THE JOURNAL of UROLOGY®
www.auajournals.org/journal/juro

JU Insight

OPEN

# Results from 22 years of Followup in the Göteborg Randomized Population-Based Prostate Cancer Screening Trial

Maria Frånlund, Marianne Månsson, Rebecka Arnsrud Godtman et al.

Correspondence: Jonas Hugosson (email: jonas.hugosson@surgery.gu.se).

*Full-length article available at auajournals.org/10.1097/JU.0000000000002696.*

**Study Need and Importance:** Results from randomized prostate cancer screening trials are inconsistent. The aim of the present study was to present very long followup data of the Göteborg 1 screening trial which started early before opportunistic prostate specific antigen (PSA) testing was peaking and with up to 20-year duration of the screening period.

**What We Found:** At 22 years of followup the prostate cancer mortality was 29% lower in the group of men who were invited every second year for PSA testing (41% in those who attended at least once) compared to a noninvited control group, but the prostate cancer incidence was 42% higher. The number of men needed to invite was 221 and the number needed to diagnose was 9 to prevent 1 prostate cancer death. Among invited men a higher prostate cancer mortality was seen among those never attending the program and among those who started the program after age 60, and the prostate cancer mortality was high 10 years after termination of the program.

**Limitations:** Limitations mainly include the increasing rate of opportunistic PSA testing during the study period in the control group and nonparticipation in the screening group, diluting the "true" effects of a well-organized PSA screening program.

**Interpretation for Patient Care:** Regular PSA testing from age 50 significantly decreases the risk of dying from prostate cancer at the expense of a rather high risk of detecting small slow-growing cancers, of which many never will need treatment. If a man chooses to participate in a prostate cancer screening program he should start around age 50. Testing should be done at least every second year and should not stop at age 70 for all men.

THE JOURNAL OF UROLOGY®

https://doi.org/10.1097/JU.0000000000002696
Vol. 208, 292-300, August 2022
Printed in U.S.A.

THE JOURNAL of UROLOGY®
www.auajournals.org/journal/juro

OPEN

# Results from 22 years of Followup in the Göteborg Randomized Population-Based Prostate Cancer Screening Trial

Maria Frånlund,[1] Marianne Månsson,[1] Rebecka Arnsrud Godtman,[1] Gunnar Aus,[2] Erik Holmberg,[3] Karin Stinesen Kollberg,[1] Pär Lodding,[1] Carl-Gustaf Pihl,[4] Johan Stranne,[1] Hans Lilja[5,6,7,8,9] and Jonas Hugosson[1]*

[1]Department of Urology, Institute of Clinical Sciences, Sahlgrenska Academy at University of Gothenburg, Sahlgrenska University Hospital, Gothenburg, Sweden
[2]Department of Urology, Carlanderska Hospital, Gothenburg, Sweden
[3]Department of Oncology, Institute of Clinical Sciences, Sahlgrenska Academy at University of Gothenburg, Sahlgrenska University Hospital, Gothenburg, Sweden
[4]Department of Pathology, Institute of Biomedicine, Sahlgrenska Academy at University of Gothenburg, Sahlgrenska University Hospital, Gothenburg, Sweden
[5]Department of Surgery (Urology Service), Memorial Sloan Kettering Cancer Center, New York, New York
[6]Department of Laboratory Medicine, Memorial Sloan Kettering Cancer Center, New York, New York
[7]Department of Medicine (Genitourinary Oncology Service), Memorial Sloan Kettering Cancer Center, New York, New York
[8]Nuffield Department of Surgical Sciences, University of Oxford, Oxford, United Kingdom
[9]Department of Translational Medicine, Lund University, Malmö, Sweden

**Purpose:** Our goal was to analyze results from 22 years of followup in the Göteborg randomized prostate cancer (PC) screening trial.

**Materials and Methods:** In December 1994, 20,000 men born 1930–1944 were randomly extracted from the Swedish population register and were randomized (1:1) into either a screening group (SG) or to a control group (CG). Men in the SG were repeatedly invited for biennial prostate specific antigen testing up to an average age of 69 years. Main endpoints were PC incidence and mortality (intention-to-screen principle).

**Results:** After 22 years, 1,528 men in the SG and 1,124 men in the CG had been diagnosed with PC. In total, 112 PC deaths occurred in the SG and 158 in the CG. Compared with the CG, the SG showed a PC incidence rate ratio (RR) of 1.42 (95% CI, 1.31–1.53) and a PC mortality RR of 0.71 (95% CI, 0.55–0.91). The 22-year cumulative PC mortality rate was 1.55% (95% CI, 1.29–1.86) in the SG and 2.13% (95% CI, 1.83–2.49) in the CG. Correction for nonattendance (Cuzick method) yielded a RR of PC mortality of 0.59 (95% CI, 0.43–0.80). Number needed to invite and number needed to diagnose was estimated to 221 and 9, respectively. PC death risk was increased in the following groups: nontesting men, men entering the program after age 60 and men with >10 years of followup after screening termination.

**Abbreviations and Acronyms**

CG = control group
ERSPC = European Randomized Study of Screening for Prostate Cancer
NND = number needed to diagnose
NNI = number needed to invite
PC = prostate cancer
PLCO = Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial
PSA = prostate specific antigen
RR = rate ratio
SG = screening group

Accepted for publication March 31, 2022.

Support: This work was supported by a grant from the Swedish Research Council to H. Lilja (VR-MH no. 2016-02974); the Swedish Cancer Society (CAN 2017/559); and David H. Koch through the Prostate Cancer Research Foundation, the Sidney Kimmel Center for Prostate and Urologic Cancers, a grant from the Specialized Program of Research Excellence (p50-CA92629) from the National Cancer Institute to Dr. Howard Scher; and a grant from the National Institutes of Health/National Cancer Institute Cancer Center Support to MSKCC (P30-CA008748), the National Institute for Health Research (NIHR) Oxford Biomedical Research Centre Program in the United Kingdom. None of the funding sources had access to the database or were involved in the collection or management of the data, nor did they have any influence on the writing of this paper.

Conflict of Interest: Hans Lilja holds patents for intact PSA assays, and is named on a patent application for a statistical method to detect prostate cancer. These patents have been licensed and commercialized as the 4Kscore® by OPKO Health. Dr. Lilja receives royalties from sales of this test and owns stock in OPKO.



