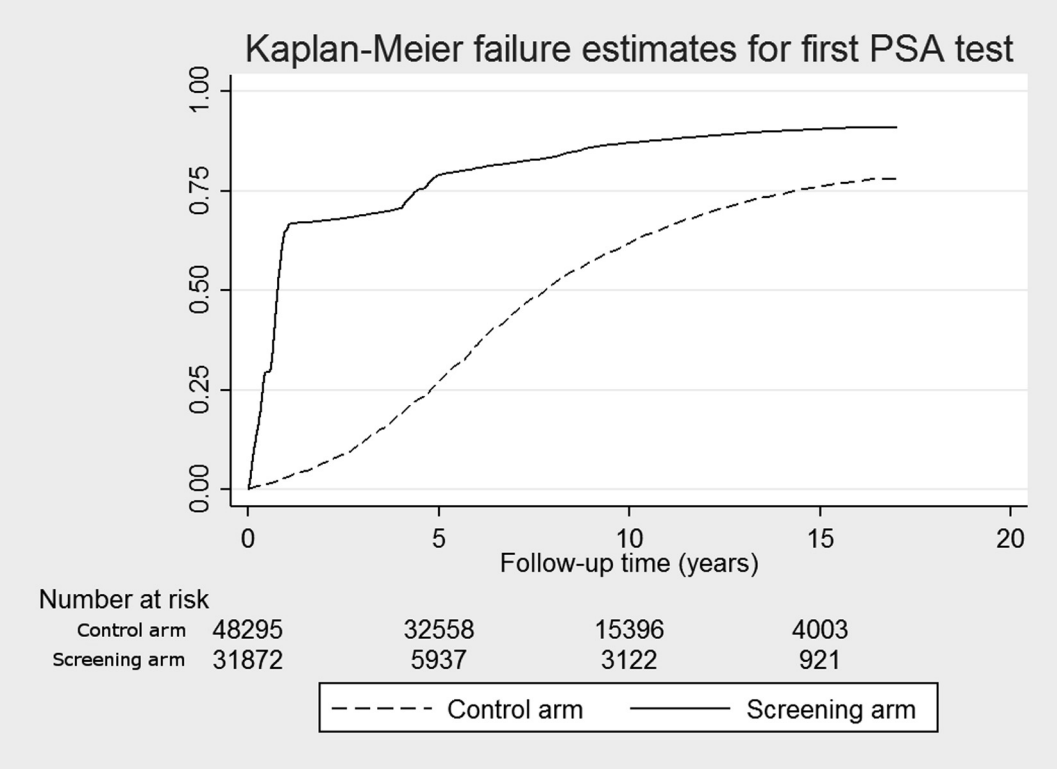

Figure 2. Incidence of PSA testing in control and screening arms

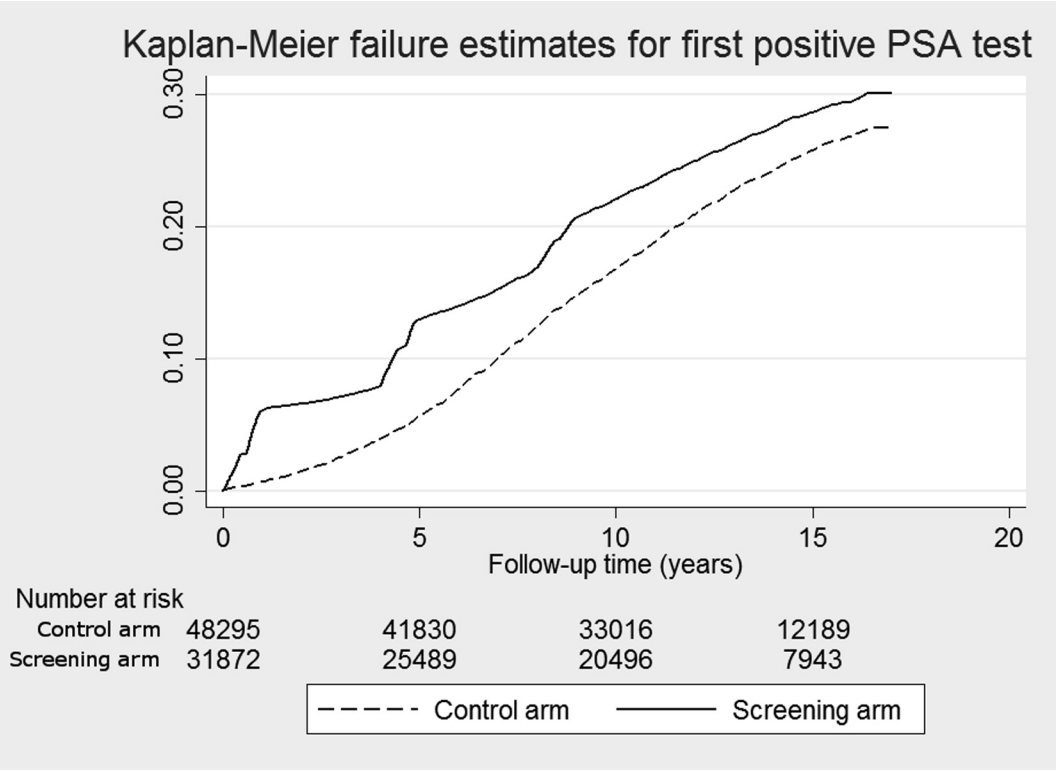

Figure 3. Incidence of positive PSA test in control and screening arms

before the trial.[6] The Dutch section of ERSPC estimated that approximately 13% of men had been screened with PSA before trial entry.[15] Our results show that fewer than 2% of men in the Finnish trial had been prescreened. However, the true proportion is likely to be higher because we only had information on the previous 1 to 3 years before screening. Also, in a study based on questionnaire data in 1996 to 1999 approximately 10% of the respondents reported previous PSA testing.[16]

In an ideal randomized trial all men in the SA but none in the CA were screened, which would yield a perfect estimate of the screening effect.[17] In reality some men in the SA are noncompliers (ie do not participate) and some in the CA undergo nonorganized screening. Both situations are violations

Table 2. *PSA testing, positive tests and T1c cancers by calendar year and trial arm*

	Screening Arm				Control Arm			
Yr	No. Pts	No. at Least 1 PSA Test (%)	No. Pos Test (%)*	No. T1c (%)	No. Pts	No. at Least 1 PSA Test (%)	No. Pos Test (%)*	No. T1c (%)
1996	7,960	5,955 (74.8)	85 (1.4)	28 (0.35)	12,342	241 (2.0)	45 (18.7)	3 (0.02)
1997	15,761	7,550 (47.9)	313 (4.1)	74 (0.47)	23,187	471 (2.0)	126 (26.8)	14 (0.06)
1998	23,347	7,266 (31.1)	383 (5.3)	87 (0.37)	35,276	1,049 (3.0)	227 (21.6)	38 (0.11)
