COMPARISON OF THE COST OF ANTIDEPRESSANTS
IN A PROSTATE CANCER SCREENING TRIAL POPULATION

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The aim of this study is to compare, in terms of the costs recorded in a comprehensive national register, the use of antidepressant drugs in both the control and screening arms of the Finnish trial.

A number of 76,223 reimbursement records for antidepressant drugs corresponding to 5,858 men in the control arm and 3,912 men in the screening arm were analysed for the period under study from 1996 to 2004.

We compared the control arm with the screening arm, the prostate-specific antigen (PSA) non-compliant group with the PSA compliant group and the group with the PSA<4 ng/mL with the PSA group≥4 ng/mL group in terms of the difference between the mean costs.

Our study showed little impact of the screening trial, of participation in the screening or of the concentration of prostate-specific antigen on the expenditure on antidepressant drugs. Further studies, based on supplementary information (i.e. quantity of antidepressant medicine) could contribute to a better assessment of the prostate cancer screening impact on mental health.

*Keywords*: cost, screening, prostate cancer, antidepressant drugs, PSA testing
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ABBREVIATIONS

ATC  Anatomical Therapeutic Chemical Classification System

DRE  Digital rectal examination

ERSPC European Randomized Study of Screening for Prostate Cancer

FinRSPC Finnish Randomised trial of Screening for Prostate Cancer

HRQL Health-related quality of life

PSA Prostate-specific antigen

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

SII Finnish Social Insurance Institution

SSRI Selective serotonin reuptake inhibitors

TA Tricyclic antidepressant

TRUS Transrectal ultrasound

WHO World Health Organization
According to the World Health Organization (WHO), prostate cancer is the second cause of cancer death, after lung cancer, in most industrialized countries.

The Finnish Randomised trial of Screening for Prostate Cancer (FinRSPC) was launched in 1996 in Helsinki and Tampere and is the largest centre of the European Randomized Study of Screening for Prostate Cancer (ERSPC) (Schröder at al., 2003; Määttänen et al., 2007).

Previous quality-of-life studies suggest that prostate cancer diagnosis decreases the quality of life related to depression (Talcott & Clark, 2005; Korfage et al., 2006).

The aim of this study is to compare, in terms of the costs recorded in a comprehensive national register, the use of antidepressant drugs in both the control and screening arms of the Finnish trial.
2.

REVIEW OF THE LITERATURE

2.1 Prostate cancer

Prostate cancer is an age-related (Holmberg et al., 1998) and an elderly disease that progresses relatively slow (Lantz et al., 2001; Heinzer & Steuber 2009). Nowadays, prostate cancer is the most common cancer in men in Europe (Ferlay et al., 2007).

Prostate cancer has the highest incidence rate of all cancers in men of all ages. The crude rate was 140.2 per 100,000 men in the year 2008 in European Union (Ferlay et al., 2008) (Figure 1). The high incidence is, of course, influenced by the screening programmes introduced in many countries of the European Union and by increased awareness (Mäkinen, 2008). Moreover, the incidence is still expected to grow due to the increased use of prostate-specific antigen (PSA) based screening and to the raising number of senior adults (Heinzer & Steuber, 2009).

In what the mortality is concerned, prostate cancer is the third cause of death in the European Union, after lung cancer and colorectum cancer, among men of all ages with a crude rate of 29.5 per 100,000 men (Ferlay et al., 2008) (Figure 1). Among men over 50 years of age, however, prostate cancer the second one after lung cancer (Perez-Niddam, et al., 1999).
In Finland, prostate cancer has a high incidence rate, internationally compared, with a crude rate of 184.4 per per 100,000 men and an age-standardised rate of 96.6 per 100,000 men in 2008 (Ferlay et al., 2008) (Figure 2). Every year there are more than 5,300 new prostate cancer cases (www.cancerregistry.fi/eng, Basic statistics, 8.8.2010).

The number of deaths by prostate cancer is annually around 800 in Finland (www.cancerregistry.fi/eng, Basic statistics, 8.8.2010). The crude rate was 30.5 per 100,000 deaths in 2008 (Ferlay et al., 2008).
The incidence of prostate cancer increased continuously even before the screening was launched (www.cancerregistry.fi/eng/, 2010) (Figure 3). According to the Finnish Cancer Registry, mortality has not changed despite the increase of the incidence.

