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Opportunistic Testing Versus Organized Prostate-specific Antigen Screening: Outcome After 18 Years in the Göteborg Randomized Population-based Prostate Cancer Screening Trial

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Abstract

Background: It has been shown that organized screening decreases prostate cancer (PC) mortality, but the effect of opportunistic screening is largely unknown.

Objective: To compare the ability to reduce PC mortality and the risk of overdiagnosis between organized and opportunistic screening.

Design, setting, and participants: The Göteborg screening study invited 10 000 randomly selected men for prostate-specific antigen (PSA) testing every 2 yr since 1995, with a prostate biopsy recommended for men with PSA ≥ 2.5 ng/ml. The control group of 10 000 men not invited has been exposed to a previously reported increased rate of opportunistic PSA testing. Both groups were followed until December 31, 2012.

Outcome measurements and statistical analysis: Observed cumulative PC incidence and mortality rates in both groups were calculated using the actuarial method. Using historical data from 1990–1994 (pre-PSA era), we calculated expected PC incidence and mortality rates in the absence of any PSA testing. The number needed to invite (NNI) and the number needed to diagnose (NND) were calculated by comparing the expected versus observed incidence and mortality rates.

Results and limitations: At 18 yr, 1396 men were diagnosed with PC and 79 men died of PC in the screening group, compared to 962 and 122, respectively, in the control group. In the screening group, the observed cumulative PC incidence/mortality was 16%/0.98% compared to expected values of 6.8%/1.7%. The corresponding values for the control group were 11%/1.5% and 6.9%/1.7%. Organized screening was associated with an absolute PC-specific mortality reduction of 0.72% (95% confidence interval [CI] 0.50–0.94%) and relative risk reduction of 42% (95% CI 28–54%). There was an absolute reduction in PC deaths of 0.20% (95% CI –0.06% to 0.47%) and a relative risk reduction of 12% (95% CI –5 to 26%) associated with opportunistic PSA testing. NNI and NND were 139 (95% CI 107–200) and 13 for organized biennial screening and 493 (95% CI 213–1563) and 23 for opportunistic screening. The extent of opportunistic screening could not be measured; incidence trends were used as a proxy.

Conclusions: Organized screening reduces PC mortality but is associated with overdiagnosis. Opportunistic PSA testing had little if any effect on PC mortality and resulted in more overdiagnosis, with almost twice the number of men needed to be diagnosed to save one man from dying from PC compared to men offered an organized biennial screening program.

Patient summary: Prostate-specific antigen (PSA) screening within the framework of an organized program seems more effective than unorganized screening.

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1. Introduction

It has been shown that screening for prostate cancer (PC) with prostate-specific antigen (PSA) testing reduces PC-specific mortality but carries a high risk of overdiagnosis [1,2]. In the European Randomized Study of Screening for Prostate Cancer (ERSPC) at 13 yr of follow-up, 781 men needed to be invited to screening and 27 men needed to be diagnosed to prevent one PC death [2]. However, no country has yet introduced a national PSA-based screening program, so PSA measurements performed on asymptomatic men with no prior PC diagnosis, aside from those enrolled in organized screening trials, are taken as part of opportunistic PSA testing.

Several studies on breast and cervical cancer screening have indicated that opportunistic screening is less effective and less cost-effective than an organized approach [3–5] and the Council of the European Union has recommended that screening for breast, cervical, and colorectal cancer should be conducted in organized programs [6]. It is currently unknown whether opportunistic PSA testing is as effective as organized PSA screening in reducing PC mortality, and whether there is a relationship between organized screening versus opportunistic testing and the risk of overdiagnosis. Despite the lack of evidence in support of opportunistic screening, there is high uptake of this form of PSA testing in many Western countries [7–10]. According to a recent estimate, >50% of all Swedish men aged 55–69 yr

have had a PSA test [10], which has resulted in rapidly increasing PC incidence during the last decades [11,12].