1999	30,766	7,873 (25.6)	503 (6.4)	108 (0.35)	47,067	2,539 (5.4)	515 (20.3)	65 (0.14)
2000	30,065	7,602 (25.3)	736 (9.7)	118 (0.39)	46,173	3,492 (7.6)	708 (20.3)	83 (0.18)
2001	29,380	8,657 (29.5)	899 (10.4)	114 (0.39)	45,293	5,994 (13.2)	1,071 (17.9)	79 (0.17)
2002	28,707	9,515 (33.1)	1,009 (10.6)	178 (0.62)	44,346	7,576 (17.1)	1,348 (17.8)	121 (0.27)
2003	27,905	10,254 (36.7)	1,107 (10.8)	147 (0.53)	43,270	9,861 (22.8)	1,777 (18.0)	144 (0.33)
2004	27,130	9,124 (33.6)	1,278 (14.0)	192 (0.71)	42,161	10,676 (25.3)	2,177 (20.4)	194 (0.46)
2005	26,300	9,405 (35.8)	1,336 (14.2)	198 (0.75)	40,941	10,859 (26.5)	2,222 (20.5)	242 (0.59)
2006	25,488	9,602 (37.7)	1,323 (13.8)	169 (0.66)	39,625	11,011 (27.8)	2,147 (19.5)	182 (0.46)
2007	24,732	9,146 (37.0)	1,241 (13.6)	131 (0.53)	38,427	9,616 (25.0)	2,106 (21.9)	151 (0.39)
2008	23,915	6,281 (26.3)	1,304 (20.8)	83 (0.35)	37,251	10,260 (27.5)	2,237 (21.8)	150 (0.40)
2009	23,201	6,436 (27.7)	1,399 (21.7)	83 (0.36)	36,143	10,542 (29.2)	2,434 (23.1)	173 (0.48)
2010	22,373	6,411 (28.7)	1,345 (21.0)	70 (0.31)	34,865	10,491 (30.1)	2,317 (22.1)	159 (0.46)
2011	21,613	4,531 (21.0)	1,007 (22.2)	52 (0.24)	33,540	7,283 (21.7)	1,629 (22.4)	152 (0.45)
2012	20,763	2,623 (12.6)	596 (22.7)	59 (0.28)	32,244	4,288 (13.3)	989 (23.1)	136 (0.42)

* Total serum PSA 4.0 ng/ml or greater, or total serum PSA 3.0 to 3.99 ng/ml and free-to-total PSA ratio less than 16% with incidence calculated by dividing by number of PSA tests.