Ageing of the population, the increase use of the PSA testing, the increased awareness, access to the health care, accuracy of cancer registration are among the factors that influence the incidence of prostate cancer (Mäkinen, 2008).
2.2 Screening for prostate cancer

Screening is part of the secondary prevention, which consists of early detection and treatment of disease (dos Santos Silva, 1999). The ultimate aim of the cancer screening is to reduce cancer-related mortality by identifying asymptomatic cancers in an early stage and thus, increasing the chances of positive answer to treatment (Miller et al., 2001; Perez-Niddam et al., 1999). Among the aims of the screening is, though, the improvement of the quality of life (Määttänen, 2007).

The detection methods of the prostate cancer include the use of the prostate-specific
antigen, digital rectal examination (DRE) and transrectal ultrasound (TRUS). The level of the PSA is elevated in men diagnosed with prostate cancer.

The screening for prostate cancer has some negative impact on the quality of life in terms of self-rated mental health due to the cancer diagnosis, on one hand (Korfage et al., 2006), and due to the decision regarding screening and treatment for cancer that men have to face earlier (Talcott & Clark, 2005).

There is still no scientific proof that the negative effects of the prostate cancer screening are exceeded by its benefits (Senfält et al., 2004) and, in consequence, the screening for prostate cancer is still a controversial issue (Holmberg et al., 1998; Parker & Emberton, 2009). Moreover, according to Holmberg et al. the prostate cancer screening is associated with a high level of uncertainty regarding factors like costs, the risk of overdiagnosing and the negative effect of the therapy.

There are two large screening trials: the USA Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial and the European Randomised Study of Screening for Prostate Cancer (ERSPC).

In the USA, 76,000 men were recruited for PLCO in years 1993-2001 and randomised, afterwards into two groups: PSA screening or usual care. The threshold used for PSA was of 4 ng/mL.

PLCO did not yet show a statistically significant decrease of mortality by prostate cancer (Parker & Emberton, 2009).

2.2.1 European randomised study of screening for prostate cancer

The European Randomised Study of Screening for Prostate Cancer (ERSPC) was considered a feasible project after two pilot studies in Belgium (1991-1993) and in the Netherlands (1992-1994). Its aim was to prove that the screening for prostate cancer has
a diminishing effect on the prostate cancer mortality and that it can be performed at an acceptable costs regarding both the quality of life and the money (Schröder at al., 2003). Finland entered the study as the third partner.

The ERSPC included 162,000 men, aged 50(55) to 70 years. The protocol included a PSA test every 4 years and a prostate biopsy for men with PSA>3 ng/mL.

The phases of the study were the same for Italy, France, Finland and Sweden: random identification of the target population that represented men aged 55 to 70 years old followed by randomization into two arms (screening and control). Men in the screening arm received an invitation letter and were screened by performing the prostate-specific antigen (PSA) blood test, after their informed consent.

For the other countries in the study (Belgium, The Netherlands, Spain, Switzerland) men aged 50 to 70 were identified and invited to screening. Following the informed consent they were randomized into two groups (screening and control).

The prostate-specific antigen (free/total PSA), digital rectal examination, transrectal ultrasound and prostate biopsies were applied as diagnostic methods in the ERSPC study.

The ERSPC has shown that a randomized controlled trial is possible in Europe (Schröder at al., 2003), proved that screening may lead to mortality by prostate cancer reduction but also provided evidence of the harm due to screening (Parker & Emberton, 2009). Anxiety is among the harmful effects of the prostate cancer screening and diagnosis.

### 2.2.2 Finnish randomised trial of screening for prostate cancer

The Finnish Randomised trial of Screening for Prostate Cancer (FinRSPC) was launched in 1996 in Helsinki and Tampere and is the largest centre of the European
Randomized Study of Screening for Prostate Cancer (ERSPC) (Schröder et al., 2003; Määttänen et al., 2006).