The aim of this study was to investigate the effectiveness of organized and opportunistic screening in reducing PC mortality, measured as the number needed to invite (NNI), and the amount of overdiagnosis, estimated as the number needed to diagnose (NND), in the Swedish center of the ERSPC.

2. Patients and methods

After approval by the ethics committee at the University of Gothenburg in 1994, the Göteborg randomized population based prostate cancer screening trial was established in 1995 (registered as Current Controlled Trials ISRCTN54449243). Since 1996, the study has contributed to the Swedish arm of ERSPC. The Göteborg study has previously been described in depth [1]. In summary, 20 000 of the men recorded in the population register as living in Gothenburg (born 1930–1944) were computer-randomized, 10 000 to a screening group and 10 000 to a control group. No informed consent was deemed necessary before randomization. Men in the screening group received written information about PSA screening together with an invitation to participate every 2 yr. Men with PSA above a threshold (2.5 ng/ml since 2005) [1] were recommended further urological work-up including prostate biopsy (Fig. 1). The upper age limit for invitation was 67–71 yr (mean 69 yr).

Information on mortality, migration outside Sweden, and PC diagnosis was obtained every 3 mo by linkage of the study database to the Swedish population registry, the Swedish cancer registry (SCR), and the regional cancer registry. The SCR has high accuracy, with

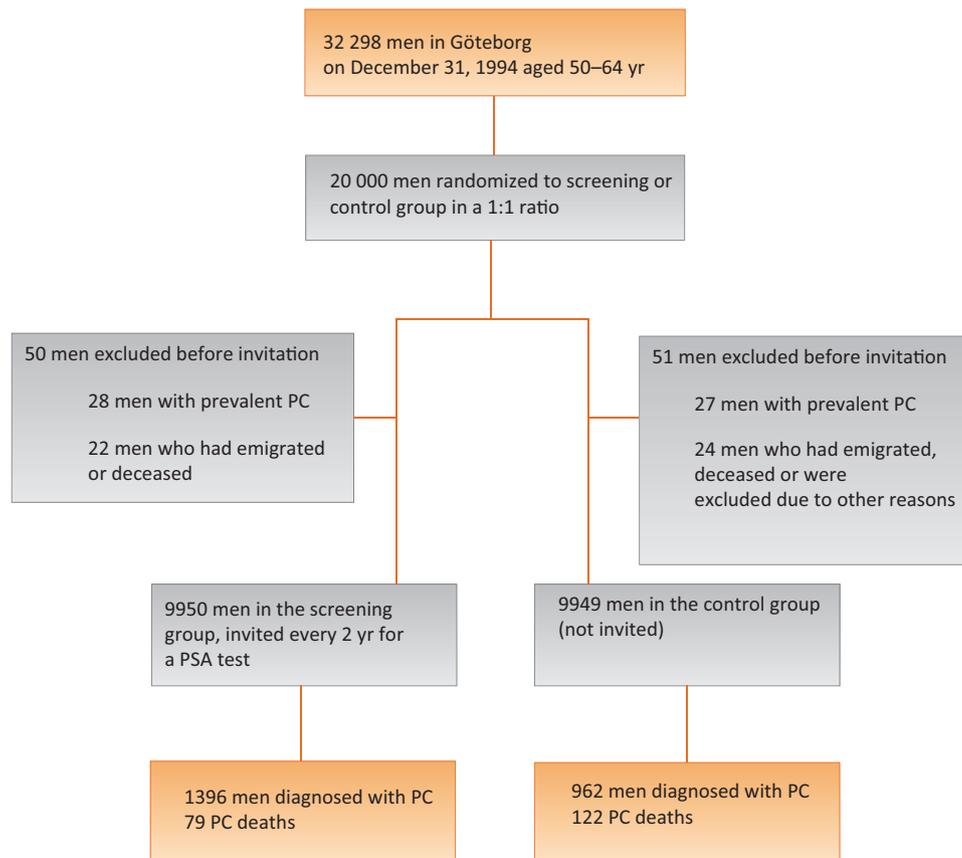


Fig. 1 – Consolidated Standards of Reporting Trials (CONSORT) diagram for the Göteborg randomized population-based prostate cancer screening trial. PSA = prostate-specific antigen; PC = prostate cancer.

