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The Finnish Population-Based Prostate Cancer Screening Trial

A clinical perspective



ACADEMIC DISSERTATION

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ACADEMIC DISSERTATION

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Dedicated to Terhi and Touko

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LIST OF ORIGINAL PUBLICATIONS

1. Mäkinen T, Auvinen A, Hakama M, Stenman U-H and Tammela TLJ (2002). Acceptability and complications of prostate biopsy in population-based PSA screening versus routine clinical practice: a prospective, controlled study. *Urology* 60:846-850
2. Mäkinen T, Tammela TLJ, Hakama M, Stenman U-H, Rannikko S, Aro J, Juusela H, Määttänen L and Auvinen A (2003). Tumor characteristics in a population-based prostate cancer screening trial with prostate-specific antigen. *Clin Cancer Res* 9:2435-2439
3. Mäkinen T, Tammela TLJ, Hakama M, Stenman U-H, Rannikko S, Aro J, Juusela H, Määttänen L and Auvinen A (2001). Prostate cancer screening within PSA range 3.0-3.9 ng/ml: a comparison of digital rectal examination and free PSA as supplemental screening tests. *J Urol* 166:1339-1342
4. Mäkinen T, Tammela TLJ, Stenman U-H, Määttänen L, Rannikko S, Aro J, Juusela H, Hakama M and Auvinen A (2002). Family history and prostate cancer screening with prostate-specific antigen. *J Clin Oncol* 20:2658-2663
5. Mäkinen T, Tammela TLJ, Stenman U-H, Määttänen L, Aro J, Juusela H, Martikainen P, Hakama M and Auvinen A (2004). Second round results of the Finnish population-based prostate cancer screening trial. *Clin Cancer Res* 10:2231-2236

ABBREVIATIONS

BPH	Benign prostatic hyperplasia
CI	Confidence interval
DNA	Deoxyribonucleic acid
DR	Detection rate
DRE	Digital rectal examination
EAU	European Association of Urology
ERSPC	European Randomized Study of Screening for Prostate Cancer
NNT	Number needed to treat
NSAIDs	Non-steroidal anti-inflammatory drugs
PC	Prostate cancer
PIN	Prostatic intraepithelial neoplasia
PLCO	Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial
PPV	Positive predictive value
PCA3	Prostate cancer gene 3
PSA	Prostate-specific antigen
RR	Ratio of detection rates (or rate ratio)
SEER	Surveillance, Epidemiology and End-Results Program
SPCG4	Scandinavian Prostate Cancer Group Study 4
TRUS	Transrectal ultrasound
TURP	Transurethral resection of the prostate
WHO	World Health Organization
%FPSA	Percentage of free prostate-specific antigen

ABSTRACT

Introduction: The Finnish Population-based Prostate Cancer Screening Trial is a part of multicenter European study launched in the mid 1990's to evaluate the effectiveness of prostate-specific antigen (PSA)-based screening. So far, no conclusive evidence exists to prove (or disprove) the effectiveness of prostate cancer screening with PSA in terms of mortality. The aim of this dissertation is to assess the early outcome measures of PSA screening in the Finnish component of the European Randomized Study of Screening for Prostate Cancer (ERSPC).

Material and methods: The Finnish trial was initiated in 1996 and involves a comprehensive population sample of 80,458 men aged 55, 59, 63 and 67 years at entry. The first round of screening was carried out 1996-1999. Each year 8,000 men were randomly assigned to the screening arm, the remainder forming the control arm. A total of 30,403 men were eligible for screening at the time of invitation. A blood sample was drawn after written informed consent from those randomized to the screening arm to determine the serum concentration of PSA. The total concentration of serum PSA was used as a principle test of screening, and all those with PSA 4.0 µg/l or higher were referred for diagnostic examinations including prostate biopsy. A supplementary screening test was offered to men with moderately elevated PSA levels (i.e., PSA 3.0-3.9 µg/l). A supplementary digital rectal examination (DRE) was used up to the end of 1998, after which it was replaced by the percentage of free prostate-specific antigen (%FPSA). The second round of screening was carried out 2000-2003 after a screening interval of four years, and the final third round came to an end in 2007. The follow-up is still insufficient for mortality assessment.

Results: Wide coverage of the target population was obtained in PSA-based prostate cancer screening as evinced by the participation rate of close to 70% in both the first and second rounds of the Finnish screening trial. Adverse effects related to sextant biopsies of the prostate were common, but relatively well tolerated. The adoption of PSA screening dramatically increased the detection of

early stage prostate cancer. The second round showed a further shift towards earlier clinical stages, and more importantly, a reduction in the detection of advanced cancer compared to the initial screening round. No support was found for family history selective screening compared with a comprehensive population approach: First, the program sensitivity of family history selective screening was inadequate and not balanced by an improvement in the program specificity to justify a selective approach. Second, no difference was observed in prognostic factors between those with and without a family history of prostate cancer, suggesting a similar potential for effectiveness. The program specificity was improved by the use of supplementary DRE and %FPSA at moderately elevated PSA levels (reducing the adverse effects of screening), but the contribution of these supplementary screening tests to the overall prostate cancer detection was only modest in the Finnish trial. Finally, our results confirmed that PSA is a powerful predictor of biopsy outcome in previously unscreened populations as demonstrated by 3.7 biopsies required per cancer in the first round of screening above a PSA cutoff of 4.0 µg/l. However, the number of biopsies per cancer increased to 5.6 at repeated screening, demonstrating the loss in positive predictive value over successive screens.

Conclusions: The Finnish Population-based Prostate Cancer Screening Trial with PSA achieved favorable findings in several process measures of screening, i.e., intermediate indicators of the final outcome (prostate cancer mortality). Although such indicators are still inconclusive for demonstrating the effectiveness of PSA screening, they support the continuation of the Finnish trial. Ultimately, the benefit of PSA screening (measured in terms of quality of life and prostate cancer mortality) should outweigh the drawbacks (which are inevitable) thereby justifying its use as a means of public health policy.