Men aged 55–67 living in the two cities represented the study population and their total number was 80,458. They were identified from the Population Register Centre of Finland. Men diagnosed with previous prostate cancer (161) and men who denied the use of their addresses (1%) were not considered as eligible for the trial (Määttänen et al., 2006). The type of randomization used in the trial was randomization before consent or Zelen-type randomization. Every year 8,000 men were randomly allocated to the screening arm of the trial, using a computer algorithm based on random numbers. These men were, then, invited for screening. The rest of the study population were part of the control arm. The first round of screening was conducted in years 1996-1999, while the second in years 2000-2004. Men in the screening arm received an invitation letter containing information about the PSA test and a questionnaire to fill out with information on urological symptoms and family history of prostate cancer. The serum PSA concentration was determined for all screening participants. Men with a PSA≥ 4 ng/mL were further referred for diagnostic examinations (DRE, TRUS and prostate sextant biopsies). All diagnoses were based on histological examination. The results, so far, include a number of 377 prostate cancer cases out of 15,685 screening participants (Mäkinen, 2008).

2.3 Antidepressants use

Korfage et al. conducted a study in 2006 with the aim of assessing the mental impact of prostate cancer diagnosis on men. According to the study there was a significant negative impact of prostate cancer diagnosis based on PSA testing. The study was questionnaire-based; participants completed the health-related questionnaire before the screening (3,800 men) and after the diagnosis (52 men). With a probability less than 0.04, the study showed that the mental and self-rated overall health worsened significantly immediate after the diagnosis.
The use of antidepressants is associated with the female sex (Rubin et al., 2008), as women are more likely to suffer of depression than men (Lantz et al., 2001). The use of antidepressants is associated with depression and, moreover, the more severe the depression, the more likely the patients receive antidepressants (O'Connor et al., 2008). In their study, Rubin et al. identify the use of antidepressant medicine with elevated depression symptoms.

Depression may have an early or late-onset (Malec et al., 2007) and may be classified in minor depression and major depression (Kumar et al., 1998). Minor depression, like prostate cancer is more prevalent in the elderly people (Kumar et al., 1998). In what our study is concerned, the results may, of course, be influenced by the time of establishing the diagnosis of depression. The harmful effects of the screening, including an increase consumption of antidepressants, if any, may become evident later than our study period (1996 - 2004).

Antidepressant drugs are considered those codes from group N06A in the Anatomical Therapeutic Chemical Classification System (ATC): N06AA non-selective monoamine reuptake inhibitors, N06AB selective serotonin reuptake inhibitors, N06AF monoamine oxidase inhibitors, non-selective, N06AG monoamine oxidase A inhibitors, N06AX other antidepressants.

The people who use antidepressant can be divided into three categories: those who take only selective serotonin reuptake inhibitors (SSRI), those who take tricyclic antidepressant (TCA) with or without SSRIs or other antidepressants or those who take other antidepressants with or without SSRIs or TCAs (O'Connor et al., 2008). This grouping is based on the effect that the use of the antidepressant have on patients with ischemic heart disease, heart failure, or diabetes (Rubin et al., 2008). The use of antidepressant medication may also be analysed according to the length of the period the drug has been used, like intermittent use and continuous use. For the purpose of our study there was no need for such categories as the study aims to compare the use of antidepressants in terms of the costs, between the control and the screening group.
2.4 Costs in the screening for prostate cancer trial

The identification and the measurement of the costs of screening is a difficult task and detailed evaluations may be unrealisable sometimes (Ekwueme et al., 2007). Some costs are often neglected like: costs of the human resources associated with a false positive test result that include energy, anxiety, time and risks due to unnecessary treatments (Kenkel, 2000).

Costing involves identifying, measuring and valuing all the changes in resources that occur during a health care intervention (Drummond & McGuire, 2001). In analysing the costs related to the prostate cancer screening, diagnosis and treatment, all three categories of costs should be estimated: direct, indirect and intangible costs, according to Miller et al. The direct costs and benefits represent the resources consumed (costs) or saved (benefits). The indirect costs and benefits are used, according to Drummond, to denote the time of the patients consumed by a programme. There are consequences difficult to measure and value, like, for example the value of improved health and the value of these consequences represent the intangible costs. In the prostate cancer screening, such costs include the pain and the suffering associated with DRE, TRUS and the biopsy.