* Correspondence: Department of Urology, Clinical Sciences, Sahlgrenska University Hospital, 413 45 Göteborg, Sweden (telephone: +46 31 342 39 05; email: jonas.hugosson@surgery.gu.se).

**Conclusions:** Prostate specific antigen-based screening substantially decreases PC mortality. However, not attending, starting after age 60 and stopping at age 70 seem to be major pitfalls regarding PC death risk.

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

Reports from the European Randomised Study of Screening for Prostate Cancer (ERSPC) have shown that variations in the screening-algorithm between different centers have a large impact on the efficacy of screening.[1–3] Within the ERSPC (where the Göteborg Trial is one center), there were differences in start and stop age, screening interval, program duration and treatments given.[4] Attempts have been made to analyze how the design of a screening program can be improved to enhance efficacy and specificity for clinically significant tumors (ie reduce mortality and decrease over detection). However, those studies have been based either on a short followup or microsimulation modelling.[5,6]

Here, we report results from 22 years of followup in the Göteborg randomized prostate cancer (PC) screening trial. Our study also focuses on pitfalls within the current screening design to elucidate how PC screening may be improved.

## MATERIAL AND METHODS

### Selection and Description of Participants

The Göteborg Randomized Population-Based Prostate Cancer Screening Trial was initiated in 1995 after approval by the Ethics Committee of the University of Göteborg, Sweden (ID No. 2019-00814). The study protocol has been described in previous publications and the trial profile is presented in Figure 1.[4,7] Since 1996, this trial has constituted the Swedish section of the ERSPC (registration No. ISRCTN54449243).

On December 31, 1994 the Swedish population register showed that 32,298 men born between January 1, 1930 and December 31, 1944 lived in the city of Göteborg. From this population, 10,000 men were randomized to a screening group (SG) and 10,000 to a control group (CG). After randomization, 106 men were excluded: 55 men with prevalent PC and 51 men who had emigrated or died before randomization.

Men assigned to the SG were invited to take prostate specific antigen (PSA; DELFIA Prostatus total/free PSA-assay; Perkin-Elmer, Turku, Finland, PMID 7543033) every second year until they reached the stop age (median 69 years, range 67–71). The oldest cohort (born 1930–1931) was invited 3 times and the youngest (born 1944) 10 times.

Participants with PSA above the corrected WHO cut-off level (3.4 ng/ml in 1995–1998, 2.9 ng/ml 1999–2004 and 2.5 ng/ml after 2004) were further invited to a clinical assessment including prostate biopsy. Men with PSA below the cut-off level or a benign biopsy were re-invited after 2 years. Men in the CG were not invited for PSA screening but were subject to opportunistic PSA testing. The final (10th) screening round was completed in 2014. Only minor changes were made in the screening algorithm during the study period.[8] The database was regularly updated through linkage with the Swedish Population Register and the Regional Cancer Register of Western Sweden to provide information on vital status, dates for moving outside the Western Region (censoring date) and PC diagnoses. For men with PC, all medical documentation was collected to establish tumor stage/grade at diagnosis, disease course and treatment(s) received. An independent committee determined cause of death according to a flow chart after analyzing all medical data.[9] The group allocation was blinded to the members of the committee.

The last date of followup for the present report was December 31, 2016. Men in the SG were classified as attenders (attended at least once) or nonattenders (never attended). Men with a PC diagnosis were further divided into subgroups based on how they were detected (screen-detected, nonscreen detected or after stop-age; Fig. 1).

### Statistical Analysis

The primary endpoints of the investigation were PC incidence and mortality, analyzed as intention-to-screen, comparing the 2 study arms. Comparisons were made between the groups in terms of rate ratios (RRs) and risk ratios (ratios of number of events per person-years and per man, respectively). Furthermore, cumulated incidences were calculated using the Kaplan-Meier approach. Competing risk estimates of cumulative incidence were calculated as described by Choudhury et al.[10] Adjusted rate RRs for PC mortality were calculated with correction for nonparticipation in the SG, in accordance with the method described earlier.[11] Comparisons of age, PSA at diagnosis, time to PC diagnosis and PC death are based on bootstrapping (the percentile method, 1,000 samples).

Number needed to invite (NNI) for screening to prevent 1 PC death was calculated as 1 divided by the absolute risk reduction in PC mortality. Number needed to diagnose (NND) was calculated as 1 divided by the absolute risk reduction in PC mortality multiplied by the excess incidence.

## RESULTS

In the SG, 7,635 men (77%) attended at least once. Altogether, 57,983 invitations were mailed to men in the study arm and 34,646 PSA tests were taken within the study (Table 1). Of the 7,635 men attending the program, 2,672 (35%) had an elevated PSA at least once and 2,525 men (33%) underwent at least 1 biopsy. Invitation to the study led to diagnosis of 1,046 cancers. During 22 years of followup, an additional 482 cancers were diagnosed in the SG, albeit outside the program, resulting in a