INTRODUCTION

So far, no conclusive evidence exists to prove (or disprove) the effectiveness of prostate cancer screening with prostate-specific antigen (PSA) in terms of mortality. Nevertheless, PSA is widely used for the early detection of prostate cancer in both primary care and urological practice. The test itself is relatively inexpensive, simple and safe to perform. It is also widely agreed that the introduction of PSA testing to previously unscreened populations dramatically increases the detection of early-stage prostate cancer. While other tests (e.g., digital rectal examination and transrectal ultrasound) proposed for prostate cancer screening have proven ineffective and costly, expectations regarding the use of PSA for screening were initially high (Chadwick et al., 1991). Soon concern was expressed, however, about the enormous potential for overdetected of prostate cancer with PSA screening (Woolf, 1995). Critics also argued that scientific efforts to assess the consequences of PSA screening are even unethical because of overdiagnosis and the adverse effects of prostate cancer treatment. Moreover, insufficient evidence on the management of screen-detected cancers cast doubts on PSA screening. Nearly two decades after the commencement of the first studies on screening with PSA, these questions remain relevant.

A major effort was launched in 1994 in Europe, when the European Randomized Study of Screening for Prostate Cancer (ERSPC) was initiated with the aim of evaluating the effect of PSA-based screening on prostate cancer mortality. The first mortality results of the ERSPC trial are expected within a few years (Auvinen et al., 1996). The Finnish Prostate Cancer Screening Trial, with a study population of 80,000 men, forms the largest component of the ERSPC (excluding the French section, which however, joined too late to be included in the first outcome analyses). The focus in this thesis was on the intermediate indicators of the effectiveness of screening as estimated on the basis of the first and second round results of the Finnish trial. A favorable impact of screening on the early outcomes is required to demonstrate an effect at the primary endpoint,

prostate cancer mortality, although they still provide inconclusive evidence on the ultimate effectiveness of screening. In addition to the surrogate measures of screening effectiveness, the feasibility of family history selective screening and the acceptance of prostate biopsy were assessed in this thesis.

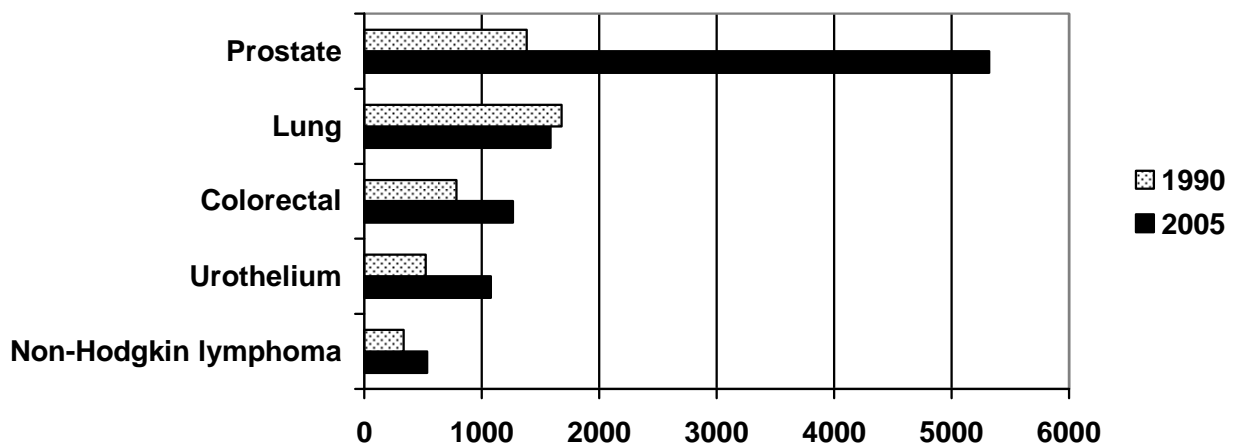
REVIEW OF THE LITERATURE

1. Occurrence of prostate cancer

1.1. Incidence

During the last few decades, the number of new prostate cancer cases has increased dramatically in affluent populations. Prostate cancer is now the most common cancer in men in Europe and North America, and second only to lung cancer globally (Ferlay et al., 2007; Parkin et al., 2005). An estimated 679,023 new prostate cancer cases were expected worldwide in 2002 (Globocan, 2002). Approximately 75% of all new prostate cancer cases occur in industrialized countries (Globocan, 2002). In the United States alone, a total of 218,890 new cases were anticipated in 2007 (i.e., roughly a third of the world total) (Jemal et al., 2007). In Finland, prostate cancer has become the most common male cancer over the last decade with 5,321 new cases diagnosed in 2005 (www.cancerregistry.fi/eng/, 2008) (Figure 1).

Figure 1. Most common male malignancies by site in Finland in 1990 and 2005 (Engholm et al., 2007).



Prostate cancer is a disease of elderly men as evinced by a 100-fold difference in cancer rate between men younger than 50 years and those older than 85 years (www.cancerregistry.fi/eng/, 2008). According to the Finnish Cancer Registry age-specific incidence ranged from 20 per 100,000 person-years in men aged 45 to 49 up to 1,198 per 100,000 person years among those older than 85 years according to the Finnish Cancer Registry during the period 2002-2006. Less than 0.1% of all new cases surface clinically before the age of 50 years. However, autopsy studies have shown microscopic foci of prostate cancer in up to 27% of men in their 30's who died from unrelated causes (Franks, 1954; Sakr et al., 1994). An incidental tumor occurs in approximately half of men in their 50s, and by the age of 85 years microscopic evidence of malignancy can be found at autopsy in more than 75% of men (Franks, 1954; Breslow et al., 1977; Montie et al., 1989). The cumulative (lifetime) risk of developing clinical prostate cancer is still significantly lower. The risk is highest in the United States, with an estimated lifetime risk of 17% (Jemal et al., 2007). It is evident that only a minority of microscopic lesions will progress to a clinical, symptomatic disease.

