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Costs of screening for prostate cancer: evidence from the Finnish Randomised study of Screening for Prostate Cancer after 20 years of follow-up using register data

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ABSTRACT

Objectives

Few empirical analyses of the impact of organised prostate cancer (PCa) screening on healthcare costs exist, despite cost-related information often being considered as a prerequisite to informed screening decisions. Therefore we estimate the differences in register-based costs of publicly-funded healthcare in the two arms of the Finnish Randomised study of Screening for Prostate Cancer (FinRSPC) after 20 years.

Methods

We obtained individual-level register data on prescription medications, as well as inpatient and outpatient care, to estimate healthcare costs for 80,149 men during the first 20 years of the FinRSPC. We compared healthcare costs for the men in each trial arm and performed statistical analysis.

Results

For all men diagnosed with PCa during the 20-year observation period, mean PCa-related costs appeared to be around 10% lower in the screening arm (SA). Mean all-cause healthcare costs for these men were also lower in the SA, but differences were smaller than for PCa-related costs alone, and no longer statistically significant. For men dying from PCa, although the difference was not statistically significant, mean all-cause healthcare costs were around 10% higher. When analysis included all observations, cumulative costs were slightly higher in the CA, however, after excluding extreme values, cumulative costs were slightly higher in the SA.

Conclusions

No major cost impacts due to screening were apparent, but the FinRSPC's 20-year follow-up period is too short to provide definitive evidence at this stage. Longer-term follow-up will be required to be better informed about the costs of, or savings from, introducing mass PCa screening.

Introduction

Although there is some evidence of the effectiveness of organised screening in reducing prostate cancer (PCa) mortality (1), there has been a dearth of published empirical analyses of the actual impact of such mass screening on healthcare costs in real-world settings. Prostate-specific antigen (PSA) –based screening potentially provides a means of altering the clinical course of the PCa and thereby improving prognosis and outcomes (2). However, a presumption is often made that early intervention will reduce healthcare costs overall ((2), (3) and (4)), and this presumption should be assessed, ideally through a pragmatic randomised controlled trial (RCT) ((5) and (6)).

The primary objective of this analysis is to compare register-based healthcare cost estimates between the two arms of the Finnish Randomised Study of Screening for Prostate Cancer (FinRSPC), primarily using intention-to-screen (ITS) –analysis after a maximum of 20 years of follow-up.

Methods

Participants and intervention

Although the European Randomized study of Screening for Prostate Cancer (ERSPC) offers comparable data from each participating centre on outcome measures such as PCa mortality (1), it is unlikely that the ERSPC can offer comparable data on healthcare costs, as costs are known to be dependent on the healthcare system in question (7). Given such differences in cost accounting and costs even within Europe, and the well-established registers of healthcare cost-related information in Finland, our study is restricted to the FinRSPC, which contributes the largest number of trial participants to the ERSPC. The analysis of healthcare costs presented here is carried out as part of the FinRSPC, the primary objective of which is to investigate the impact of mass PSA-screening on PCa mortality (8). Secondary objectives of the FinRSPC include the investigation of the trial's impact on costs and health-related quality-of-life, and then the combination of these sources of information to provide information on cost-effectiveness (9). The target population of the FinRSPC was selected from the Finnish population registry and consists of men born in 1929–1944 and residing in the Helsinki or Tampere region during the recruitment period (1996–99, total randomised

n=80,458). The main exclusion criterion was PCa-diagnosis before the date of randomisation (this information was obtained from the Finnish Cancer Registry, (FCR)). Further details about the study design can be obtained from Booth et al. (10). The men in the screening group (screening arm, SA) were invited to the screening test (serum PSA) at a local clinic. The men in the reference group (control arm, CA) received no invitation as part of the trial.