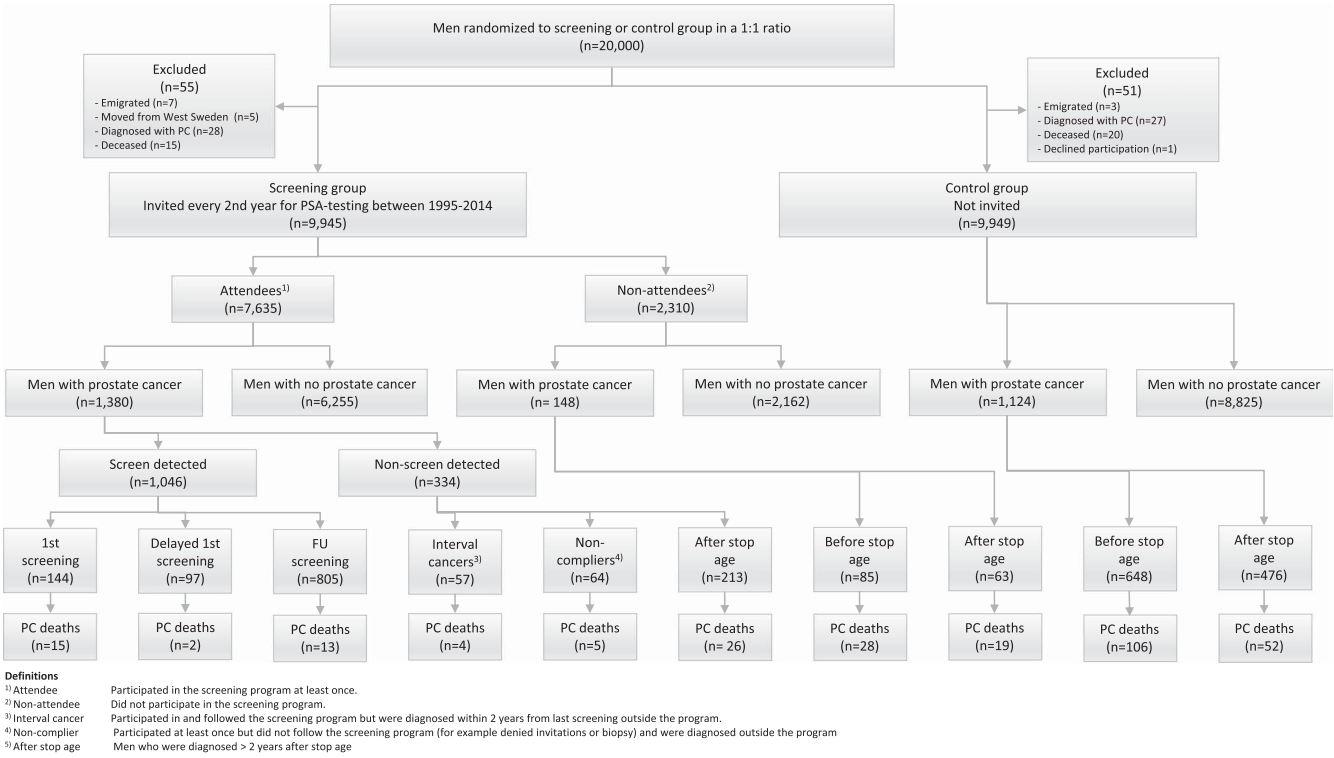


**Figure 1.** Flow chart, 22 years of screening. *FU*, followup.

total of 1,528 cancers in this group. The corresponding number of PC diagnoses in the CG was 1,124. Figure 1 shows the numbers of PC cases and PC deaths in different subgroups of men.

Figure 2, *A* shows the cumulative PC incidence curves. At 22 years, the cumulative incidence was 18.6% in the SG and 14.3% in the CG, an absolute difference of 4.3% (95% CI, 3.1–5.5). Taking competing risk into account reduced the incidence to 15.9% and 11.8% in the SG and CG, respectively.

Time from randomization until 10% of men in the SG and CG received a PC diagnosis based on cumulative PC incidence was 11.0 years and 15.8 years, respectively ($p < 0.001$).

Median age at randomization was the same in both groups, 56 (IQR 53–61), while the median age at diagnosis was 66.3 in the SG and 69.2 in the CG ($p < 0.001$). Median PSA at PC diagnosis was lower in men in the SG compared to men in the CG (5.1 vs. 8.6 ng/ml, $p < 0.001$). Table 2 shows the difference in tumor risk group distribution and treatments between the 2 study arms.

A total of 112 men died of PC in the SG compared with 158 in the CG (RR=0.71, 95% CI, 0.55–0.91, p=0.005). The cumulative risk of PC death at 22 years was 1.55% in the SG and 2.13% in the CG, an absolute reduction of 0.59% (95% CI, 0.15–1.03; Fig. 2, *B*). Taking competing risk into account reduced the cumulative mortality to 1.2% and 1.7% in the SG and CG, respectively. Time from randomization until 1% of men in the SG and CG died of PC based on cumulative PC mortality was 18.1 and 15.2 years, respectively (p=0.003). Table 3 shows PC incidence and mortality over the years.

For men who died from PC, median age at randomization was 58.5 years (IQR 55.8–62.6) in the CG and 60.7 years (IQR 57.2–63.0) in the SG.

A total of 144 PCs were detected at first invitation (Fig. 1). These cancers were generally more advanced than cases detected during subsequent screening rounds (Table 4). Of the 144 cancers, 80 (56%) occurred in men ≥60 years of age at the time of invitation. Fifteen of those 144 men died of PC and 9 of the 15 (60%) were aged ≥60 years at randomization. Another 97 PCs were diagnosed at delayed first screen but those resulted in only 2 PC deaths. The rate of interval cancers was low and led to very few deaths (4). In men who participated in the program and were diagnosed during followup screens (second–tenth round), PC death rate was also low (13 of 805 PC cases).

In the SG, 213 men were diagnosed more than 2 years after stop age. Median age at time of diagnosis was 76.1 years (IQR 73.2–78.8). Twenty-six of these 213 men (12%) died from PC and 23 of these 26 men left the study with a median PSA of 2.3 ng/ml (IQR 1.6–3.2). Median age at death for these 26 men was 80.4 years (IQR 76.6–82.9).

A total of 2,310 men (23%) in the SG never attended the program and 148 of those were diagnosed with PC.