The incidence of prostate cancer varies widely between populations and countries. Geographically the highest rates are seen in North America and Scandinavia, whereas the risk is lowest in Asia. The age-standardized incidence of prostate cancer ranges from 0.3 in Bangladesh and 1.7 in China up to 124.8 per 100,000 person-years in the United States according to estimates for 2002 (Globocan, 2002). Many factors such as access to and quality of health care, as well as the accuracy of cancer registration may account for these differences. A wide variation in age-adjusted incidence between groups of different ethnic backgrounds residing within the same geographical region suggests, however, that differences are unlikely to be accounted for by non-biological factors alone, indicating the existence of different genetic susceptibility for prostate cancer. In the United States, for example, the age-standardized incidence of 243.0 per 100,000 person-years in African-Americans was more than 50% higher than the rate in white men (156.0 per 100,000 person-years), and nearly 150% higher than that among those of Asian origin (104.2 per 100,000 person-years) in

1999-2003 (Jemal et al., 2007). On the other hand, the increasing rates of clinical prostate cancer among migrants from low-risk countries (such as Japan) to areas of higher risk also indicate the importance of environmental and/or lifestyle factors (Shimizu et al., 1991). Much less variation between countries has been reported for the occurrence of latent prostate cancer than in clinical cases, which suggests that differences in risk are due to factors affecting a late stage of carcinogenesis (progression from preclinical to clinical stage) (Breslow et al., 1977; Yatani et al., 1982).

During the last few decades, incidence rates have been heavily influenced by increasing awareness and health care activity for the management of disorders related to the prostate. Within a relatively short period of time from the 1970's to the 1990's, the average age-adjusted incidence of prostate cancer increased several fold e.g., in the United States. Much of the early increase in the 1970's and early 1980's was assumed to be attributable to increasing utilization of transurethral resection of the prostate (TURP) for benign prostatic hyperplasia (BPH) (Merrill et al., 1999). Histological evaluation of TURP specimens commonly reveals an incidental tumor in approximately 10% of patients with no prior clinical suspicion of prostate cancer (Merrill & Wiggins, 2002). The rate of incidental tumors has been suggested to be leveling off due to extensive PSA driven case-finding (Zigeuner et al., 2003). Effective medical therapies currently available for BPH also reduce the need for surgical intervention, limiting the number of cancers found by chance (Wei et al., 2005).

A steep increase occurred in the incidence of prostate cancer in the late 1980's paralleling the introduction of PSA testing. The measurement of serum PSA concentration was first approved by the United States Food and Drug Administration as a method of monitoring disease progression in 1986, but it was rapidly adopted for screening purposes. As a consequence of this, the incidence of prostate cancer increased rapidly 1988-1992 in the United States, and then declined sharply until around 1995. After 1995, prostate cancer incidence began to rise again at a less rapid rate (Jemal et al., 2007). Similar patterns of prostate cancer incidence have also been observed in several other

populations. In Finland, the age-standardized incidence has more than doubled from 40.0 per 100,000 person-years from the period 1987-1991 to 115.1 per 100,000 in 2005 (www.cancerregistry.fi/eng/, 2008). A long-term increase in both the relative and absolute number of new prostate cancer cases was reversed in 2006 among Finnish men. It is of interest to see whether this reflects a more permanent change in the occurrence of prostate cancer. The falling rates have commonly been explained by an exhaustion of the supply of latent cancers, although this assumption is heavily biased e.g., by possible changes in effort undertaken for early detection of the disease.

In addition to the aforementioned factors, population aging also heavily influences the occurrence of prostate cancer. Inevitably, increasing life-expectancy and high fertility after the Second World War are still increasing the absolute number of new prostate cancer cases worldwide, and will continue to strain health resources in the future. By 2050, over 1.8 million new prostate cancer cases are expected to occur worldwide, i.e., an approximately 200% increase on the present situation (Parkin et al., 2001a; Parkin et al., 2001b).

1.2. Mortality

Prostate cancer is a significant public health problem with an estimated annual total of 221,000 deaths globally (i.e., 5.8% of all cancer deaths in men) in 2002 (Globocan, 2002). In several industrialized countries, prostate cancer is the second leading cause of cancer death in men (exceeded only by lung cancer). Among all causes of death, however, prostate cancer is much less prominent. In Finland, for example, prostate cancer deaths represent only one tenth of those resulting from ischemic heart diseases (www.stat.fi/til/ksyyt/tau.html, 2008). As a result of widespread PSA testing, the ratio of incidence to mortality has increased disproportionately. Indeed, only 1 in 30 men currently diagnosed with prostate cancer in the United States is likely to die of it

(Jemal et al., 2005). Because of the aging population of the world, prostate cancer is likely to remain a major life-threatening disease in the future.

Prostate cancer mortality (like incidence) differs substantially between populations. African-American men have the highest prostate cancer mortality rate in the world, and they are twice as likely to die of it than e.g., white Americans (Clegg et al., 2002). In general, mortality rates are high in Europe (especially in Scandinavia), North America, Australia/New Zealand, the Caribbean, parts of South America and sub-Saharan Africa, whereas the lowest rates have been reported in Asia (Globocan, 2002).

Prostate cancer mortality was rising in most countries until the late 1980's (Hsing et al., 2000). However, death rates are now falling in some parts of the world (Oliver et al., 2001; Feuer et al., 2002; Kvåle et al., 2007). In the United States, the declining trend in mortality began in the early 1990's, and was the largest seen for any cancer in the Surveillance, Epidemiology and End-Results Program (SEER) during 1992-2001 (Feuer et al., 2002). The average decline was 2.7% in black men (1993-2001) and 4.2% among white men (1994-2001). In Finland, prostate cancer mortality increased slightly from the 1980's, and peaked in 1996 (www.stat.fi/til/ksyyt/tau.html, 2008). After that, the trend was reversed with an average annual decline of 1.9% from 1996 to 2004 (Kvåle et al., 2007). At the same time, the absolute number of prostate cancer deaths has remained around 800 cases per year (www.stat.fi/til/ksyyt/tau.html, 2008). Declining trends have also been observed for Canada, the United Kingdom, France and Italy, but the long-term trend of rising death rates has persisted, or remained static in several other countries (e.g., in Scandinavia excluding Finland and Norway) (Oliver et al., 2001; Kvåle et al., 2007).