Materials and analytical methods

The research protocol for the current study was approved by Finnish data-protection authorities and by the National Institute for Health and Welfare (THL). The protocol was also reviewed by the Tampere University Hospital Ethics committee (reference number R05053). After receiving study approval, we were permitted to collate and link the data supplied by a number of registries to the FinRSPC database, using each man's unique Finnish personal identity code for retrieval. This study was undertaken in close co-operation with the FCR, with resources and expertise from the FCR helping to create, maintain and improve the FinRSPC trial database and its links with the FCR's cancer register (11). The main data sources used in this study are described in the **Appendix**: these are the FinRSPC trial database, the Care Register for Health Care (CRHC) and the prescription-medicine reimbursement register (PMRR). The costs of the screening intervention have been estimated to be approximately 50 euros per screen (including the organisation of the invitation, the drawing of the blood sample and the PSA determinations) and this figure is used in all analyses. All total or average euro amounts we report in our results are rounded to the nearest 100 euros, as this gives a suitable level of precision for these cost estimates. The information on screening and healthcare costs from all the above sources is specific to each man in the trial and the date of each cost item is also recorded. PCa-related costs could be identified using the PCa identifier available in the PMRR and, in the case of the CRHC data, using the ICD-10 code C61. We followed cost-analysis guidelines for the analysis of costs ((14), (15), (16) and (17)) and examined differences between the arms using two-sided two-sample *t*-tests, with bootstrapping where appropriate to confirm the robustness of our results (18).

Results

Altogether there were 31,867 men in the SA and 48,282 men in the CA (Figure 1). Cost-related data were recorded in at least one of the registers used for 48,097 men in the CA (100%) and 31,753 men in the SA (100%). Cost records were not found for 198 men in the CA and for 119 men in the SA. These men may not have used hospital care or may not have been reimbursed for prescription medications during this follow-up period. No records from either register were found for one man in the SA who was diagnosed with, and subsequently died of, PCa. The frequencies of primary treatments were as follows: surgery (SA 26%, CA 19%), radiotherapy (SA 35%, CA 40%), endocrine treatment (SA 15%, CA 20%) and expectant management (SA 23%, CA 18%), with primary treatment missing for 1–2% of men in each arm.

After 20 years of follow-up, health care costs were around 40% higher on average for men diagnosed with PCa, and around 70% higher on average for men who died from PCa, compared to all men in the trial (Table 1). The mean healthcare costs of the 80,149 men in the FinRSPC did not differ markedly between the arms, but a statistically significant difference, with lower costs in the CA, was observed when 'extreme observations' were excluded from our analysis (Table 1). However, the difference between the two arms in terms of cumulative all-cause costs appears to be small (Figure 2). Further, all-cause healthcare costs for men diagnosed with PCa, adjusted for the number of men in each arm, were higher in the SA, with a steadily increasing differential (Figure 3). Similarly, higher PCa-related cost estimates were seen for diagnosed men in the SA, with noticeable differences at follow-up years 1, 4 and 8 (corresponding to the screening rounds) (Figure 4). For healthcare costs of men who died from PCa during the follow-up, the difference increased after follow-up years 5 and 10 (corresponding to a year or more after the first and second screening rounds), with higher costs for the SA (Figure 5). Similar findings were obtained when the graph for the men who eventually died from PCa was restricted to focus only on PCa-related average costs (Figure 6).

In Table 1 we also use the risk classification utilised by the ERSPC to show how the PCa-related cost estimates for all diagnosed men vary with risk-stage at diagnosis. When comparing average PCa-related cost estimates for all diagnosed men there is a statistically significant difference, with the SA incurring

lower costs. However, this result is not observed for all the separate risk-stage subgroups. The mean cost estimates for PCa-related healthcare for men with low-risk, intermediate-risk, high-risk, or metastatic tumours at diagnosis and those for men with tumour information missing at diagnosis, although not statistically significant, are either higher for the CA, higher for the SA, or do not show differences in mean costs. As an adjunct to the ITS analysis, for the SA we report the mean costs for both those prostate cancers detected due to screening (SD) and for clinically-detected PCa (CD) (Table 1). The effect sizes presented indicate that the comparison of PCa-related costs for men who died from PCa has the largest effect size (i.e., substantive significance, as indicated by the Cohen's *d* -measure), although this comparison of means did not achieve conventional levels of statistical significance (Table 1).