**Table 1.** *Number and outcome of participants in relation to screening visits*

| | Screening Visit | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| No. | 1st | 2nd | 3rd | 4th | 5th | 6th | 7th | 8th | 9th | 10th | Total |
| 1st invitation round (1995–1996): | | | | | | | | | | | |
| Invited | 9,881 | – | – | – | – | – | – | – | – | – | 9,881 |
| Participating | 5,855 | – | – | – | – | – | – | – | – | – | 5,855 |
| Raised PSA | 660 | – | – | – | – | – | – | – | – | – | 660 |
| PC | 144 | – | – | – | – | – | – | – | – | – | 144 |
| 2nd invitation round (1997–1999): | | | | | | | | | | | |
| Invited | 9,507 | – | – | – | – | – | – | – | – | – | 9,507 |
| Participating | 580 | 4,681 | – | – | – | – | – | – | – | – | 5,261 |
| Raised PSA | 66 | 541 | – | – | – | – | – | – | – | – | 607 |
| PC | 15 | 98 | – | – | – | – | – | – | – | – | 113 |
| 3rd invitation round (1999–2000):* | | | | | | | | | | | |
| Invited | 8,745 | – | – | – | – | – | – | – | – | – | 8,745 |
| Participating | 460 | 783 | 4,034 | – | – | – | – | – | – | – | 5,277 |
| Raised PSA | 79 | 129 | 622 | – | – | – | – | – | – | – | 830 |
| PC | 29 | 23 | 108 | – | – | – | – | – | – | – | 160 |
| 4th invitation round (2001–2002): | | | | | | | | | | | |
| Invited | 7,840 | – | – | – | – | – | – | – | – | – | 7,840 |
| Participating | 291 | 398 | 651 | 3,282 | – | – | – | – | – | – | 4,622 |
| Raised PSA | 49 | 63 | 124 | 498 | – | – | – | – | – | – | 734 |
| PC | 13 | 13 | 19 | 87 | – | – | – | – | – | – | 132 |
| Not invited (passed stop age) | – | – | – | – | – | – | – | – | – | – | 867 |
| 5th invitation round (2003–2004): | | | | | | | | | | | |
| Invited | 6,666 | – | – | – | – | – | – | – | – | – | 6,666 |
| Participating | 207 | 341 | 428 | 547 | 2,591 | – | – | – | – | – | 4,114 |
| Raised PSA | 38 | 62 | 54 | 109 | 352 | – | – | – | – | – | 615 |
| PC | 10 | 10 | 6 | 20 | 65 | – | – | – | – | – | 111 |
| Not invited (passed stop age) | – | – | – | – | – | – | – | – | – | – | 1,620 |
| 6th invitation round (2005–2006): | | | | | | | | | | | |
| Invited | 5,754 | – | – | – | – | – | – | – | – | – | 5,754 |
| Participating | 118 | 188 | 291 | 334 | 470 | 2,077 | – | – | – | – | 3,478 |
| Raised PSA | 34 | 34 | 51 | 61 | 104 | 418 | – | – | – | – | 702 |
| PC | 13 | 6 | 14 | 11 | 20 | 81 | – | – | – | – | 145 |
| Not invited (passed stop age) | – | – | – | – | – | – | – | – | – | – | 2,252 |
| 7th invitation round (2007–2008): | | | | | | | | | | | |
| Invited | 4,163 | – | – | – | – | – | – | – | – | – | 4,163 |
| Participating | 68 | 93 | 141 | 230 | 266 | 376 | 1,439 | – | – | – | 2,613 |
| Raised PSA | 20 | 11 | 24 | 42 | 64 | 87 | 294 | – | – | – | 542 |
| PC | 8 | 3 | 3 | 11 | 10 | 11 | 45 | – | – | – | 91 |
| Not invited (passed stop age) | – | – | – | – | – | – | – | – | – | – | 2,895 |
| 8th invitation round (2009–2010): | | | | | | | | | | | |
| Invited | 2,986 | – | – | – | – | – | – | – | – | – | 2,986 |
| Participating | 47 | 75 | 86 | 113 | 158 | 182 | 287 | 967 | – | – | 1,915 |
| Raised PSA | 16 | 19 | 16 | 21 | 21 | 38 | 61 | 180 | – | – | 372 |
| PC | 7 | 3 | 4 | 6 | 5 | 5 | 9 | 42 | – | – | 81 |
| Not invited (passed stop age) | – | – | – | – | – | – | – | – | – | – | 3,598 |
| 9th invitation round (2011–2012): | | | | | | | | | | | |
| Invited | 1,846 | – | – | – | – | – | – | – | – | – | 1,846 |
| Participating | 21 | 27 | 40 | 50 | 67 | 109 | 106 | 168 | 539 | – | 1,127 |
| Raised PSA | 5 | 5 | 5 | 9 | 9 | 15 | 27 | 43 | 98 | – | 216 |
| PC | 2 | 2 | 0 | 3 | 2 | 3 | 4 | 9 | 20 | – | 45 |
| Not invited (passed stop age) | – | – | – | – | – | – | – | – | – | – | 4,264 |
| 10th invitation round (2013–2014): | | | | | | | | | | | |
| Invited | 595 | – | – | – | – | – | – | – | – | – | 595 |
| Participating | 8 | 6 | 19 | 17 | 18 | 19 | 33 | 34 | 64 | 166 | 384 |
| Raised PSA | 0 | 1 | 4 | 4 | 2 | 3 | 6 | 7 | 13 | 37 | 77 |
| PC | 0 | 1 | 2 | 2 | 0 | 1 | 3 | 3 | 0 | 18 | 30† |
| Not invited (passed stop age) | – | – | – | – | – | – | – | – | – | – | 5,012 |
| Total (1995–2014): | | | | | | | | | | | |
| Invitations | | | | | | | | | | | 57,983 |
| PSA tests | | | | | | | | | | | 34,646 |
| Elevated PSA tests | | | | | | | | | | | 5,355 |
| Men with PC | | | | | | | | | | | 1,052‡ |
| Invitations in men alive not sent due to passed stop age | | | | | | | | | | | 20,508 |

* Men born between 1932 and 1944 with a total PSA <1 ng/ml in the second screening round were not invited to the third screening round. A total of 1,902 of these men participated in the fourth screening round and have a fictive mean total PSA, which has been calculated retrospectively using the total PSA values from rounds 2 and 4.
† Nine with PSA <3 ng/ml.
‡ Six men were diagnosed after they emigrated from the West Region of Sweden and were excluded from the analysis.