Among the factors that influence the cost for prostate cancer screening the biopsy rate is considered to be the most important (Ellison et al, 2002). Factors that influence the use of antidepressants include the price of the drug, the inflation, the income, the willingness to pay, the production costs, the changes of the price during the years, age, the severity of the disease, comorbidities, etc. (McPake & Normand, 2008). When the costs are in the past, however, and in the same money, already established, there is no need for inflation adjustment. In our study it was not necessary to adjust for such factors as we compared two groups that, in case of the existence of any factor, would have been influenced in the same way by these factors.

Price of the drug considered as intangible costs of the trial is influenced over time by the quantity of drug, concentration, negotiation between the pharmaceutical company
and the government, reimbursement scheme, cost of production and distribution, etc. (Drummond, 2005; Morris et al. 2007). In our study, we could not analyse the impact of these factors on cost because of the lack of data, and thus, we have used a top-down approach of costing using pre-existing data and not decomposing the cost in quantities and prices (Morris et al., 2007).

In the cost analysis, the use of the independent samples t-test is recommended (Thomson & Barber, 2000) even if the distribution of the costs is usually right skewed as the costs cannot be negative (Drummond, 2005). According to Drummond, means of the costs should be reported whenever the source of the cost data is a randomized trial. It is desirable to calculate mean costs and confidence intervals around the mean, when doing the cost analysis (McPake & Normand, 2008). There is an increased use of the method of non-parametric bootstrapping, but this method is, in the same time, criticized.

Costs, the risk of overdiagnosis and the negative side-effects of the prostate cancer therapy are among the uncertainties associated with the screening for prostate cancer (Holmberg et at., 1998). Information on health-related quality of life (HRQL) and the health costs of screened and unscreened participants should be considered along with the reduction in mortality from screening, when deciding the healthcare policy (Miller et al., 2001).
3. PURPOSE OF THE STUDY

The purpose of this study is to assess the impact of prostate cancer screening on the mental health, in terms of the expenditure on antidepressant drugs, in the Finnish part of the European Randomized Study of Screening for Prostate Cancer (ERSPC).

The specific aims are:
1. To compare the costs between the two groups of the screening trial: control arm and screening arm
2. To compare the costs between the two parts of the screening arm: PSA compliant and PSA non-compliant
3. To compare the costs between the two components of the PSA compliant group, according to the PSA level: PSA < 4 ng/mL and PSA ≥ 4 ng/mL.
Comparison of the cost of antidepressants in a prostate cancer screening trial population

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ABSTRACT

Previous quality-of-life studies suggest that prostate cancer diagnosis decreases the quality of life related to depression. The aim of this study is to compare, in terms of the costs recorded in a comprehensive national register, the use of antidepressant drugs in both the control and screening arms of the Finnish trial.

A number of 76,223 reimbursement records for antidepressant drugs corresponding to 5,858 men in the control arm and 3,912 men in the screening arm were analysed for the period under study from 1996 to 2004.

We compared the control arm with the screening arm, the PSA non-compliant group with the PSA compliant group and the group with the PSA<4 ng/mL with the PSA group≥4 ng/mL group in terms of the difference between the mean costs. Over the whole period, there was a statistically significant difference between the screening and the control arm (1.44 Euro, 95% CI 0.62 to 2.26), mean cost was higher in the control arm, but of small effect size ( R²<0.01). The mean cost for the PSA non-compliant was 68.29 €, for the PSA compliant group was 70.25 €, resulting in a small difference of -1.96 € (95% CI -3.32 to 0.60), difference that has neither a statistical nor a financial significance. Comparing by screening rounds and PSA test, we found that, in round 1, the mean cost difference was of 1.78 € (95% CI -0.85 to 4.40) and was not statistically significant, while in round 2 the difference of 5.18 € (95% CI 2.23 to 8.11) was statistically significant, but the effect size is very small ( R²=0.003).

Our study showed little impact of the screening trial, of participation in the screening or of the concentration of prostate-specific antigen on the expenditure on antidepressant drugs. Further studies, based on supplementary information (i.e. quantity of antidepressant medicine) could contribute to a better assessment of the prostate cancer screening impact on mental health.