Discussion

For all men diagnosed with PCa, screening reduced mean PCa-related costs (by around 1100€, or less than 10% (see Table 1)). However, classification of PCa-related costs by risk stage at diagnosis indicates that this result may be subject to a 'reversal paradox' (19), whereby this overall result may not faithfully represent the direction or size of each of the risk-stage subgroups. Further, for all diagnosed men, the reduction in mean all-cause healthcare costs was less than when focussing on PCa-related costs alone (i.e., around 700€, or around 1%). In addition, cumulative PCa-related healthcare cost estimates for these same diagnosed men, adjusted for the number of men in each trial arm, were slightly higher in the SA (around 100€, or less than 10% (see Figure 4)).

Two important issues need to be considered when interpreting all our findings, first and foremost, the sample size required to show statistically significant results, secondly, opportunistic PSA testing (also known as contamination). Firstly, the statistical power calculations for the FinRSPC are based on the primary outcome of disease-specific mortality. Therefore, the FinRSPC is not powered to evaluate all-cause costs, any more than it is suitably powered to detect differences in all-cause mortality, as only a minority of total mortality is directly related to PCa. In addition, the original sample-size estimates would likely need to be at least doubled in order to take into account the unexpected levels of contamination encountered in the trial (20), alternatively, the duration of follow-up would need to be extended beyond 20 years. Further, the comparisons of the relatively small subgroup of men who died from PCa (N=925) have fairly low precision given the observed heterogeneity in costs between patients. Secondly, unorganised or non-systematic PSA-testing can dilute the observed effect of the mass-screening intervention. Instead of the comparator being a complete absence of screening, the comparator in the FinRSPC is less organised and less systematic screening. Widespread contamination likely dilutes PCa-mortality benefit, any differences in health-related quality of life, as well as the differences in costs observed here. Therefore, our results should be interpreted against the possibility of high levels of contamination in the CA, reflected for instance in the high cumulative incidence (4.5%) of T1c cancers (impalpable cancers detectable only by PSA testing (21)) in the CA (22).

It should also be noted that for men diagnosed with PCa, the overall costs were higher for the SA than for the CA, when adjusted for the size of each trial arm (figures 3 and 4), even though the mean healthcare costs for all men diagnosed with PCa were lower in the SA (Table 1). Importantly, these all-cause cumulative cost differentials could be explained by men with indolent disease being followed up clinically over extensive periods of time due to overdiagnosis. These cases could also involve some lead-time, increasing total costs. Similarly, the higher mean PCa-related costs in the SA men who died from PCa could be due to some of these first 925 recorded PCa deaths including some of the more aggressive and rapidly progressing cancers. Precision medicine, with treatment tailored to the underlying molecular aberrations, holds promise for treating advanced PCa, but such interventions are currently at a largely experimental stage and not widely used. Targeted treatment has the potential to change the economic impact of screening, but currently it is impossible to predict whether early detection by screening will allow definitive treatment (with its potential for cost savings, increased life expectancy, or improved quality of life), or merely delay disease progression (with its potential for increasing costs or decreased quality of life). In large part, any impact on costs will depend on both the differences in the time patients live with advanced PCa, as well as on the relative mortality, between the two trial arms.

One further interpretation of our risk-stage subgroup analysis and analysis of screen-detected versus clinically-detected PCa (Table 1, and from other analyses not reported here due to restricted space), suggests men in the SA diagnosed via PSA-screening could have received more systematic care, or just more care in general, than those men in the CA. Analysis suggests that mean all-cause healthcare costs were lower for men with screen-detected PCa than for men in the screening arm overall, and lower for men with screen-detected low-risk tumour at diagnosis than for men in the screening arm overall. However, for all other diagnosed men, mean healthcare costs were higher amongst men with screen-detected prostate cancer than for men in the screening arm overall. Further, the increasing differential observed in all-cause cost estimates for men diagnosed with PCa could also be explained by the screening intervention resulting in an increased awareness of health issues, or simply an increased supply of, or demand for, health services not directly related to PCa.

Strengths of the study

The novelty of our results is emphasized by the fact that a systematic literature search failed to identify studies reporting the analysis of real-world data on PCa-screening related healthcare costs from any RCT, despite finding a number of studies on related topics (e.g., (23), (24), (25), (26), (27), (28), (29), (30) and (31)).