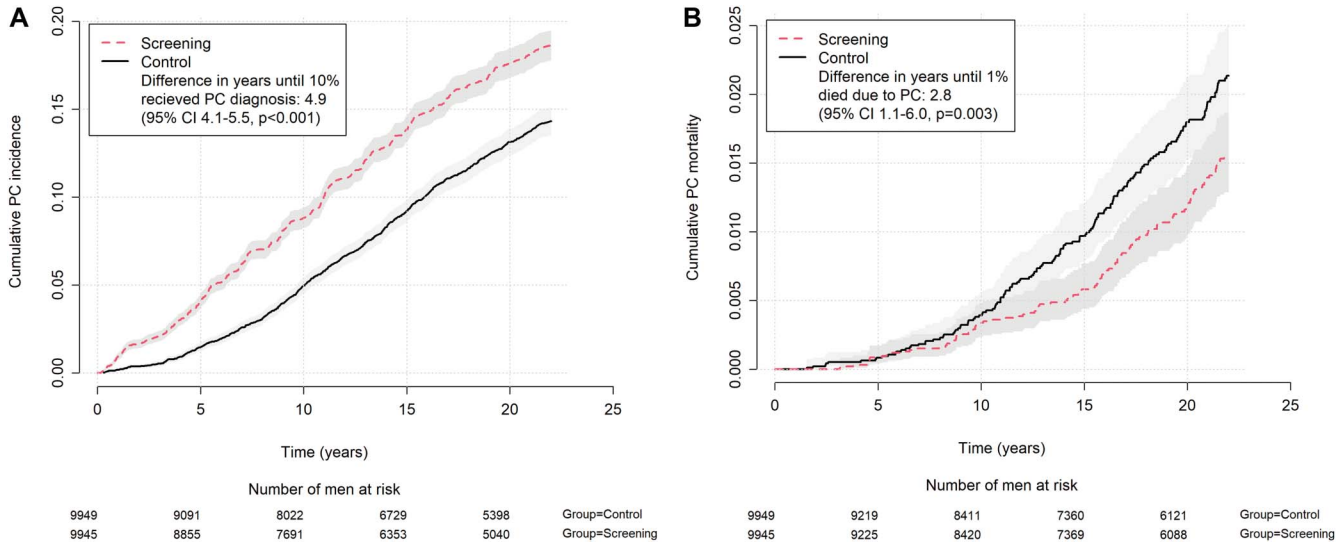


**Figure 2.** *A*, observed PC incidence up to December 31, 2016 (19,894). *B*, observed PC mortality up to December 31, 2016 (19,894).

Median age at diagnosis was 68.8 years (IQR 64.1–73.7). PC incidence at 22 years was lower in nonattenders (148, 6.4%) than in both attenders (1,380, 18.1%) and men in the CG (1,124, 11.3%). PC-specific mortality at 22 years was higher in nonattenders (47, 2.0%) than in attenders (65, 0.9%; Fig. 2, *B*).

## DISCUSSION

This report provides evidence that an organized screening program with 22 years of followup reduces PC mortality by ~30% compared to the concurrent rate of nonorganized opportunistic PSA testing and by ~40% among men attending at least once. This could not be explained by differences in treatment, which per risk group was similar between the arms (Table 2). The absolute risk difference in PC mortality per man randomized increased over time while the relative difference decreased. The continued decrease in absolute mortality in the screening compared to the CG is reflected in a decreasing NNI, which now is 217. Comparing with other cancer screening programs, this is low and should thus be considered in terms of efficacy when evaluating different general health policies.[12,13] As incidence rates in the 2 arms continue to approach each other, a number of 9 men NND is comparable to that of breast cancer screening.[12] This number may, however, be falsely low due to the high rate of opportunistic screening in the CG. It is also far from the NND of 48, which was initially reported from ERSPC, leading to the fear of an enormous overdiagnosis rate.[2] We now conclude that this was mainly due to a too short followup. As NND keeps declining, even further followup of this trial and other trials is essential. The relative reduction of PC mortality decrease over time is mainly explained by the fact that men in our program stopped screening at an average age of 69 years. Men diagnosed after the stop age constitute a substantial part of PC deaths in the SG. In a previous report, we found that the positive effect of screening on PC mortality disappears approximately 10 years after stop age.[14] As half of all men in the Western world who die from PC are above the age of 80,[15] discontinuing screening for all men at age 70 may be too early. However, the selected stop age must be balanced with increased risk of overdiagnosis associated with screening elderly men.[16,17]

Another result from this study is that men who had their first screening after age 60 had an increased risk of being diagnosed with advanced disease at their first screening visit and later death from PC. The optimal start age for PC screening remains to be evaluated but earlier start of screening does not seem to be associated with a significantly higher risk of overdiagnosis.[18] A third result from this study is the doubled mortality rate in men who did not attend screening compared to those who attended (2.0% versus 0.9%). As these men also have a higher overall mortality,[14] their "true" RR will be even higher. On the other hand, early deaths prevent potential later attendance—maybe some men were in fact "potential attenders" had they lived longer. Hence, an immortal time bias exists, which makes calculations about nonattenders' "true" RR difficult.

However, there is a need to more accurately assess whether the decision to decline screening participation is a well-informed one or whether it is based on other factors. A man's choice should always be respected, yet it is important to identify which factors play major roles in the decision to attend or not.

**Table 2.** *Risk group classification and primary treatment of cancers detected*

| | CG (1,124 PC detected) | | | | | SG (1,528 PC detected) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | All PC | Low Risk PC | Intermediate Risk | High Risk | Advanced | All PC | Low Risk PC | Intermediate Risk | High Risk | Advanced |
| No. pts | 1,114* | 269 | 434 | 206 | 136 | 1,528† | 723 | 510 | 174 | 89 |
| No. primary treatment (%): | | | | | | | | | | |
| Prostatectomy | 329 (30) | 95 (35) | 162 (37) | 34 (16) | 8 (6) | 549 (36) | 232 (32) | 236 (46) | 54 (31) | 9 (10) |
| Radiation | 118 (11) | 11 (4) | 43 (10) | 52 (25) | 2 (1) | 118 (8) | 40 (6) | 47 (9) | 30 (17) | 0 |
| Surveillance | 388 (35) | 158 (59) | 177 (41) | 27 (13) | 0 | 662 (43) | 440 (61) | 191 (37) | 21 (12) | 0 |
| Endocrine treatment | 268 (24) | 5 (2) | 48 (11) | 91 (44) | 122 (89) | 184 (12) | 4 (1) | 33 (6) | 66 (38) | 79 (89) |
| Unknown | 11 (1) | 0 | 4 (1) | 2 (1) | 4 (4) | 15 (1) | 7 (1) | 3 (1) | 2 (1) | 1 (1) |
| Median yrs age at diagnosis (IQR) | 69 (65, 73) | 67 (63, 70) | 69 (66, 73) | 70 (66, 75) | 69 (65, 74) | 66 (63, 69) | 65 (62, 68) | 67 (64, 70) | 69 (65, 76) | 71 (66, 77) |
| No. T3, T4 PC (%) | – | – | – | 69 (33) | 81 (60) | – | – | – | 67 (39) | 58 (65) |
| No. PC deaths | 156 | 1 | 22 | 48 | 82 | 112 | 3 | 19 | 31 | 55 |

Low risk—T1, not N1 or M1, and GS ≤6 and PSA <10 ng/ml. Intermediate risk—T1-2, but not N1 or M1, with a GS ≤7, PSA <20 ng/ml or both; and not meeting the criteria for low risk. High risk—T1-4, but not N1 or M1, with a GS >8, PSA <100 ng/ml or both; and not meeting the criteria for low or intermediate risk. Advanced—N1 or M1, or PSA >100 ng/ml. Unknown—includes 11 cases detected at autopsy.