Keywords: cost, screening, prostate cancer, antidepressant drugs, PSA testing
1. Introduction

According to the World Health Organization (WHO), prostate cancer is the second cause of cancer death, after lung cancer, in most industrialized countries. In Finland, prostate cancer has a high incidence rate, internationally compared, with an age-standardised rate of 96.6 per 100,000 men in 2008.

Previous quality-of-life studies suggest that prostate cancer diagnosis decreases the quality of life related to depression. On the one hand, it was proven that the mental health worsened significantly due to the prostate cancer diagnosis. On the other hand, since prostate cancer is a slowly progressive disease specific for the elderly people and, since PSA has become widely available, men face much earlier the decision about participation in the screening trial, about taking the prostate-specific antigen (PSA) test and about a possible treatment when the diagnosis is positive. For this reason assessing the impact of the screening, diagnosis and treatment on the quality of life has become an important issue. Some negative harmful side effects of the prostate cancer screening (the psychological distress, the complications due to the diagnosis tests and the treatment related side-effect) are inevitable, but the benefits of the trial should outweigh them, improvement of the quality of life being considered as one of the aims of cancer screening.

The aim of this study is to compare, in terms of the costs recorded in a comprehensive national register, the use of antidepressant drugs in both the control and screening arms of the Finnish trial.
2. Materials and methods

The trial

The Finnish Randomised trial of Screening for Prostate Cancer (FinRSPC) was launched in 1996 and is the largest trial of the European Randomized Study of Screening for Prostate Cancer (ERSPC). FinRSPC started in two cities, Helsinki and Tampere, and had a high participation rate of 69% in both rounds. The first round was completed in 1996–1999 and the second in 2000-2004. A total number of 80,458 men between the ages of 55-67 years identified, from the Population Register of Finland, represented the study population. Annually, 8,000 men were randomly allocated to the screening arm and about 12,000 men to the control arm. Men in the screening arm were invited to the screening test preceded by an invitation letter and informed consent. The screening test measured the concentration of prostate-specific antigen in serum, with a PSA cut-off point of 4.0ng/mL. Men with a PSA ≥ 4 ng/mL were referred for diagnostic examination such as digital rectal examination, transrectal ultrasound and direct biopsy.

Data

The sources of data for our study are the Finnish trial database and the Finnish Social Insurance Institution (SII). SII provides information on all reimbursements for the cost of medicine prescribed by a physician. The SII data used in this study consists of individual-level records of reimbursement for all drugs under the National Health Insurance scheme. Data from both sources were linked and analysed for a ten-year period (1995-2004). The variables included in the study were: the day of purchasing the drug, the code from the Anatomical Therapeutic Chemical Classification System (ATC), the cost of the drug as the amount of the reimbursement, the randomization group according to the screening trial (the control arm and the screening arm), and the concentration of the prostate-specific antigen in ng/mL for both rounds of the trial. All men involved in the screening trial were assigned a trial identification number. The
definition of cost used here is the amount of expenditure on drugs by both the SII and the patients. Cost was expressed in Finnish Markka for the period 01.01.1995–31.12.2001 and in Euro (€), for the period 01.01.2002–31.12.2004. Antidepressant drugs were considered to be those with the following codes from group N06A in ATC: N06AA non-selective monoamine reuptake inhibitors, N06AB selective serotonin reuptake inhibitors, N06AF monoamine oxidase inhibitors, non-selective, N06AG monoamine oxidase A inhibitors, N06AX other antidepressants.

Data analysis

From the total of 5.7 million records for all ATC codes, the records with missing data (4164) and the records with unknown ATC code (4540) were ignored. FinRSPC was launched in May 1996 and therefore we excluded from the analysis all men reimbursed prior to 1996 (72,835 records). Our study period was 1996–2004 and, thus, we analysed 76,223 reimbursement records for antidepressant drugs corresponding to 5858 men in the control arm and 3,912 men in the screening arm. All costs were adjusted to the 2002 Euro rate considering that 1 Euro=5.94573 Finnish Markka, in order to allow the comparability for the whole study period. Mean cost difference and the confidence intervals around the difference\(^{13}\) were calculated for the following groups: the two groups of the screening trial: control arm and screening arm, among the people in the screening arm: PSA compliant and PSA non-compliant, for those in the PSA compliant group: PSA < 4 ng/mL and PSA ≥ 4 ng/mL.