Table 1 – Prostate cancers diagnosed in the study groups

	Screening group		Control group	
Men randomized (n)	10000		10000	
Men invited (n)	9950		9949	
Prostate cancer cases (n)	1396		962	
Median age at diagnosis (yr)	65.8		67.8	
Median PSA at diagnosis (ng/ml)	4.9		8.7	

	Prostate cancer cases, n (%)		Prostate cancer cases, n (%)	
	Screen-detected	Not screen-detected	Screen-detected	Not screen-detected
Number	1022 ^a	374	361	601 ^b
Low risk ^c	613 (60)	84 (22)	128 (35)	125 (21)
Intermediate risk ^d	331 (32)	138 (37)	168 (47)	192 (32)
High risk ^e	63 (6.2)	73 (19)	42 (12)	127 (21)
Advanced ^f	13 (1.3)	54 (14)	10 (2.8)	107 (18)
Unknown	2 (0.2)	25 (6.7)	13 (3.6)	50 (8.3)
Prostate cancer deaths	79		122	

PSA = prostate-specific antigen.

^a Includes nine cases detected as a result of an erroneous invitation.

^b Includes eight cases diagnosed at autopsy.

^c T1, not N1 or M1, Gleason score ≤ 6 , and PSA < 10 ng/ml.

^d T1–2, not N1 or M1, and Gleason score ≤ 7 and/or PSA < 20 ng/ml.

^e T1–4, not N1 or M1, and Gleason score ≥ 8 and/or PSA < 100 ng/ml.

^f N1 and/or M1 and/or PSA ≥ 100 ng/ml.

underreporting at only 3.7% [13]. In men diagnosed with PC from the screening group and the control group, clinical data and the reason for diagnosis were prospectively collected. Cause of death among men with PC was ascertained from medical records using a standard algorithm [14].

The median time to diagnosis was calculated with the Kaplan-Meier method. The time to diagnosis was calculated from the study start (January 1, 1995) to the date of diagnosis. The log rank test was applied to test the difference in time to diagnosis. Expected PC incidence and mortality in the absence of PSA screening were predicted using historical data from the SCR on PC incidence and PC mortality from Statistics Sweden for the period 1990–1994. We used 1-yr age-group incidence and mortality rates to mirror the actual age distribution in all randomized men. To adjust for exclusion of prevalent PC cases, we used the observed mortality rate for prevalent cases and subtracted this from the expected mortality. Expected cumulative mortality and incidence were estimated as 1 minus the Ederer II survival estimate [15]. Observed cumulative PC incidence and mortality were calculated as 1 minus the actuarial survival estimate. Follow-up time was calculated from study start (January 1, 1995) to date of an event (PC diagnosis or PC death). Men who did not have an event were censored (date of death, emigration, or December 31, 2012). Standard errors were estimated using the Greenwood method [16]. Confidence intervals (CIs) were calculated on the log cumulative hazard scale and transformed back to the survival scale. We used the notions NNI, as the analysis was an intention-to-screen analysis, and NND, as a large proportion of the screen-detected PCs were followed via active surveillance [17]. NNI for organized screening was calculated as 1/expected minus observed cumulative mortality in the screening group. NNI for opportunistic screening was calculated in the same way but for the control group. In this group, NNI does not relate to the number of men invited but rather expresses the number of men in the control group exposed to opportunistic screening to prevent one PC death. NND for organized and opportunistic screening was calculated as 1/(mortality reduction \times excess incidence) when comparing the observed and expected cumulative PC incidence in each group. NNI and NND for organized screening were calculated for the last 7 yr of follow-up, but NNI and NND for opportunistic screening could only be calculated after 15 yr, as this was