* Ten men had no treatment (detected on autopsy) and 69 men had unknown risk group in the CG; 5 men who died from PC had an unknown risk group.

† In the SG 32 men had unknown risk group; 18 men had prostatectomy, 1 man had radiation, 11 surveillance and 2 men had endocrine treatment.

No association between screening and reduced PC mortality has been found in neither the CAP trial (RR 0.96; 95% CI, 0.85–1.08)[19] nor the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO; RR 0.93, 95% CI, 0.81–1.08).[20] The CAP trial was based on a single screening test. Our data illustrate that the first screening round detects more advanced and incurable cancers, which dilutes differences in PC mortality between the 2 arms. This observation is supported by data from the Finnish branch of the ERSPC.[21] A comparison of our investigation with the PLCO study clearly reveals that the background risk of dying from PC is very different.[20] Considering the CGs, despite the younger age of the CG in our study vs the PLCO study, PC mortality was higher in our study, indicating that opportunistic screening was probably frequent in the PLCO CG, resulting in lower than expected mortality, ie 5.9/10,000 person-years (men aged 55–64) at 17 years of followup in the PLCO study compared to 7.7/10,000 person-years (ages 50–65) at 18 years in our study (Table 3). It seems doubtful that there would be such a large difference in background risk between men in the United States and

**Table 3.** *Incidence and mortality rates at 14, 18 and 22 years of followup*

| | 14 Yrs Followup | 18 Yrs Followup | 22 Yrs Followup |
|---|---|---|---|
| No. men screening/No. control | 9,945/9,949 | 9,945/9,949 | 9,945/9,949 |
| PC incidence: | | | |
| No. PC cases screening/No. control | 1,136/715 | 1,390/956 | 1,528/1,124 |
| Person-yrs screening/person-yrs control | 116,925/120,735 | 141,297/146,569 | 161,456/168,212 |
| RR (95% CI) | 1.64 (1.49, 1.80) | 1.51 (1.39, 1.64) | 1.42 (1.31, 1.53) |
| Rate difference per 1,000 person-years (95% CI) | 3.79 (3.08, 4.51) | 3.31 (2.65, 3.98) | 2.78 (2.17, 3.40) |
| Risk ratio (95% CI) | 1.59 (1.45, 1.75) | 1.45 (1.34, 1.58) | 1.36 (1.26, 1.47) |
| Risk difference per 1,000 men (95% CI) | 42.36 (33.88, 50.84) | 43.68 (34.13, 53.22) | 40.67 (30.52, 50.82) |
| Cumulative incidence difference (95% CI) | 4.5% (3.6%, 5.5%) | 4.7% (3.7%, 5.8%) | 4.3% (3.1%, 5.5%) |
| PC mortality: | | | |
| No. PC deaths screening/No. control | 42/76 | 77/118 | 112/158 |
| Person-yrs screening/person-yrs control | 124,217/124,139 | 152,760/152,620 | 177,091/177,152 |
| RR (95% CI) | 0.55 (0.37, 0.82) | 0.65 (0.48, 0.88) | 0.71 (0.55, 0.91) |
| RR p value | 0.002 | 0.003 | 0.005 |
| RR, attender adjusted (95% CI) | 0.42 (0.27, 0.68) | 0.54 (0.38, 0.77) | 0.59 (0.43, 0.80) |
| RR, attender adjusted p value | <0.001 | <0.001 | <0.001 |
| Rate difference per 1,000 person-yrs (95% CI) | −0.27 (−0.45, −0.10) | −0.27 (−0.45, −0.09) | −0.26 (−0.44, −0.08) |
| Risk ratio (95% CI) | 0.55 (0.37, 0.82) | 0.65 (0.48, 0.88) | 0.71 (0.55, 0.91) |
| Risk difference per 1,000 men (95% CI) | −3.42 (−5.56, −1.28) | −4.12 (−6.87, −1.37) | −4.62 (−7.86, −1.38) |
| NNI (95% CI) | 293 (178, 847) | 243 (144, 782) | 217 (127, 768) |
| NND | 13 | 11 | 9 |
| Cumulative incidence difference (95% CI) | −0.4% (−0.7%, −0.2%) | −0.5% (−0.9%, −0.2%) | −0.6% (−1.0%, −0.1%) |
| All-cause mortality | | | |
| No. all-cause deaths screening/No. control | 1,956/1,945 | 2,788/2,782 | 3,806/3,735 |
| Person-yrs screening/person-yrs control | 124,217/124,139 | 152,760/152,620 | 177,091/177,152 |
| RR, all-cause mortality (95% CI) | 1.01 (0.94, 1.07) | 1.00 (0.95, 1.06) | 1.02 (0.97/1.07) |
| Rate difference per 1,000 person-yrs (95% CI) | 0.08 (−0.91, 1.06) | 0.02 (−0.94, 0.98) | 0.41 (−0.55, 1.37) |
| Risk ratio (95% CI) | 1.01 (0.94, 1.07) | 1.00 (0.95, 1.06) | 1.02 (0.97, 1.07) |