These comparisons were analysed over the whole study period, for each year and over the two rounds of screening, 1996-1999 and 2000-2004.

Although the costs were right skewed, as they usually are,\(^{14}\) the differences between groups were compared using the independent samples t-test.\(^{15}\) Results were verified by the bootstrap method and r-squared (R\(^2\)) was calculated to measure the effect size.\(^{16}\) For the whole analysis Stata 10 was employed. The results were considered from both a statistical point of view and an financial one.\(^{17}\)
3. Results

Comparison by the trial arm

Out of 76,223 observations, 45,246 were for the control arm, corresponding to 5,858 men and, respectively, 30,977 observations were for the screening arm, corresponding to 3,912 men. Overall results show weak evidence of differences in the mean costs between the control and the screening arm. The mean cost was of 71.12€ in the control arm and 69.68 € in the screening arm. For the whole period the difference in mean cost was 1.44 €, p<0.001 (95% CI 0.62 to 2.26). There is a statistically significant difference, but only a small effect size, R^2<0.01. Annually, there appears to be no discernable statistically significant difference between the control and the screening arm in the years 1996-1997 or 2000-2004 (Table 1). In the years 1998 and 1999 there is a statistically significant difference. In 1998, the mean cost difference was 6.80 € (95% CI 4.32 to 9.29) but, again the strength of this difference is of small effect size (R^2=0.004). In 1999, the mean cost difference was 4.73 €, p<0.001 (95% CI 2.46 to 7.00) and the effect size is negligible (R^2=0.002). The mean cost, however, was higher for the control arm than for the screening arm for the whole period and for 1996-2000. For the years 2001-2004, the mean cost for the screening arm is higher but there is not a statistically significant difference for these years between the two arms of the trial.

The analysis was rerun using the bootstrap t-test because the distribution of costs was skewed. The difference was significant at p = 0.001.

Comparison by the compliance to the PSA test

In the PSA non-compliant group, we had 9,011 records to analyse for 1,131 men and in the PSA compliant group we had 21,966 records for 2,781 men. Over the whole study period, the mean cost for the PSA non-compliant was 68.29 € and for the PSA compliant group 70.25 €, resulting in a small difference of -1.96 € (95% CI -3.23 to 0.60), difference that has neither a statistical nor a financial impact. Although the mean
cost for the PSA compliant group is generally higher than for the PSA non-compliant group (Table 2), we found a statistically significant difference of 9.06 € only in 2004, p<0.001 (95% CI 5.26 to 12.87), when, actually the mean cost for the PSA non-compliant group is higher. The effect size has a very small value of 0.0049. From the financial point of view we could say that a difference of 9 Euro in 2004 is significant in favour of the first group. The mean cost difference for the years 1997, 1998 and 1999 is, again, financially significant (-6.54 €, -5.96 € and -5.57€) but not statistically significant. No statistically significant difference was found when compared by the two rounds of screening.

Comparison by result of the PSA test

The PSA compliant group was divided into two groups based on the concentration in ng/mL of the prostate-specific antigen, considering the value of 4 as the cut-off level in order to compare by result of the PSA test. We therefore analysed in round 1 – 17,466 records for 2,258 men whose value of PSA was less than 4, and 1,833 records for 236 men whose PSA result was equal and higher than 4, and in round 2 – 15,073 records for 1,888 men with PSA<4 and, respectively, 1,471 records for 214 men with PSA≥4. In round 1, the mean cost difference is of 1.78 € (95% CI -0.85 to 4.40), and is not statistically significant, while in round 2 the difference of 5.18 € (95% CI 2.23 to 8.11) is statistically significant, but the effect size is very small (R² = 0.003) (Table 3). The mean cost is in both rounds higher for the group with a PSA concentration less than 4. When comparing the mean cost per person in the two rounds we found a difference of 60.41 € (95% CI -10.31 to 131.11) in the first round which has no statistical significance. In the second round the difference was 300.52 € (p<0.001, 95% CI 217.94 to 383.10), a difference that has both financial and statistical significance. The mean cost was, however, higher for the group whose concentration of prostate-specific antigen was less than 4.
4. Discussion