the first time at which the observed mortality was lower than the expected mortality (Table 2). CIs for NNI were calculated according to Altman and Andersen [18]. When calculating CIs for the absolute and relative risk reduction, the standard error (SE) for the expected values was assumed to be zero, as the expected mortality was based on the whole population in Gothenburg. The 95% CI for the absolute risk reduction was calculated as expected minus observed cumulative mortality $\pm 1.96 \times SE_{\text{observed}}$. The 95% CI for the relative risk reduction was calculated as $100 \times (1 \text{ minus the upper limit of the 95\% CI for observed mortality/expected mortality})$ and $100 \times (1 \text{ minus the lower limit of the 95\% CI for observed mortality/expected mortality})$. Statistical analyses were performed using STATA Statistical Software 12.1 (StataCorp, College Station, TX, USA) and IBM SPSS Statistics 20 (IBM, IBM Corp., Somers, NY, USA).

3. Results

Following randomization, a total of 101 men were excluded (Fig. 1). During 18 yr of follow-up, 1396 men were diagnosed with PC in the screening group, of whom 1022 were diagnosed as a result of organized screening, compared to 962 cancer cases detected among controls, of whom 361 were asymptomatic men diagnosed by opportunistic screening. In the screening group, 87% complied with the biopsy recommendation. The median age and PSA at diagnosis were 65.8 yr (interquartile range [IQR] 62.2–68.3 yr) and 4.9 ng/ml in the screening group, and 67.8 yr (IQR 64.2–71.3 yr) and 8.7 ng/ml, respectively, in the control group. The median time from randomization to diagnosis was 8.6 yr in the screening group and 10.3 yr in the control group ($p < 0.001$). The observed cumulative incidence of PC in the screening group and control group at 18 yr was 16% and 11%, and the expected PC incidence was 6.8% and 6.9%, respectively (Fig. 2). Tumors detected by opportunistic screening were more advanced than those detected by organized screening (Table 1).

Table 2 – Number needed to invite (NNI) and number needed to diagnose (NND) for different follow-up lengths

	Follow-up						
	12 yr	13 yr	14 yr	15 yr	16 yr	17 yr	18 yr
NNI^a							
Screening	1/(0.00620 – 0.00403) = 461	1/(0.00739 – 0.00489) = 400	1/(0.00885 – 0.00502) = 261	1/(0.01056 – 0.00592) = 216	1/(0.01245 – 0.00713) = 188	1/(0.01458 – 0.00850) = 164	1/(0.01695 – 0.00977) = 139
Control	–	–	–	1/(0.01067 – 0.00972) = 1053	1/(0.01255 – 0.01171) = 1190	1/(0.01471 – 0.01349) = 820	1/(0.01707 – 0.01504) = 493
NND							
Screening	NNI × (0.10970 – 0.03053) = 36	NNI × (0.11969 – 0.03566) = 34	NNI × (0.12689 – 0.04126) = 22	NNI × (0.13663 – 0.04740) = 19	NNI × (0.14636 – 0.05383) = 17	NNI × (0.15449 – 0.06075) = 15	NNI × (0.16145 – 0.06819) = 13
Control	–	–	–	NNI × (0.09125 – 0.0480) = 46	NNI × (0.10042 – 0.05437) = 55	NNI × (0.10917 – 0.06130) = 39	NNI × (0.11456 – 0.06874) = 23

^a NNI could not be assessed before 15 yr of follow-up because no mortality reduction was discernible before that point in time.

In the screening group, 79 men died from PC, compared to 122 men in the control group. The observed cumulative PC mortality at 18 yr in the screening group and control group was 0.98% and 1.5%, and the expected PC mortality was 1.7% and 1.7%, respectively. Organized screening resulted in pronounced mortality reduction, with absolute reduction of 0.72% (95% CI 0.50–0.94%) and relative risk reduction of 42% (95% CI 28–54%). Exposure to an increasing rate of opportunistic PSA testing, as documented in previous reports relevant to our control group [9,10], did not result in any significant difference between the observed and expected PC mortality during any period of the follow-up (absolute reduction of 0.20% [95% CI –0.06% to 0.47%], relative risk reduction 12% [95% CI –5% to 26%]; Fig. 3).