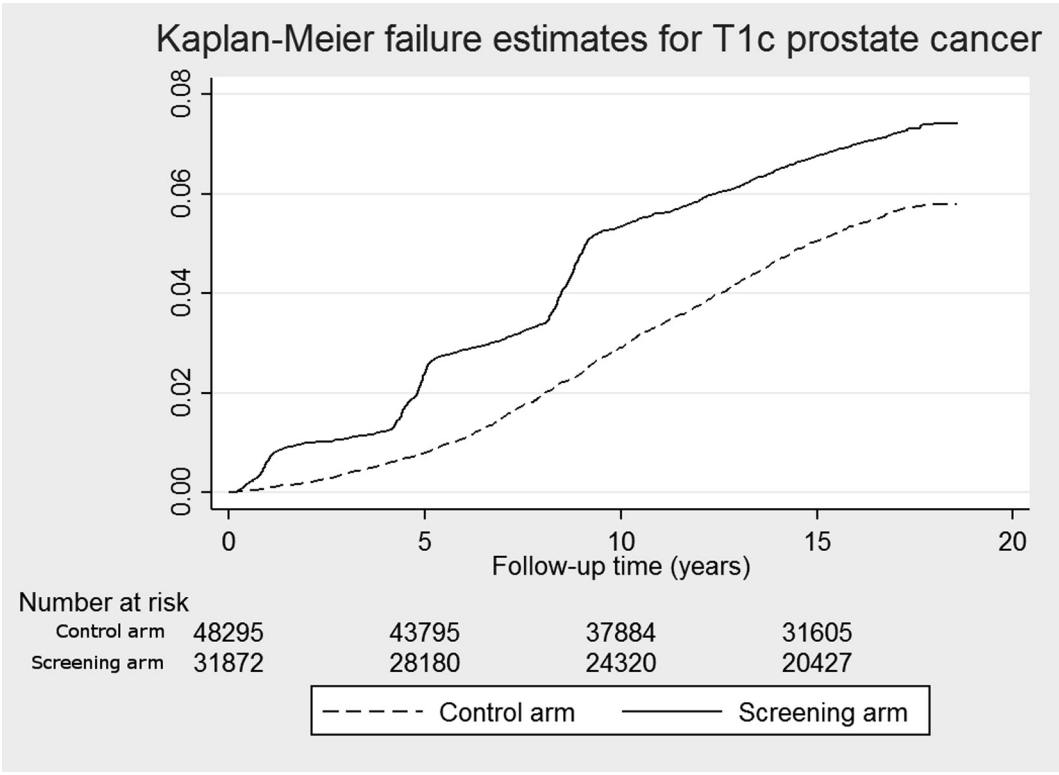

Figure 4. Incidence of T1c prostate cancer in control and screening arms

of the allocation and dilute the screening effect. They can be controlled for with a counterfactual method that builds an estimate of the screening effect by extrapolation.[18] Such a method has been used in the ERSPC trial.[19,20] Unfortunately such methods cannot fully compensate for the intent to treat principle, which should always be the basis of any randomized trial.

As reported in the PLCO trial, in addition to the high prevalence of PSA testing before randomization, 52% of men in the CA were tested at least once compared to 78% in the SA.[11] A recent report showed that as many as 90% of men in the CA were tested before or during the trial.[12]

The Dutch section of ERSPC reported that 40% of men in the CA were tested with PSA at least once during the 13 years of followup.[21] The Italian center estimated that approximately 30% of participants had been tested for PSA during the previous year in 1997 and 2001 based on interviews.[16] To our knowledge the Swedish section of ERSPC has not published its contamination results to date.

When ERSPC was designed, contamination in the CA was pre-estimated to be approximately 20%.[19,22,23] Our results indicate that during the first 4-year period the proportion of tested men in the CA was indeed approximately 20% but this increased quickly. By the end of the active screening period 58% of men in the CA had undergone PSA testing at least once. The high T1c incidence of 5% in the CA reflects this test frequency. In comparison, the risk of any PCa in Finland by age 75 years is approximately 10%.[24] During the trial no national guidelines recommended PSA testing in asymptomatic men.