The analysis of the cost defined for the purpose of this study as the amount of Euro reimbursed by SII combined with the amount of expenditure by the patient, showed no statistically significant difference for the screening arm, PSA compliant group or for the group with a PSA level $\geq$4 ng/mL. The study shows statistically significant differences between the mean cost of antidepressant use in the control and screening arm for the whole period and for two years (1998, 1999), but the mean cost is higher in the control group and the effect size is rather negligible. We considered that the difference is due to the large number of observations. Comparing inside the screening group by the compliance to the PSA test, we may say that compliance to the test may slightly increase the expenditure on antidepressant drugs although this conclusion is based on a difference considered significant from the financial point of view, rather than from a statistical one. When we made the comparison in the PSA compliant group according to the cut-off level of 4 of the PSA test we found that there was a statistically significant difference in the second round in both the mean cost and the mean cost per person, in favour for the first group in the analysis (PSA<4 ng/mL).

Screening for prostate cancer is associated with uncertainty regarding factors like costs, risk of overdiagnosing and negative effects and it still remains a controversial issue.\textsuperscript{18} There is still no scientific evidence that the harms of the prostate cancer screening are exceeded by the benefits.\textsuperscript{19} Prostate cancer screening has a psychological impact especially among anxiety-prone individuals.\textsuperscript{7}

In this study we analysed the cost of antidepressant drugs, defined as the amount of reimbursement. Information on the quantity and concentration of drugs was not available and therefore no analysis of the use of antidepressants was made.

Price of the drug considered as intangible costs of the trial\textsuperscript{14} is influenced over time by the quantity of drug, concentration, negotiation between the pharmaceutical company and the government, reimbursement scheme, cost of production and distribution, etc.\textsuperscript{14,20}
Because of the lack of data we could not analyse the impact of these factors on cost, and thus we have used a top-down approach of costing using pre-existing data and not decomposing the cost in quantities and prices.\textsuperscript{20}

There are drugs that can be purchased and used outside the reimbursement scheme and those drugs are not included in our analysis.

In conclusion, our study showed no impact of the screening trial, of participation in the screening or of the concentration of prostate-specific antigen on the expenditure on antidepressant drugs. The results of our study and the association between the use of antidepressant drugs and elevated depression symptoms\textsuperscript{21} and the association between the female gender and depression or antidepressant use,\textsuperscript{22} make us conclude that prostate cancer screening has little impact on depression.

**Conflict of interest statement**
None declared.

**References**


Table 1. Mean cost by group and year in the Finnish prostate cancer trial, 1996–2004

<table>
<thead>
<tr>
<th>Year</th>
<th>Control arm</th>
<th>Screening arm</th>
<th>Mean diff (95% CI)</th>
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<td>-4.73   ( p&lt;0.001 )</td>
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<td>65.42</td>
<td>-0.99</td>
</tr>
<tr>
<td>Total</td>
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<td>69.68</td>
<td>1.44   ( p&lt;0.001 )</td>
</tr>
<tr>
<td>1996-1999</td>
<td>65.09</td>
<td>61.38</td>
<td>3.71   ( p&lt;0.001 )</td>
</tr>
<tr>
<td>2000-2004</td>
<td>74.20</td>
<td>73.87</td>
<td>0.33</td>
</tr>
</tbody>
</table>
Table 2. Mean cost by compliance to PSA test and year in the Finnish prostate cancer trial, 1996–2004