Modelling studies, such as those found during our systematic search, offer estimates or forecasts of costs which are based on assumptions, which often, in turn, are based on modelled estimates of primary or secondary outcomes. On the other hand, our analysis describes the cost data recorded on the basis of observed outcomes. Such description will have relevance for economic evaluation using data from other ERSPC countries to the extent that, e.g., trial protocols are comparable. For this reason, despite only being from one participating centre in the ERSPC, our results may still be highly indicative of the relative difference in costs between the trial arms in other European countries. We were able to apply ITS analysis on a large and representative population over a 20-year period, with fairly comprehensive data on costs of hospital-care and prescription medication use and, hence, obtain accurate and potentially generalizable cost estimates. Further, our data-driven approach requires few assumptions concerning costs or outcomes for the men followed up in the FinRSPC over 20 years. Our data also capture most costs arising from the major disadvantage of PSA screening, i.e., the overdiagnosis of indolent PCa. This is evidenced by, e.g., the overall costs due to PCa being higher in the SA than in the CA (Figure 3 and Figure 4), despite men in the SA having lower PCa-related mean costs (Table 1). Although the precision of our results is adversely affected by the observed heterogeneity in costs, we have extensive observations from a publicly-funded and centralised healthcare system, with highly comparable data over the study period.

Limitations of the study

Firstly, our study covers a period which included major changes in PCa-treatment protocols. However, this limitation would be true of any pragmatic study in this field. The CRHC does not always provide sufficient

information on procedures to provide precise details of all treatments for all periods, therefore we reported the frequencies of primary treatments using the high-quality FinRSPC trial database.

Secondly, we were unable to cover primary healthcare costs because, until recently (2014), no national primary healthcare registers or databases existed in Finland. Although data including primary-care costs were collected using questionnaires alongside the FinRSPC (10), that questionnaire data does not provide comparable data to the data used in this register-based study. However, the main responsibility for PCa management is with tertiary care, including the most expensive therapeutic procedures. A related limitation is the possibly limited applicability of our analysis outside the context of countries with mainly publicly-funded healthcare.

Thirdly, consistent cost weights were not available for each year during our study period. Although we used the 2009 cost weights for all years, and these weights were not adjusted in any way, not accounting for health-sector inflation and not undertaking discounting, it seems unlikely that this would have a large negative impact on the policy relevance of our study. Any such adjustments to the cost estimates would likely affect the two arms equally (32) and our choice to round these estimates to the nearest 100€ is likely to negate any such adjustments in any case (33). Perhaps most importantly, we have attempted to present costs in an appropriate manner for a policy-oriented readership.

Unfortunately, no robust method seems to exist to extrapolate the observed cost estimates from those men who have already died, to those who may die from PCa in the coming years (34). A related limitation is that although potentially declining during the study period, overdiagnosis or overtreatment may still be one contributing factor in our results (35). Despite such limitations, our estimates are expected to be indicative and representative of the main costs drivers in a publicly-funded healthcare system, even though they do not represent the exact costs of all services used as a result of screening. Further, the analysis presented here does not provide a definitive assessment of the impact of costs on PSA-based mass screening. The full impact of screening on health-care costs will only be clear after all the men are deceased, and the FinRSPC cohort is relatively immature in this respect (63% of men are still alive). Of all men, 1.2% had died from PCa during the 20-year follow-up period, while the expectation is that PCa mortality will eventually reach over 2% in this population (2).

Conclusion

No major cost impacts due to screening were apparent, but after 20 years of follow-up, the FinRSPC trial shows that for all diagnosed men, mean PCa-related costs were lower in the screening arm. However, in addition, mean healthcare costs for the men who died from PCa appear to be substantively higher in the screening arm. These estimates of differences in mean healthcare costs should be interpreted in the light of low statistical power, the effects of PSA-contamination within the trial, and with the knowledge that these estimates of average costs may be impacted by extreme observations and cover up differences between risk subgroups. In conclusion, the 20-year follow-up of this large cohort is too short to give definitive evidence about the healthcare costs of PSA screening. Longer-term follow-up will be required to be better informed about the costs of, or savings from, introducing PSA-based mass screening.