It has been extensively debated to what extent the declining death rates may be a consequence of PSA screening. Only inconclusive evidence is currently available to show the mortality benefit (if any) attributable to PSA screening, whereas a number of controversies in the relationship between the uptake of PSA testing and prostate cancer death rates have been pointed out (Oliver et al.,

2001). Mortality rates are falling in the United States, where PSA testing is extensively utilized, but not in Australia, where PSA testing is also widely used (Oliver et al., 2001). In Canada, the greatest declines in prostate cancer mortality were seen in regions with the smallest increases in prostate cancer incidence, the latter representing a surrogate for the intensity of PSA screening (Coldman et al., 2003). In the United States, the trend in prostate cancer mortality was reversed around 1991, approximately 5 years after the introduction of widespread PSA testing (Chu et al., 2003). It has been suggested that declining mortality over the last decade is primarily due to a decrease in metastatic disease, and not to an improvement in the survival of these patients (Chu et al., 2003). This supports the potential benefit of early detection because stage-reduction is a necessary prerequisite for the effectiveness of screening, as later discussed. Nevertheless, mortality began to fall too soon to be attributed to the use of PSA testing.

Another likely reason for the decreasing death rates is advances in the clinical management of prostate cancer. A trend towards more aggressive management of localized prostate cancer has been observed over the past 20 years as evinced by a dramatic increase in the number of radical prostatectomies performed in the United States (Jemal et al., 2002). The first concrete evidence of mortality benefit attributable to radical surgery of prostate cancer was not available until 2005 (Bill-Axelson et al., 2005). Yet in absolute terms the reduction in prostate cancer mortality with radical therapy seems only moderate, and is unlikely alone to account for the changes in death rates. No conclusive evidence is available to evaluate the impact of advances in radiation therapy (e.g., neoadjuvant endocrine therapy and technical achievements enabling higher radiation doses) on mortality. Endocrine therapy for advanced and metastatic prostate cancer has also undergone some improvements over the last few decades with the introduction of medical androgen deprivation therapy. Although the effectiveness of medical castration is practically comparable with the surgical procedure, it may be more acceptable, and thus improve compliance with endocrine therapy extending survival among patients with advanced prostate cancer. The initiation of endocrine

therapy earlier in the course of disease may also to some extent reduce death rates (Iversen et al., 2004).

Other factors which may have influenced the changing rate of prostate cancer mortality include decrease in the underlying incidence of prostate cancer, increase in competing causes of death, as well as artifact, e.g., caused by misattribution of prostate cancer deaths (Feuer et al., 1999). It is unlikely that decrease in the occurrence of aggressive prostate cancer would account for changing trends in mortality, given that overall incidence is increasing in most countries where mortality trends have reversed. Yet the changes in the true occurrence of prostate cancer are difficult to estimate because of the strong influence of case detection, especially the intensity of PSA testing. A possible increase in competing causes of death is also difficult to estimate, but it does not seem a plausible explanation in light of current knowledge of other life-threatening conditions. Mortality trends may be also influenced by death-cause evaluation. Misclassification of cause of death may result in a 3-20% bias in the reports on prostate cancer mortality (Newschaffer et al., 2000; Albertsen et al., 2000; Mäkinen et al., 2008).

2. Development and progression of prostate cancer

2.1. Etiology and pathogenesis of prostate cancer

The natural history of prostate cancer, and in particular its progression to a clinical disease is insufficiently known. Androgens are crucial for the malignant transformation of the prostatic epithelium, as demonstrated by the fact that men castrated prior to puberty do not develop prostate cancer (Huggins & Hodges, 1941). According to a stem cell hypothesis, prostate cancer originates from an androgen-dependent stem cell population in the glandular tissue (Bonkhoff & Remberger, 1996).

Adenocarcinomas comprise more than 95% of all prostatic tumors (Gleason, 1992). More than two thirds of them arise in the peripheral zone, one fourth in the transition zone and the remainder in the central zone (McNeal et al., 1988). Multifocality is a typical feature of prostate cancer confounding the assessment of tumorigenesis (Ruijter et al., 1999).

Only few candidate lesions have been proposed as precursors for prostate cancer. Prostatic intraepithelial neoplasia (PIN) was first described in 1965 and later proposed as a premalignant lesion for prostate cancer (McNeal, 1965; McNeal et al., 1986). Low and high grade variants have been recognized according to the severity of the histologic changes (Bostwick, 1989). Specifically, an association between high grade PIN and prostate cancer has been regarded as overwhelming. Like prostate cancer, most high grade PIN lesions evolve in the peripheral zone of the prostate (Qian et al., 1997). High grade PIN has been found to co-exist in approximately 80% of all cases of prostate cancer (McNeal et al., 1986). Similar cytologic and genetic changes are commonly seen in high grade PIN and adjacent foci of prostate cancer (Alers et al., 1995; Emmert-Buck et al., 1995). The prevalence of high grade PIN in prostate biopsy is approximately 5% (Bostwick et al., 1995). The chance of finding prostate cancer at repeat biopsy after initial diagnosis of high grade PIN has varied 23-51% (O'Dowd et al., 2000; Kronz et al., 2001; Park et al., 2001).

Recently, the significance of PIN has been disputed by accumulating evidence from large population-based studies showing that its predictive value is diminished in the era of widespread PSA testing (Postma et al., 2004). In the Dutch section of the ERSPC, PIN was not predictive of prostate cancer either at prevalence or incidence screen with a screening interval of four years (Postma et al., 2004). This challenges the current recommendations indicating a re-biopsy and close follow-up for men found with an isolated PIN.

Lesions suspicious for prostate cancer, also known by the term atypical small acinar proliferation, have been proposed as lesions predictive of prostate cancer (Iczkowski et al., 1998). This lesion is characterized by proliferation of the prostatic glands with abnormal architectural patterns, but

cytonuclear atypia is insufficient for a definite diagnosis of prostate cancer (Yang et al., 2002). Lesions suspicious for prostate cancer are seen in 1.5-4.8% of prostate biopsies (DeMarzo et al., 2003). In previously unscreened population, the risk of prostate cancer at repeat biopsy was somewhat elevated if a lesion suspicious for prostate cancer was found at initial biopsy (Postma et al., 2004). However, the association disappeared during successive screening visits (Postma et al., 2004).