**Table 4.** *Characteristics of subgroups of PC detected in 1,528 patients in the SG*

| | PC Diagnosed in Attendees* | | | | | | PC in Nonattendees† (148) |
|---|---|---|---|---|---|---|---|
| | Detected at 1st Screen "Prevalent Ca" (144) | Delayed 1st Screening (97) | Followup Screening (805) | Interval Ca‡ (57) | Noncompliers§ (64) | Detected after the Screening Period (213) | |
| Median yrs age at randomization (IQR) | 59.6 (56.5—62.6) | 55.4 (52.8—59.2) | 55.1 (51.9—59.0) | 57.3 (54.4—60.7) | 54.8 (52.8—58.4) | 60.0 (57.1—63.1) | 57.3 (53.8—61.9) |
| Median yrs age at diagnosis (IQR) | 60.5 (57.4—63.7) | 64.4 (61.1—67.2) | 65.9 (62.8—67.7) | 66.7 (62.5—68.9) | 65.6 (62.9—67.8) | 76.1 (73.3—78.8) | 68.8 (64.1—73.5) |
| Median yrs from randomization to diagnosis (IQR) | 0.9 (0.6—1.2) | 6.8 (4.9—10.8) | 8.9 (5.4—12.9) | 8.8 (5.7—11.0) | 8.9 (6.1—12.7) | 17.1 (14.3—19.7) | 10.3 (5.4—16.6) |
| Median PSA at diagnosis (IQR) | 6.2 (4.0—11.1) | 5.5 (4.0—9.2) | 4.1 (3.4—5.4) | 4.6 (3.6—7.2) | 6.5 (4.2—12.0) | 10.0 (6.4—22.0) | 19.0 (7.6—59.0) |
| Median free-to-total PSA ratio at diagnosis (IQR) | 11.8 (8.6—15.3) | 15.2 (11.3—20.7) | 19.4 (14.1—24.7) | Not available | Not available | Not available | Not available |
| No. advanced PC (%)‖ | 4 (3) | 4 (4) | 5 (0.6) | 4 (7) | 3 (5) | 28 (13) | 41 (28) |
| No. high risk PC (%)¶ | 19 (13) | 11 (11) | 36 (4.5) | 3 (5) | 5 (8) | 57 (27) | 43 (29) |
| No. intermediate risk PC (%)** | 59 (41) | 32 (33) | 247 (30.7) | 20 (35) | 27 (42) | 88 (41) | 37 (25) |
| No. low risk PC (%)†† | 62 (43) | 50 (52) | 515 (64) | 25 (44) | 26 (41) | 28 (13) | 17 (11) |
| No. risk category not known (%) | 0 | 0 | 2 (0.2) | 5 (9) | 3 (5) | 12 (6) | 10 (7) |
| No. PC deaths (%) | 15 (10) | 2 (2.1) | 13 (1.6) | 4 (7.0) | 5 (7.8) | 26 (12) | 47 (32) |
| No. PC deaths within 5 yrs after diagnosis | 1 | 1 | 3 | 3 | 3 | 22 | 30 |
| No. PC deaths 5—10 yrs after diagnosis | 6 | 0 | 6 | 0 | 1 | 3 | 10 |
| Median yrs from randomization to PC death (IQR) | 11.6 (9.2—14.0) | 10.5 (8.0—13.1) | 15.2 (10.1—17.5) | 6.5 (4.6—10.3) | 8.6 (8.3—12.8) | 18.0 (16.5—20.3) | 15.9 (9.7—19.9) |
| Median yrs from diagnosis to PC death (IQR) | 10.7 (8.4—12.8) | 6.4 (4.2—8.7) | 6.6 (5.7—12.2) | 2.5 (1.3—6.1) | 4.0 (3.4—7.5) | 1.8 (0.9—4.0) | 3.8 (1.6—7.7) |
| Median yrs age at PC death (IQR) | 71.8 (70.3—72.7) | 68.5 (67.9—69.2) | 74.6 (70.8—75.6) | 70.8 (69.0—73.4) | 68.5 (66.3—74.7) | 80.4 (77.0—82.7) | 73.4 (70.1—77.5) |

* Participated in the screening program at least once.
† Invited but never participated in the screening program.
‡ Participated in the screening program but diagnosed within 2 years from last screening (outside the program).
§ Participated at irregular intervals and was later diagnosed outside the screening program >2 years after last screen, or denied biopsy.
‖ PSA ≥100 ng/ml and/or N1 and/or M1.
¶ PSA <100 ng/ml and GS ≥8 and/or T1-T4, not N1, not M1.
** PSA 10—99 ng/ml and/or Gleason 7 and/or T2.
†† PSA <10 ng/ml and GS 3+3 and T1.

those in Sweden. A much more likely explanation is that men in the PLCO study were extensively screened before inclusion but also during and after the screening period.[22,23] Interestingly, Shoag and co-authors reported that among the men in the SG within PLCO and who died from PC, 53.6% were either never screened as part of their trial or had an initial positive screen.[24]

Opportunistic PSA testing has increased considerably over the 22-year study period within our study and seems to be even higher compared to contemporary series from Sweden.[25,26] However, the situation at study start was very different from that in the U.S. with approximately 5% of men tested in our cohort before they entered into the study. During the study period, the PC mortality in Sweden has decreased by 40% in men aged 60—79 years.[27] Whether this is explained by earlier diagnosis or better treatment strategies could be discussed[28] but earlier diagnosis and better risk stratification is often a prerequisite for new and more effective treatments so it is difficult to analyze these separately. It is not unreasonable to believe that the high rate of opportunistic screening that has taken place will lead to a gross underestimation of the true effects of PSA screening but also to an underestimation of the rate of overdiagnosis. Hence, even though these unique, long-term followup results make for a strong contribution to the field, indicating that repeated PSA screening yields a reduction in PC mortality, the challenge of overdiagnosis remains unresolved. For that problem, the ongoing Göteborg-2 Study and others will address the more exact effects of specific diagnostic tools.[29]

This study has strengths and limitations. Major advantages include the population-based design, the long and almost complete followup of all randomized men, and the high validity of Swedish Registries.[30] Limitations mainly include the high rate of opportunistic screening in the CG and nonparticipation in the SG diluting the "true" effects of organized PSA screening.

## CONCLUSIONS

This extended 22-year followup report of the Göteborg screening study provides further evidence of the efficacy of serial PSA testing. With longer followup, the rate of overdiagnosis decreases but the NND of 9 still indicates that overdiagnosis is not negligible. Increasing the adherence to the program, starting before age 60 and not stopping at age 70 for all men may further improve the efficacy with PC screening but should be balanced by the risk of overdiagnosis.