Figures and figure captions

Figure 1: Flowchart illustrating the groups for which register-based healthcare costs are estimated.

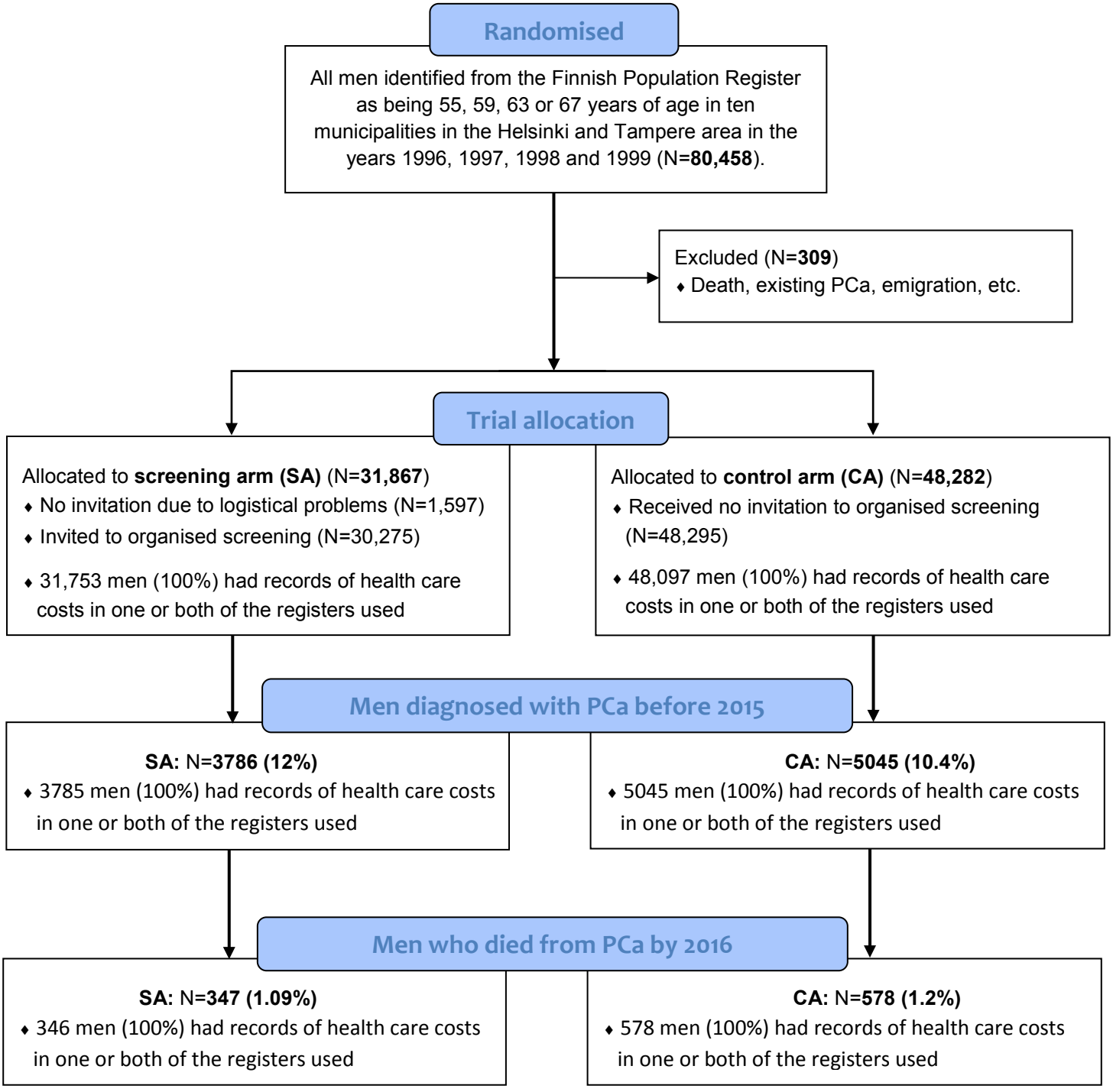

Figure 2: All-cause cost estimates of healthcare and medications between 1996 and 2016 for all men in the FinRSPC (N=80,149) by arm, cumulative average costs adjusted to the size of each trial arm.