Atypical adenomatous hyperplasia, usually arising in the transition zone of the prostate, closely resembles well-differentiated prostate cancer. It has been suggested as a potential precursor for cancers arising in the transition zone, but the evidence is much less convincing than that for high grade PIN (Bostwick & Qian, 1995).

Prostatic atrophy is a more recently proposed premalignant lesion of prostate cancer (Platz & De Marzo, 2004). It has been hypothesized that atrophy results from chronic inflammation. Several forms of prostatic atrophy have been described. Simple atrophy and post atrophic hyperplasia are highly proliferative lesions, which are also known by the common term proliferative inflammatory atrophy (DeMarzo et al., 2003). Sclerotic atrophy is a third, less common form of atrophy which has been described to occur in the prostate (Ruska et al., 1998). Proliferative inflammatory atrophy especially has been linked to prostate cancer because of its spatial relationship with cancer in radical prostatectomy specimens, and some molecular changes in common with prostate cancer and PIN (Putzi & De Marzo, 2000; Tsujimoto et al., 2002). Yet atrophy is a very common lesion, e.g., its simple form can be found in more than 90% of men biopsied because of an elevated PSA level (Postma et al., 2005). Moreover, no association with prostate cancer has been observed in a screening setting (Postma et al., 2005).

The association of benign prostatic hyperplasia (BPH) with prostate cancer has long been debated (Greenwald et al., 1974; Armenian et al., 1974). BPH is clinically the most common of the benign conditions affecting the prostate. Its occurrence begins to increase after the age of thirty in contrast

to prostate cancer, which is rarely diagnosed before the age of forty. Nearly all BPH arises in the transition zone while prostate cancer is most commonly seen in the peripheral zone of the gland (McNeal et al., 1988). Moreover, deoxyribonucleic acid (DNA) alterations have been shown to be distinctly different in BPH and prostate cancer (Malins et al., 1997). The temporal association between BPH and prostate cancer is hence more likely attributable to a similar age pattern than a common pathway in disease progression.

2.2. Natural history of prostate cancer

A great deal of uncertainty prevails in the understanding of the natural history of prostate cancer. Autopsy studies have shown that prostate cancer can be found in more than half of men in their fifth decade of life (Sakr et al., 1994). By the eighth decade, three-fourths of men have histological evidence of latent prostate cancer (Franks, 1954). However, the lifetime risk of clinical prostate cancer is several times lower than the rate found by autopsy studies. Currently, the highest risk of 17% has been reported for men living in the United States, but in the future widely introduced PSA testing may still reduce this difference between the lifetime risk (incidence) and autopsy prevalence (by increasing overdiagnosis) (Jemal et al., 2007).

Because of the slow development of the disease, the majority of prostate cancers are unlikely to kill the patient. Studies from Connecticut and Sweden have reported the long-term outcome for patients with a localized prostate cancer managed expectantly over a period of more than 20 years (Johansson et al., 2004; Albertsen et al., 2005b). They confirmed that most patients with an early stage prostate cancer have a favorable outcome even without any attempt at cure. After 20 years of follow-up, highly differentiated tumors, i.e., Gleason score 2-4, 5 and 6, were associated with respective disease-specific mortality of 7%, 14% and 27% (Albertsen et al., 2005b). Conversely,

men with aggressive cancer (i.e., Gleason score 7 or higher) faced a high risk of disease progression and eventual death from prostate cancer (i.e., 45-66%) if left untreated (Albertsen et al., 2005b).

The most important limitation of the studies from both Connecticut and Sweden is the fact that the study cohorts (tumors) are likely to differ significantly from the current population of men with early stage prostate cancer. Both the Swedish and American studies were conducted in the 1970's and early 1980's (before the widespread use of PSA testing). Moreover, a substantial number (i.e., 48-71%) of cases were detected incidentally at operations for BPH, which is generally associated with a better prognosis than if diagnosed on clinical basis (Cantrell et al., 1981).

Predicting and understanding the long-term outcome for men with newly diagnosed prostate cancer has become particularly challenging in the PSA era. First, the use of PSA allows the diagnosis of prostate cancer several years earlier than on the basis of clinical symptoms. As a consequence of this, survival may appear improved even if the time of death is not actually postponed (i.e., lead-time bias) (Auvinen et al., 2002). Second, overdiagnosis attributable to PSA testing is inevitable. E.g., in the Dutch section of the ERSPC, the proportion of indolent cases has been estimated to be close to 50% of all detected cases (Draisma et al., 2003). The applicability of earlier data to patients now is likely to be distorted by both of these factors. So far, virtually no data are available concerning the long-term outcome of cancers detected by means of PSA.

2.3. Risk factors of prostate cancer

A risk factor is anything that increases a person's chance of developing a disease. Possible risk factors for the occurrence of prostate cancer have been extensively studied. Yet only few risk factors have been established for prostate cancer. Of these, the most important are age, ethnicity and genetic factors. An overview of commonly suggested factors associated with the risk of developing prostate cancer is given in Table 1.

Table 1. Overview of commonly suggested factors associated with the risk of developing prostate cancer (PC).

Risk factor	Association*	Comment
Age	+	Incidence of PC increases markedly with age (e.g., www.cancerregistry.fi/eng/ , 2008)
Ethnicity	+	Wide variation in incidence of PC by race (Jemal et al., 2007)
Family history	+	Several meta-analyses. E.g., a review of 24 studies (Bruner et al., 2003)
Diet		
Dairy products	(+)	High intake suggestive of a small increase in risk according to a meta-analysis of 12 studies (Gao et al., 2005)
Calcium	(+)	An increased risk associated with a high intake of calcium (Dagnelie et al., 2004)
Meat	(+)	Most reported associations positive or null (Dagnelie et al., 2004)
Dietary fat	+/-	No consistent relationship (Dagnelie et al., 2004)
		Dietary linolenic acid associated with an increased risk of PC in a meta-analysis of 9 studies (Brouwer et al., 2004)
		Evidence for omega-3 fatty acid contradictory in a systematic review of 17 studies (MacLean et al., 2006)
Vitamin D	+/-	No consistent relationship (Dagnelie et al., 2004) Suggested association U-shaped (Tuohimaa et al., 2004)
Phyto-estrogens	(-)	Protective in meta-analysis of 8 studies (Yan & Spitznagel, 2005)
Lycopene	(-)	High tomato intake related to reduced risk in meta-analysis of 21 studies (Etminan et al., 2004)