Our results highlight the challenge of a population based cancer screening trial. The setting changes from "to screen or not to screen" to "to screen in an organized or in an opportunistic fashion."[11,25,26] Thus, the results of a highly contaminated trial do not answer the original dichotomy but rather the new quantitative comparison of whether it is enough to screen opportunistically or whether organized screening is more beneficial. Consequently the conclusion from a highly contaminated trial reporting no substantial mortality benefit such as PLCO cannot be that no screening is as good as organized screening because there is no group representing no screening.

This study has 2 major limitations. 1) We have no information on PSA testing in the private clinics. For instance, of the 2,180 men in the CA who were diagnosed with T1c cancer 424 (19.4%) had no PSA test findings available in our laboratory data, likely indicating PSA testing in the private sector. Thus, the true proportion of men with at least 1 PSA test in the CA could possibly be up to 20% higher. 2) We

have no information on whether PSA tests were used for screening asymptomatic men (true contamination) or for diagnostic purposes in patients with prostate related symptoms. The latter is likely to be frequent as the proportion of elevated PSA results was clearly higher in the CA and it increased as men grew older. At the Dutch center 50% of opportunistic PSA testing was true contamination and 50% was diagnostic testing.[21]

Using the overall PSA test frequency as an indicator of opportunistic screening overestimates its frequency because true contamination cannot be extracted from all contamination to perform revised mortality estimates. If we extrapolate the missing data from the private clinics (a 1.2-fold increase in PSA tests) and consider that approximately 50% of PSA testing represents true contamination, we could estimate that by 4, 8 and 12 years of followup 11%, 29% and 38% of men in the CA, respectively, had been tested with PSA at least once. Furthermore, we have no information on the extent of diagnostic testing (ie biopsy) following the PSA test (effective contamination).

CONCLUSIONS

PSA testing frequency in the CA was initially low but it became higher as 18% of men in the CA were tested at least once by 4 years, 48% at 8 years and 63% at 12 years. The relative mortality reduction in the screening arm has been less pronounced in the Finnish trial than at the Swedish and Dutch ERSPC centers. Contamination in the CA is likely a reason for this result.

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EDITORIAL COMMENT

Two multicenter trials have investigated the effectiveness of PSA testing on prostate cancer mortality. PLCO was performed in the United States, where PSA testing was widespread, with a 99% intervention rate and an 86% control rate, thus, comparing organized to opportunistic testing.[1] This small absolute difference in PSA use lowered study power to detect the postulated expected mortality reduction between the arms.[1] In contrast, ERSPC was done in 8 European countries, where PSA testing was initially rare, and it showed significant benefit.[2] However, exposure to PSA also increased in Europe with time.

Kilpeläinen et al report 63% PSA contamination at 12 years in the control arm of ERSPC Finland. As with PLCO, contamination diluted differences in deaths between study arms. This raises an important health policy question. Compared to no screening, organized PSA testing can effectively reduce prostate cancer mortality but increase the number of cancers detected. The effect of opportunistic PSA testing appears to be more heterogeneous as it often follows no protocol. In the worst case there is little if any effect on mortality but it merely results in over diagnosis.[3]

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REPLY BY AUTHORS

Randomized cancer screening trials tend to concentrate on the screening arm because the information is readily available on those who are screened. However, the relative difference between the trial arms (eg in incidence and mortality) appears to be more dependent on the event rate in the control arm. Opportunistic PSA testing has become widespread but the pace and extent of such testing vary among populations. Furthermore, it is not only testing but also the rigor of the diagnostic followup procedures that ultimately affects incidence and mortality.

To date testing in the control arms of various trials has been reported incompletely, rarely distinguishing testing among symptomatic vs asymptomatic men (differential diagnostics vs screening). Inference on the impact of opportunistic screening has mainly been based on circumstantial data on testing frequency in the control arm but no solid evidence based on indications for testing. We are looking at the shadows of these trials much like the men tied to chairs in Plato's Allegory of the Cave.

Thus, the mortality impact, if any, of current opportunistic PSA testing remains unclear. A quarter of a century ago PSA testing was uncommon and the benefits of organized screening could be demonstrated when screening naïve populations. Now we can only compare different frequencies and intensities of screening.