Figure 3: All-cause cost estimates of healthcare and medications between 1996 and 2016 for men diagnosed with PCa in the FinRSPC by arm, cumulative average costs adjusted to the size of each trial arm.

Figure 4: PCa-related cost estimates of healthcare and medications between 1996 and 2016 for men diagnosed with PCa by arm, cumulative average costs adjusted to the size of each trial arm.

Figure 5: All-cause cost estimates of healthcare and medications between 1996 and 2016 for the men who have died from PCa, cumulative average costs per man who died from PCa in each trial arm.

Figure 6: PCa-related cost estimates of healthcare and medications between 1996 and 2016 for the men who have died from PCa, cumulative average costs per man who died from PCa in each trial arm.

Table

Table 1: Comparisons and statistical tests of the cost estimates

Estimated register-based healthcare costs	Median in CA *(IQR in CA)*	Median in SA *(IQR in SA)*	Mean in CA	Mean in SA	Difference between means *(standard error)*	Two-sided *t*-test	Cohen's *d* effect size	Mean in SA, according to mode of detection
All-cause cost estimates for **all men in the trial**	24,900 € *(32,700 €)*	25,400 € *(33,000 €)*	**36,500 €**	**36,300 €**	**-200 €** *(400 €)*	*p*=0.64	<0.01	N.R.
All-cause cost estimates for **all men in the trial** (excluding 'extreme' observations†)	24,900 € *(32,700 €)*	25,400 € *(33,000 €)*	31,800 €	32,200 €	**400 €** *(200 €)*	***p*<0.05**	≈0.01	N.R.
All-cause cost estimates for **diagnosed men**	39,200 € *(42,500 €)*	38,800 € *(40,500 €)*	**51,900 €**	**51,300 €**	**-600 €** *(1,100 €)*	*p*=0.59	≈0.01	**SD**: 50,300 € **CD**: 52,000 €
PCa-related cost estimates for **diagnosed men**	8,800 € *(12,800 €)*	7,700 € *(12,600 €)*	**15,300 €**	**14,200 €**	**-1,100 €** *(400 €)*	***p*<0.01**	≈0.06	**SD**: 14,700 € **CD**: 13,800 €
PCa-related cost estimates for men with **low-risk**†† tumour at diagnosis	5,900 € *(9,700 €)*	5,700 € (8,900 €)	11,600 €	11,000 €	**-600 €** *(600 €)*	*p*=0.35	≈0.04	**SD**: 11,400 € **CD**: 10,200 €
PCa-related cost estimates for men with **intermediate-risk** tumour at diagnosis	8,100 € *(9,400 €)*	7,800 € *(10,100 €)*	13,200 €	13,400 €	**200 €** *(700 €)*	*p*=0.76	≈-0.01	**SD**: 15,000 € **CD**: 12,500 €
PCa-related cost estimates for men with **high-risk** tumour at diagnosis	12,300 € *(17,700 €)*	11,800 € *(18,700 €)*	20,600 €	20,400 €	**-200 €** *(1000 €)*	*p*=0.85	<0.01	**SD**: 24,500 € **CD**: 18,400 €
PCa-related cost estimates for men with **metastatic** tumour at diagnosis	15,000 € *(25,100 €)*	15,600 € *(26,100 €)*	23,900 €	24,000 €	**100 €** *(2000 €)*	*p*=0.94	>-0.01	**SD**: 36,000 € **CD**: 21,900 €
PCa-related cost estimates for men with tumour information **missing** at diagnosis	6,800 € *(7,800 €)*	7,400 € *(9,200 €)*	8,500 €	8,500 €	**0 €** *(800 €)*	*p*=0.95	<0.01	**SD**: 6,500 € **CD**: 8,500 €
All-cause cost estimates for **men who have died from PCa**	47,600 € *(57,100 €)*	51,900 € *(53,400 €)*	**60,000 €**	**65,100 €**	**5,100 €** *(4,600 €)*	*p*=0.27	≈-0.08	**SD**: 71,000 € **CD**: 62,400 €
PCa-related cost estimates for **men who have died from PCa**	22,100 € *(35,600 €)*	23,600 € *(38,600 €)*	**31,400 €**	**33,000 €**	**1,700 €** *(2,100 €)*	*p*=0.43	≈-0.05	**SD**: 43,700 € **CD**: 27,900 €