Risk factor	Association*	Comment
<i>Continue (Table 1)</i>		
Selenium	(-)	Protective in meta-analysis of 16 studies (Etminan et al., 2005)
Vitamin E	(-)	A negative association with serum levels of vitamin E and PC risk (Dagnelie et al., 2004) Vitamin E intake protective among current or past smokers (Heinonen et al., 1998)
Alcohol	0	No relation with PC in most studies (Dagnelie et al., 2004)
Other		
Prostatitis	(+)	Meta-analysis of 11 case-control studies (Dennis et al., 2002)
Obesity	+/-	Weak association in meta-analysis of 56 studies (particularly for advanced PC) (MacInnis & English, 2006) Reduced risk of non-aggressive PC (Freedland & Platz, 2007)
Androgens	0	Crucial in etiopathogenesis, but no association between androgen levels and PC risk (Roddam et al., 2008)

* + Evidence consistent for a positive association for an increased risk of PC, (+) Some evidence showing a positive association for an increased risk of PC, +/- No consistent relationship with PC risk, (-) Some evidence showing a protective effect against PC, 0 No relation with PC

2.3.1. Age and ethnicity

The association of age with prostate cancer is indisputable. The incidence of prostate cancer increases faster with age than that of any other major cancer. In the United States, for example, the probability of being diagnosed with prostate cancer is only 1 in 19,299 for men younger than 40 years, 1 in 45 for men aged 40 to 59 years, and 1 in 7 for men aged 60 to 79 years (Jemal et al., 2003).

Abundant epidemiological evidence is also available to support the view that ethnicity is a major risk factor for the development of prostate cancer. Substantial variation occurs in prostate cancer incidence between populations of different ethnic backgrounds. In the United States, for example, the highest rates have been observed for African-American men whereas men of Asian origin have a substantially lower risk of developing prostate cancer (Jemal et al., 2007). Differences are likely to be attributable to both genetic and environmental factors, as evinced by the increase of prostate cancer risk among Japanese men after immigration to North America (Shimizu et al., 1991). Yet the incidence among Japanese immigrants remains still lower than that in other ethnic groups residing within the same geographical region (Cook et al., 1999). It is unlikely that lifestyle and dietary habits alone account for these observed variations of prostate cancer risk between different races.

2.3.2. Family history

The strongest risk factor for prostate cancer, excluding age, is family history. Twin studies suggest that the genetic component of the risk of prostate cancer is greater than in any other cancer (Lichtenstein et al., 2000). An increased risk of prostate cancer has been shown for men with a positive family history, especially if any first-degree relatives have been affected (Bruner et al., 2003; Johns & Houlston, 2003; Zeegers et al., 2003). A meta-analysis of 33 epidemiological

studies showed a rate ratio (RR) of 3.4 (95% CI 3.0-3.8) for men with an affected brother compared to an RR of 2.2 (95% CI 1.9-2.5) for men with an affected father (Zeegers et al., 2003). The risk was also shown to increase with the number of relatives affected: An RR of 2.6 (95% CI 2.3-2.8) was seen among men with one first-degree relative compared to 5.1 (95% CI 3.3-7.8) in men with two or more first-degree relatives affected. Men with a family history on the maternal side, or with relatives diagnosed at an early age, are also more likely to be diagnosed with prostate cancer than those without any affected family members (Zeegers et al., 2003). However, familial risk estimates may be confounded by an increased risk of finding an incidental tumor upon seeking medical advice because of the first cancer in a family (detection bias) (Bermejo & Hemminki, 2005). Presumably this issue is more relevant for prostate cancer with a high prevalence of incidental tumors than for most other cancers.

Irrespective of the strong evidence for genetic factors, highly penetrant susceptibility genes for prostate cancer have proven difficult to find. Identification of prostate cancer genes is particularly challenging because of the late onset of the disease, high background incidence of sporadic prostate cancer and inconsistent criteria for hereditary forms of the disease. Large twin studies have suggested that the majority of hereditary prostate cancer risk may be attributable to recessive and/or multiple interacting genetic variants (Risch, 2001). Each such variant may be expected to confer a small increase in overall risk. If the variant is common, it may contribute significantly to the population attributable risk of the disease. In the Swedish population-based Family Cancer Database up to 20.6% of all prostate cancer in Sweden could be attributed to familial risk factors (Hemminki & Czene, 2002).

Several candidate susceptibility loci for prostate cancer have been proposed among high-risk families (Table 2). However, subsequent studies have failed to demonstrate that any of these loci contribute to a substantial number of high-risk families. Due to extensive locus heterogeneity, it is likely that more than one gene can produce a very similar clinical phenotype of prostate cancer.

Proposed loci (or genes) for prostate cancer susceptibility are still insufficiently known, and the prevalence of each individual locus (or gene) conferring predisposition for prostate cancer is too low to be of clinical relevance in understanding disease burden at population level (Ntais et al., 2003; Li & Tai, 2006; Sun et al., 2006; Zheng et al., 2008). However, combined information of different genetic markers may resolve this issue in the future. According to a recent study from Sweden, five selected chromosomal regions commonly associated with prostate cancer together with family history were estimated to account for almost half of all prostate cancer cases among Swedish men (Zheng et al., 2008). None of the five regions in this study did much on their own to raise prostate cancer risk. However, the risk of prostate cancer was nine-fold higher in men with at least four abnormal markers together with positive family history than in those with none of these factors. None of the markers studied were significantly associated with the aggressiveness of prostate cancer either alone, or together, leaving the clinical significance of detected tumors unascertained.

Table 2. Examples of susceptibility loci (or genes) suggested for prostate cancer.