After 18 yr, NNI and NND were 139 (95% CI 107–200) and 13 for organized screening, and 493 (95% CI 213–1563) and 23, respectively, for opportunistic screening. NNI and NND between the screening and control group were 190 (95% CI 115–549) and 9 (Table 2).

4. Discussion

To the best of our knowledge, this is the first study comparing organized and opportunistic PSA screening using NNI and NND. The results indicate that similar to breast and cervical cancer screening, organized screening is more effective than opportunistic screening in reducing disease-specific mortality. After 18 yr, PC incidence in the control group had increased by almost 70% compared to the pre-screening era, indicating considerable uptake of opportunistic screening in the control group. This is further supported by the fact that almost 40% of the cancers in the control group were diagnosed through opportunistic screening in asymptomatic men. It is likely that many more men in the control group reporting modest micturition symptoms were also actually screen-detected. The increase in incidence was apparent by 3 yr after the study start (Fig. 2). Despite this large increase, the observed PC mortality in the control group was never significantly lower

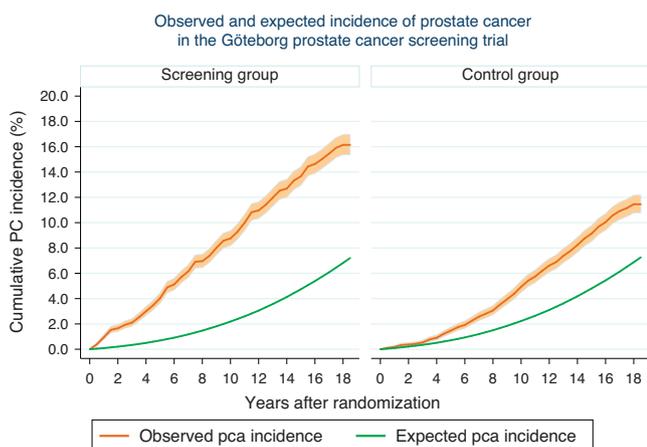


Fig. 2 – Observed and expected prostate cancer incidence analyzed up to December 31, 2012 (n = 19 899). Expected values are based on incidence in Gothenburg 1990–1994. The shaded area denotes the 95% confidence interval. PC = prostate cancer.

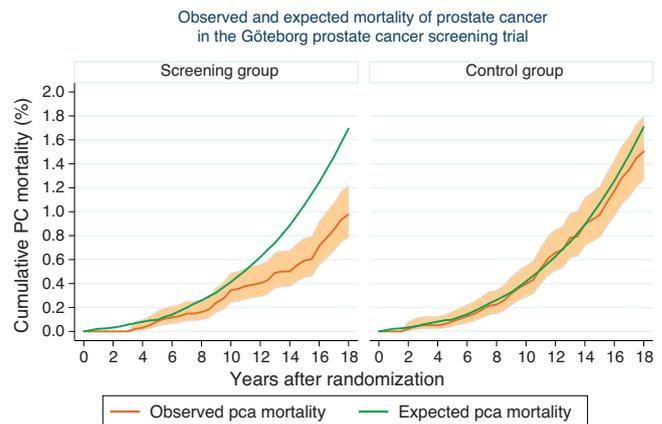


Fig. 3 – Observed and expected prostate cancer mortality analyzed up to December 31, 2012 (n = 19 899). Expected values are based on PC mortality in Gothenburg 1990–1994 minus PC mortality due to prevalent cases. The shaded area denotes the 95% confidence interval for the observed cumulative mortality. PC = prostate cancer.

than the expected mortality, while men randomized to organized screening had a relative risk reduction of 42% for PC death (Fig. 3). In the screening group, NNI to prevent one PC death was 139 at 18 yr. The corresponding value in the control group was 493. This large discrepancy in NNI shows the difference in the ability to reduce PC mortality between organized and opportunistic PSA screening. More important is the difference in NND, as it reflects the rate of overdiagnosis. Almost twice the number of men needed to be diagnosed to save one man from dying from PC with opportunistic screening compared to men offered an organized biennial screening program (NND 23 vs 13). When the screening group was instead compared to the control group, NNI and NND were 190 and 9, respectively, at 18 yr. These data show that the background use of PSA testing in the control group results in underestimation of both the mortality reduction and the amount of overdiagnosis (measured as NND) when the screening group is compared to the control group. Our results also suggest that opportunistic screening detects tumors at a later stage when compared to organized screening, as the men in the control group were older at diagnosis and screen-detected tumors in the control group were more advanced than those in the screening group (Table 1).