## REFERENCES


1. Schroder FH, Hugosson J, Roobol MJ et al: Screening and prostate-cancer mortality in a randomized European study. N Engl J Med 2009; **360:** 1320.
2. Schroder FH, Hugosson J, Roobol MJ et al: Screening and prostate cancer mortality: results of the European Randomised Study of Screening for Prostate Cancer (ERSPC) at 13 years of follow-up. Lancet 2014; **384:** 2027.
3. Kilpelainen TP, Tammela TL, Malila N et al: Prostate cancer mortality in the Finnish randomized screening trial. J Natl Cancer Inst 2013; **105:** 719.
4. Hugosson J, Carlsson S, Aus G et al: Mortality results from the Goteborg randomised population-based prostate-cancer screening trial. Lancet Oncol 2010; **11:** 725.
5. Gulati R, Gore JL and Etzioni R: Comparative effectiveness of alternative prostate-specific antigen-based prostate cancer screening strategies: model estimates of potential benefits and harms. Ann Intern Med 2013; **158:** 145.
6. Carlsson SV, de Carvalho TM, Roobol MJ et al: Estimating the harms and benefits of prostate cancer screening as used in common practice versus recommended good practice: a microsimulation screening analysis. Cancer 2016; **122:** 3386.
7. Hugosson J, Godtman RA, Carlsson SV et al: Eighteen-year follow-up of the Goteborg Randomized Population-Based Prostate Cancer Screening Trial: effect of sociodemographic variables on participation, prostate cancer incidence and mortality. Scand J Urol 2018; **52:** 27.
8. European Randomized Study of Screening for Prostate Cancer. 2014. Available at https://www.erspc.org/prostate-cancer/erspc-background/#study-protocol.
9. De Koning HJ, Blom J, Merkelbach JW et al: Determining the cause of death in randomized screening trial(s) for prostate cancer. BJU Int, suppl., 2003; **92:** 71.
10. Choudhury JB: Non-parametric confidence interval estimation for competing risks analysis: application to contraceptive data. Stat Med 2002; **21:** 1129.
11. Cuzick J, Edwards R and Segnan N: Adjusting for non-compliance and contamination in randomized clinical trials. Stat Med 1997; **16:** 1017.
12. Gotzsche PC and Nielsen M: Screening for breast cancer with mammography. Cochrane Database Syst Rev 2009; **4:** CD001877.
13. Towler B, Irwig L, Glasziou P et al: A systematic review of the effects of screening for colorectal cancer using the faecal occult blood test, hemoccult. BMJ 1998; **317:** 559.
14. Grenabo Bergdahl A, Holmberg E, Moss S et al: Incidence of prostate cancer after termination of screening in a population-based randomised screening trial. Eur Urol 2013; **64:** 703.
15. Engholm G, Ferlay J, Christensen N et al: NORDCAN: Cancer Incidence, Mortality, Prevalence and Survival in the Nordic Countries, Version 8.1 (28.06.2018). Association of the Nordic Cancer Registries. Danish Cancer Society. Available at http://www.ancr.nu.
16. Vickers AJ, Sjoberg DD, Ulmert D et al: Empirical estimates of prostate cancer overdiagnosis by age and prostate-specific antigen. BMC Med 2014; **12:** 26.
17. Heijnsdijk EA, Wever EM, Auvinen A et al: Quality-of-life effects of prostate-specific antigen screening. N Engl J Med 2012; **367:** 595.
18. Godtman RA, Carlsson S, Holmberg E et al: The effect of start and stop age at screening on the risk of being diagnosed with prostate cancer. J Urol 2016; **195:** 1390.
19. Martin RM, Donovan JL, Turner EL et al: Effect of a low-intensity PSA-based screening intervention on prostate cancer mortality: the CAP randomized clinical trial. JAMA 2018; **319:** 883.
20. Pinsky PF, Miller E, Prorok P et al: Extended follow-up for prostate cancer incidence and mortality among participants in the Prostate, Lung, Colorectal and Ovarian randomized cancer screening trial. BJU Int 2019; **123:** 854
21. Kilpelainen TP, Pogodin-Hannolainen D, Kemppainen K et al: Estimate of opportunistic prostate specific antigen testing in the Finnish randomized study of screening for prostate cancer. J Urol 2017; **50:** 198.
22. de Koning HJ, Gulati R, Moss SM et al: The efficacy of prostate-specific antigen screening: impact of key components in the ERSPC and PLCO trials. Cancer 2018; **124:** 1197.
23. Tsodikov A, Gulati R, Heijnsdijk EAM et al: Reconciling the effects of screening on prostate cancer mortality in the ERSPC and PLCO trials. Ann Intern Med 2017; **167:** 449.
24. Shoag J, Mittal S, Halpern JA et al: Lethal prostate cancer in the PLCO cancer screening trial. Eur Urol 2016; **70:** 2.
25. Nordstrom T, Aly M, Clements MS et al: Prostate-specific antigen (PSA) testing is prevalent and increasing in Stockholm County, Sweden, despite no recommendations for PSA screening: results from a population-based study, 2003-2011. Eur Urol 2013; **63:** 419.
26. Kollberg KS, Holmberg E, Josefsson A et al: Prostate specific antigen (PSA) and biopsy contamination in the Göteborg-1 randomized population-based prostate cancer screening trial. Submitted J Urol 2022.
27. Hugosson J: Stopping screening, when and how? Transl Androl Urol 2018; **7:** 46.
28. Etzioni R, Tsodikov A, Mariotto A et al: Quantifying the role of PSA screening in the US prostate cancer mortality decline. Cancer Causes Control 2008; **19:** 175.
29. Kohestani K, Mansson M, Arnsrud Godtman R et al: The GÖTEBORG prostate cancer screening 2 trial: a prospective, randomised, population-based prostate cancer screening trial with prostate-specific antigen testing followed by magnetic resonance imaging of the prostate. Scand J Urol 2021; **55:** 116.
30. Mattsson B and Wallgren A: Completeness of the Swedish Cancer Register. Non-notified cancer cases recorded on death certificates in 1978. Acta Radiol Oncol 1984; **23:** 305.