Loci/Gene	Chromosome region	Comment
HPC1/RNASEL	1q24	A major susceptibility locus (Smith et al., 1996) RNASEL gene proposed to form the molecular basis of this association (Wang et al., 2002)
PCAP	1q42	High-risk families of German and French origin (Berthon et al., 1998)
HPCX	Xq27-q28	High-risk families in the United States, Finland and Sweden (Xu et al., 1998)
CAPB	1p36	One or more cases of primary cancer (Gibbs et al., 1999) Early-onset prostate cancer (Badzioch et al., 2000)
HPC20	20q13	Late-onset disease and fewer family members affected (Berry et al., 2000).
MSR1	8p22	Chromosome 8p commonly deleted in prostate cancer (Xu et al., 2002)
-	8q24	Population attributable risk as high as 8% among Icelanders Associated with a higher risk in African Americans (Amundadottir et al., 2006)

2.3.3. Dietary factors

An influence of diet on prostate cancer risk has been suggested in numerous epidemiological studies. Particularly, high consumption of fat, meat and dairy products has been proposed to carry an increased risk of prostate cancer (Howell, 1974). Even though the results of epidemiological studies have often been inconsistent, some dietary components are consistently associated with prostate cancer. For example, high intake of dairy products has been related with a small increase in prostate cancer risk (Gao et al., 2005). Calcium has also been associated with an increased risk of prostate cancer (Chan et al., 2001). In the Physicians' Health Study, a cohort of men was followed prospectively for dietary calcium intake in relation to subsequent risk of prostate cancer. Men consuming more than 600 mg calcium per day were 1.32 (95% CI 1.08-1.63) times more likely to be diagnosed with prostate cancer compared to those consuming 150 mg calcium per day or less (Chan et al., 2001). This finding was supported by a large Swedish case-control study (Chan et al., 1998). Diets rich in meat have also been linked to a risk of developing prostate cancer, but the evidence remains inconclusive (Dagnelie et al., 2004). One hypothesis postulates that specifically the preparation of meat (e.g., grilling and frying) at high temperatures is responsible for this association, resulting in potent carcinogens which have been correlated with some other types of cancer. High intakes of polyunsaturated fat, especially α -linolenic acid, have also been linked to increased prostate cancer risk (Giovannucci et al., 1993; Brouwer et al., 2004).

Several dietary factors have also been proposed to be inversely related to prostate cancer risk. One explanation for the lower incidence of prostate cancer in Asia than in Western populations is high consumption of dietary phyto-estrogens. It has been assumed that phyto-estrogens could theoretically modulate androgenic activity in the prostate. Soybean products rich in phyto-estrogens especially have shown a prophylactic effect against prostate cancer (Yan & Spitznagel, 2005). Frequent intake of tomato-based products has also been associated with reduced risk of prostate

cancer. Tomatoes contain a potent antioxidant, lycopene. A prospective study of 2,481 men revealed 16% lower risk among men consuming large amounts of lycopene compared to those with small consumption (Giovannucci et al., 2002). A slight preventive effect against prostate cancer was also found in a meta-analysis of 21 observational studies on the consumption of lycopene and tomato-based products (Etminan et al., 2004). A high intake of tomato sauce has also been shown to reduce circulating levels of PSA (Chen et al., 2001). Of dietary fats, omega-3 fatty acid has been proposed to be protective against prostate cancer. However, in a systematic review of omega-3 fatty acid consumption one study reported an association with a reduced risk of prostate cancer whereas 15 studies failed to demonstrate a significant association (MacLean et al., 2006).

Selenium and vitamin E have been also associated with a reduced risk of prostate cancer (Clark et al., 1998; Heinonen et al., 1998). Selenium inhibits tumorigenesis in human tumor cells, including prostate cancer (Redman et al., 1997). A cancer prevention trial among 1,312 patients with a history of skin cancer revealed interestingly a 66% lower risk of prostate cancer in the selenium group than in the placebo group, although no effect was observed for the prevention of skin cancer (primary outcome measure) (Clark et al., 1998). A recent meta-analysis also suggests that selenium may prevent the risk of developing prostate cancer (Etminan et al., 2005). Alpha-tocopherol is the most powerful antioxidant of the compounds collectively known as vitamin E. In a large Finnish cancer prevention study among current or past smokers, those receiving α -tocopherol had a prostate cancer incidence of 11.7 per 100,000 compared to 17.8 per 100,000 among those taking placebo (Heinonen et al., 1998). On the other hand, men on β -carotene (an A vitamin precursor) supplementation showed an elevated risk for prostate cancer in the same study. Because the trial was primarily designed to examine prevention of lung cancer among smokers, it remains unknown how applicable the results are to non-smokers. Vitamin D has also been suggested to affect the risk of prostate cancer (Tuohimaa et al., 2004). However, the evidence is conflicting since both high and low levels of vitamin D are associated with an increased risk of prostate cancer (Tuohimaa et al., 2004). The

major source of vitamin D is through the action of sunlight in the skin. One hypothesis is that the increased risk of prostate cancer found in northern geographical regions and in African-American men may be attributable to low levels of vitamin D.

2.3.4. Other factors

Obesity, like prostate cancer, has become an increasing health concern. It is associated with many health conditions. Evidence for an association between obesity and prostate cancer, however, is conflicting. A recent meta-analysis suggests that obesity is associated with an increased risk for both advanced prostate cancer and overall disease (MacInnis & English, 2006). On the other hand, obesity has also been associated with a reduced risk of non-aggressive disease (Freedland & Platz, 2007). However, a number of confounding factors make it difficult to study the exact role of obesity in the development of prostate cancer. For example, obesity is likely to affect screening behavior for prostate cancer (Scales, Jr. et al., 2007). Biological differences also occur between obese and normal weight men. Lower levels of PSA have been observed in overweight men, which is likely to affect disease ascertainment, and eventual risk of being diagnosed with prostate cancer (Baillargeon et al., 2005). However, the evidence linking obesity with indicators of prostate cancer outcome (e.g., biochemical recurrence and Gleason score) is currently more consistent, suggesting a somewhat poorer prognosis for obese than for normal weight men (Amling et al., 2004; Rohrmann et al., 2003). A possible explanation for this is that indicators of prostate cancer outcome are less affected by factors influencing disease ascertainment. Increased levels of insulin-like growth factor 1 and estrogenic compounds together with decreased sex hormone-binding globulin have been proposed to be involved with the biological link between obesity and prostate cancer (Wolk et al., 1998; Moyad, 2002). The association between obesity and prostate cancer seems to be complex,

and it is likely to be influenced by both biological and non-biological (i.e., disease ascertainment) causes.