There are several possible explanations for why opportunistic screening is less effective in reducing mortality, including inadequate screening intensity, screening of a population who would not benefit from screening because of comorbidity and/or age, inadequate follow-up after a positive screening, and less effective treatment. The importance of screening intensity has been demonstrated in several other studies. Stattin et al [19] recently showed that more intense opportunistic screening resulted in lower PC mortality when compared to less intense opportunistic screening. The relative risk of PC mortality in high- versus low-incidence counties, adjusted for time period, was 0.81 [19]. Results from separate centers in the ERSPC trial also support more intense screening. The Swedish and Dutch centers, which have the most intense screening algorithms, are also the two centers that have reported the largest mortality reductions [1,2,20]. Conversely, the Finnish center, which has a less intense algorithm, has reported much lower mortality reduction [21]. Comparison of the Swedish and Finnish centers is interesting, as there are large similarities in the background populations, the same randomization procedure has been applied, and the countries have similar health care systems. The large mortality reduction in Sweden (44%) compared to the more modest reduction in Finland (15%) can probably be partly explained by different screening intensities [1,21].

Our results stand in contrast to results from the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial, which could not show any difference in PC mortality between men randomized to organized screening and those randomized to a control group (opportunistic screening) [22]. There are several possible explanations for these results. The most important is probably that the PLCO population was heavily prescreened: approximately 44% of men in the trial had at least one PSA test before the study

started [23]. This prescreening probably reduced the number of aggressive and deadly PCs, making it more difficult to show a difference in mortality. Although the PLCO included four times as many men as the Göteborg study and men in the PLCO were older, the number of PC deaths in the PLCO study was only just over double that in the Göteborg study [1,22]. This clearly indicates that the opportunistic screening that had taken place in the USA before the PLCO study start was effective in identifying men at risk of dying from PC and strongly reduced the baseline risk of a randomized man dying from PC. This is also supported by the fact that the PC death rate in the USA has decreased by more than 40% from its peak in 1993 [24]. Even if it is debatable how much of this decrease is associated with PSA screening, it is clear that the widespread screening in the USA has substantially contributed to the PC mortality reduction [25]. In our study, opportunistic screening did not result in a mortality reduction similar to that in the USA, and Sweden, which has one of the highest PC mortality rates in the world, has had almost stable PC mortality since the 1960s [11]. This raises the question of why opportunistic screening has led to a reduction in PC mortality in the USA but not in Sweden. The most probable explanation is that opportunistic screening has been more intense in the USA. Another possible explanation is less effective and aggressive treatment, especially of locally advanced/high-risk disease. This risk group is more common among those detected with opportunistic screening than with organized screening (Table 1). It has been reported that only 18% of those with locally advanced disease in Sweden received curative treatment [26], compared to 49% reported from the Surveillance, Epidemiology and End Results registry in the USA [27]. Our results are also in contrast to two studies that investigated whether more aggressive PC screening and treatment in the Seattle area led to lower PC mortality than in Connecticut, which had less intense screening and treatment. The results revealed no difference in PC mortality after 11 yr and 15 yr of follow-up [28,29]. However, the difference in screening intensity between the two areas was probably too small (rate ratio 1.35) and the men included were probably too old (>65 yr) to detect a beneficial effect of screening.