<table>
<thead>
<tr>
<th>Year</th>
<th>Non-compliant</th>
<th>Compliant</th>
<th>Mean diff (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1996</td>
<td>57.24</td>
<td>58.18</td>
<td>-0.94</td>
</tr>
<tr>
<td>1997</td>
<td>57.80</td>
<td>64.34</td>
<td>-6.54</td>
</tr>
<tr>
<td>1998</td>
<td>55.72</td>
<td>61.68</td>
<td>-5.96</td>
</tr>
<tr>
<td>1999</td>
<td>59.58</td>
<td>65.15</td>
<td>-5.57</td>
</tr>
<tr>
<td>2000</td>
<td>68.01</td>
<td>71.86</td>
<td>-3.85</td>
</tr>
<tr>
<td>2001</td>
<td>75.39</td>
<td>78.20</td>
<td>-2.81</td>
</tr>
<tr>
<td>2002</td>
<td>81.37</td>
<td>85.86</td>
<td>-4.49</td>
</tr>
<tr>
<td>2003</td>
<td>72.93</td>
<td>72.00</td>
<td>0.93</td>
</tr>
<tr>
<td>2004</td>
<td>72.16</td>
<td>63.10</td>
<td>9.06</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>( p&lt;0.001 )</td>
</tr>
<tr>
<td>Total</td>
<td>68.29</td>
<td>70.25</td>
<td>-1.96</td>
</tr>
<tr>
<td>1996-1999</td>
<td>69.41</td>
<td>69.84</td>
<td>-0.43</td>
</tr>
<tr>
<td>2000-2004</td>
<td>68.85</td>
<td>70.39</td>
<td>-1.54</td>
</tr>
</tbody>
</table>
Table 3. Mean cost by serum concentration of prostate-specific antigen (PSA) and round in the Finnish prostate cancer trial, 1996 - 2004

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean cost difference by rounds</th>
<th>Mean cost per person</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Round 1</td>
<td>Round 2</td>
</tr>
<tr>
<td>PSA &lt; 4 ng/mL</td>
<td>70.01 (CI 69.19-70.82)</td>
<td>70.86 (CI 69.97-71.74)</td>
</tr>
<tr>
<td>PSA ≥ 4 ng/mL</td>
<td>68.23 (CI 65.76-70.69)</td>
<td>65.68 (CI 63.17-68.19)</td>
</tr>
<tr>
<td>Mean difference</td>
<td>1.78 (CI -0.85-4.40)</td>
<td>5.18 (CI 2.23-8.11)</td>
</tr>
</tbody>
</table>
4.

REPORT OF THE RESEARCH PROCESS

As a student at the Tampere School of Public Health in the Master's in Public Health Programme, I enjoyed very much taking the courses on Basics of Health Economics and Methods and Theories of Health Economics. This was due to the excellent teaching of Professor Pekka Rissanen and the availability for questions and discussions of his assistant, Neill Booth.

Due to my background in Mathematics and Economics and to my previous working experience in cancer research, I decided to delve deeper into the knowledge of health economics by undertaking the research on the costs in the prostate cancer screening trial.

The idea of studying the reimbursement of the antidepressant medicine came out during our seminars on the master's thesis and based on our discussion about the impact on mental health of the prostate cancer screening.

With the kind help of Neill Booth, I was able to use Stata 10 and the database from Kela (Social Insurance Institution of Finland) containing all the reimbursements of the drugs for the period 1995–2004, drugs used by the people recruited for the prostate screening trial.

The research required my learning of how to use the Stata software.

The study question of the research was the comparison of the costs of antidepressants used in the Finnish randomized trial of screening for prostate cancer (FinRSPC). The preliminary timetable had four phases: literature review, learning Stata, data analysis and article writing.

My personal contribution to this research was consulting and selecting the literature on the impact of prostate cancer screening on mental health, writing the research plan,
analysing the database, suggesting the groups for which the comparison should be made, assessing the results and drawing out the conclusions, everything being done under the guidance of Neill Booth.

The results have been verified and discussed with Anna-Maija Koivisto and Professor Pekka Rissanen and have already been partially presented in an oral presentation at the European Conference on Health Economics, Helsinki, July 2010. The manuscript has been submitted to and reviewed by the *European Journal of Cancer*. 
ACKNOWLEDGEMENTS

I would like to express my deepest gratitude to my supervisors: Assistant Neill Booth and Professor Pekka Rissanen. I am very grateful for their support and assistance throughout the whole process of this research. Many thanks to Neill for his patience with me in learning Stata and in moving forward on and off with the research. I am grateful to Lecturer Anna-Maija Koivisto who reviewed all the statistical work and assisted me whenever I needed.

I am grateful to Professor Clas-Håkan Nygård for the constructive suggestions offered during the years of my studies.

A lot of gratitude goes to Chioma and Beatrice, my friends and colleagues, and to our international coordinator, Ms. Catarina Ståhle-Nieminen: I was always able to continue the work despite the challenge because of their optimism and encouragement.
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