CA = control arm; **SA** = screening arm; **IQR** = interquartile range; N.R. = Not relevant; † = the cut-off point for extreme observations used was: 3rd quartile + (3*IQR);
SD = PCa detected via the screening intervention; **CD** = clinically-detected PCa; †† = We used the stage classification used by the European Randomized Study of Screening for Prostate Cancer (ERSPC) (1)

Appendix

The FinRSPC trial database contains information about all PCa diagnoses before 2015 obtained from the nationwide Finnish Cancer Registry, (FCR). The FCR has been shown to have comprehensive coverage of all solid cancers diagnosed in Finland (12), but these diagnoses data from the FCR were also confirmed from medical records as part of the FinRSPC. This trial database also includes data from Statistics Finland's Causes-of-death statistics (available from: http://www.stat.fi/til/ksyyt/kas_en.htm), which has, since the start of the FinRSPC in 1996, applied the 10th revision of the International Classification of Diseases (ICD-10). For a sample of men from the FinRSPC, the official causes of death were reviewed by an independent expert review panel and found to be in close agreement (overall agreement 98%, κ=0.95) (13).
For the period of the study (1996−2016), the two main registers containing information on healthcare utilisation and costs were the CRHC and the PMRR, i.e., the Care Register for Health Care ("Hilmo" in Finnish, produced by THL) and the Prescription-Medicine Reimbursement Register ("Lääkeostotiedot" in Finnish, produced by the Social Insurance Institution of Finland (Kela)) . Since 2010, the CRHC has consistently included records of both outpatient and inpatient visits to both secondary and tertiary health care. The interested reader can refer to https://www.thl.fi/en/web/thlfi-en/statistics/information-on-statistics/register-descriptions/care-register-for-health-care for further details on the CRHC. Prior to 2010, only inpatient records were available from the CRHC, so for this earlier period, we used all available outpatient records collated by the two hospital administrations in the districts of Pirkanmaa and Uusimaa. On the advice of the producers of the CRHC, the 2009 Nordic diagnosis-related groups (NordDRG) classification system is used here for inpatient care episodes prior to 2010. For episodes in 2010 and later, the 2015 NordDRG classifiers are used. Whenever it is possible to calculate a NordDRG-based cost for both inpatient and outpatient costs, the 2009 NordDRG costing weights are applied. When this is not possible (in a few instances and largely prior to 2010) we use the municipal billing records from the administrative databases in the hospital districts of Pirkanmaa and Uusimaa to estimate the costs. The PMRR contains the exact costs of prescription medications sold through retail pharmacies, but does not include information on prescription medications supplied by hospital pharmacies. Another restriction of the nationwide PMRR is that information limited to only those prescription medications reimbursed under the Health Insurance Act at any point in time. The interested reader can refer to http://www.kela.fi/web/en/inclusion-of-medicines for further information on the reimbursement status of medicines.

Conflicts of interest

Kimmo Taari has taken part in a congress with support from Astellas and received research funding from Medivation, Astellas, Pfizer and Orion. Teuvo Tammela has acted as a consultant for Orion Pharma, Bayer AG and Ferring and received research funding from Medivation, Pfizer and Lidds Ab. Anssi Auvinen, Neill Booth, Pekka Rissanen, and Kirsi Talala have nothing to disclose.

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Roles of the Funding Sources

The funding allowed collection of the data over a long period and allowed Booth to work with the data and postpone analyses until more data was available, rather than being pressured into early publication. There was no role of for-profit healthcare companies in the writing of the manuscript.

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