A major strength of the present study is that it is randomized and population-based, and the groups should therefore be comparable. As men in the control group were not aware of their participation in a PSA screening trial, their pattern of PSA testing should mirror the pattern of opportunistic PSA screening among urban Swedish men of the same age during this period. The comparison with historical data has weaknesses of course. We cannot rule out the possibility that changes in the recording, treatment, and natural course of PC occurred during the study period; however, both groups were compared with the same historical population, so any difference would affect both groups identically and should not have influenced the overall results. We regard the comparison with a historical population as a major strength, as it gives a unique possibility to estimate the effect of screening in comparison with a situation without screening. The proportion of men

who had taken a PSA test before the study start has been estimated at only 3% [1], and the increase in PC incidence, indicating a rise in PSA screening in Sweden, started around 1997. The main limitation of the study is that we were unable to directly measure the extent and pattern of opportunistic screening and prostate biopsies in our control group and instead used incidence trends. Incidence trends have been used in other studies to estimate screening intensity [10,19]. One of these studies reported that the cumulative uptake of opportunistic PSA screening in Sweden for men aged 55–69 yr increased from zero in 1997 to 56% in 2007 [10]. In the Swedish national prostate cancer register, 46% of all PCs in 2012 were diagnosed in asymptomatic men at health check-ups, indicating that opportunistic screening is common in Sweden [30]. In our study, compliance with biopsy recommendation following a positive screening test was high (87%) in the screening group. The corresponding value for opportunistic screening in the control group is unknown, but is likely to be much lower. In the Dutch center of the ERSPC, only 7–8% of those with PSA ≥ 3.0 ng/ml in the control arm underwent biopsy within 6 mo [31]. It could be argued that the results regarding opportunistic screening are only applicable to opportunistic screening performed in a comparable way to that for our control group. However, the incidence and mortality trends seen in Sweden are not unique and resemble those seen in several other European countries, such as Finland, Germany, and the Netherlands, indicating that our results can be generalized [11]. There is no universally agreed method for estimating overdiagnosis. In the present paper, we used NND as an estimate. If overdiagnosis had instead been estimated as the excess incidence after introducing screening, it would have appeared as if opportunistic screening were associated with less overdiagnosis than organized screening. If reducing overdiagnosis were only about minimizing the numbers of men being diagnosed with PC, opportunistic screening would seem to be a reasonable alternative. However, we believe that it is important to relate excess incidence to the beneficial effects of screening, and while organized screening effectively reduced PC mortality, opportunistic screening had no or only a very limited effect on PC mortality during 18 yr of follow-up. Therefore, when excess incidence was related to the mortality reduction and overdiagnosis estimated as NND, opportunistic screening resulted in more overdiagnosis than organized screening (NND 23 vs 13). Concerns have also been raised about whether the difference in mortality between the study arms could be attributable to different treatments policies in the two arms. However, the absolute majority of men in both arms of the Göteborg study were treated in the same university hospital. Thus, even if such an effect cannot be completely ruled out, it should have only a minor impact on the outcome [1].

5. Conclusions

Our results indicate that organized intense screening effectively reduces PC mortality but is associated with considerable overdiagnosis; after 18 yr of follow-up, 13 men must be diagnosed to prevent one PC death compared to a

situation with no PSA testing. Opportunistic PSA testing had little if any effect on PC mortality, and was associated with greater overdiagnosis in comparison to organized screening, as estimated by NND. If, after careful counseling, a man chooses to participate in PSA screening, this should be in an organized program at relevant intervals combined with adequate follow-up. Our data suggest that opportunistic PSA testing causes considerable harm and leads to little if any benefit.

Author contributions: Rebecka Arnsrud Godtman 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.

Study concept and design: Arnsrud Godtman, Stranne, Hugosson.

Acquisition of data: Arnsrud Godtman, Holmberg, Hugosson.

Analysis and interpretation of data: Arnsrud Godtman, Holmberg, Lilja, Stranne, Hugosson.

Drafting of the manuscript: Arnsrud Godtman, Stranne, Hugosson.

Critical revision of the manuscript for important intellectual content: Arnsrud Godtman, Holmberg, Lilja, Stranne, Hugosson.

Statistical analysis: Arnsrud Godtman, Holmberg.

Obtaining funding: Arnsrud Godtman, Lilja, Hugosson.

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