Androgens are known to play an important role in controlling the growth and proliferation of normal prostate cells as well as prostate cancer cells (Huggins & Hodges, 1941). Men castrated before puberty and those with congenital abnormalities in androgen metabolism are known to have a minimal risk of developing prostate cancer. Nevertheless, androgen levels determined either prospectively, or at the time of diagnosis, have not been convincingly associated with an increased risk of prostate cancer (Hsing, 2001). A recent collaborative analysis covering 18 prospective studies on endogenous sex hormones found no association between sex hormone levels and the risk of prostate cancer (Roddam et al., 2008).

Some epidemiological evidence exists for a link between inflammation (prostatitis), as well as ascending urethral infections (e.g., sexually transmitted diseases) and prostate cancer (Dennis et al., 2002). Inflammation has an established role in the etiology of a number of other malignancies (e.g., hepatocellular and esophageal cancer), but the role in prostate cancer is less clear (De Marzo et al., 2007). Nevertheless, clinical prostatitis was associated with a relative risk of 1.57 (95% CI 1.01-2.45) for prostate cancer in a recent meta-analysis (Dennis et al., 2002). Infections (particularly sexually transmitted diseases) have also been linked to the risk of subsequent development of prostate cancer, but clear and consistent findings remain elusive (Dennis et al., 2002).

Smoking has a strong impact on the carcinogenesis of several cancers. For prostate cancer, only limited evidence has been found to support a connection between tobacco and prostate cancer. A modest increase has been observed for men smoking cigarettes (Odds ratio 1.8) and for chewing tobacco (Odds ratio 2.1) (Hsing et al., 1990). Another study observed a somewhat elevated risk of dying from prostate cancer among smokers: the risk was directly associated with the number of cigarettes smoked per day. Compared to nonsmokers, the risk was 1.21-fold in men smoking 25 or fewer cigarettes per day and 1.45-fold among those smoking more (Coughlin et al., 1996). In

Finland, a slight excess of incident prostate cancer cases was found in a large study of almost 30,000 male smokers with the primary aim of assessing the role of α -tocopherol and β -carotene in the prevention of cancer (Malila et al., 2006). An excess of prostate cancer was observed for both the placebo group and the entire study population in addition to the well known smoking-related cancers. These findings together add to the limited evidence indicating that smoking may alter a person's chances of developing prostate cancer.

Several other factors have also been extensively studied to identify factors predisposing to the development of prostate cancer. In a Danish study, no relationship between amount or type of alcohol consumption and prostate cancer could be found (Albertsen & Gronbaek, 2002). Contradictory evidence has been also reported for e.g., vasectomy, social class and sexual activity (Pienta & Esper, 1993; Peterson & Howards, 1998; Nielsen et al., 2007).

2.4. Prevention of prostate cancer

Prostate cancer is a potential candidate for preventive measures due to the long latency of the disease, high prevalence, endocrine dependency, availability of serum markers (e.g., PSA) and, most importantly, epidemiological data suggesting that variation in prostate cancer incidence may be influenced by environmental factors. Currently there is no proven method for preventing the development of prostate cancer. However, both pharmacological and nutritional factors have been extensively studied in the search for preventive measures. Pharmacological prevention, for example, may use drugs affecting intraprostatic testosterone metabolism. Abundant evidence exists that androgens influence the development of prostate cancer. The hypothesis that finasteride, an inhibitor of steroid 5- α -reductase, may influence the development of prostate cancer by reducing androgenic stimulation of the prostate was tested in the Prostate Cancer Prevention Trial (Thompson et al., 2003). This study showed a reduction in cumulative incidence from 24.4% in the

placebo group compared to 18.4% in the finasteride group (Thompson et al., 2003). Notwithstanding this favorable finding in prostate cancer risk, serious concerns were raised by the trial. First, the likelihood of being diagnosed with prostate cancer in the placebo group was four times higher than expected. Cumulative incidence approached the prevalence of latent cancers found at autopsy in men in their fifth decade of life, although the men recruited were defined as low-risk population on the basis of PSA and digital rectal examination at baseline. Second, a greater number of high-grade cancers was found in the finasteride group. It is debatable whether the latter is artefactual, or truly attributable to the effects of finasteride on tumor dedifferentiation. In light of current evidence, finasteride does not seem to be an attractive agent for preventing the development of prostate cancer. The sexual side effects of finasteride are also likely to lessen the attractiveness of the drug as a preventive agent for prostate cancer.

Dutasteride is another 5- α -reductase inhibitor which is currently being investigated for the prevention of prostate cancer (Andriole et al., 2004a). No results are available so far. However, retrospective analysis of data from trials designed to study dutasteride in patients with benign prostatic hyperplasia suggest that dutasteride may also prevent the development of prostate cancer (Andriole et al., 2004b). Moreover, a short-term dutasteride treatment has been shown to induce histopathological changes in prostate cancer suggestive of its potential chemopreventive role (Iczkowski et al., 2005).

Non-steroidal anti-inflammatory drugs (NSAIDs) play a role in inflammation, and may also be involved in the malignant transformation of cells. Limited evidence has suggested that NSAIDs may possess activity preventing prostate cancer. An inverse association (Odds ratio 0.34, 95% CI 0.23-0.58) was reported in a case-control study between the use of over-the-counter NSAIDs and prostate cancer (Nelson & Harris, 2000). In a large cohort study of 90,100 men, the use of aspirin was associated with a relative risk of 0.76 (95% CI 0.60-0.98) (Habel et al., 2002). In a Mayo Clinic cohort study NSAID usage was also linked with a decreased risk (rate ratio 0.45, 95% CI 0.28-0.73)

of developing prostate cancer (Roberts et al., 2002). The COX-2 isoform (i.e., a target of NSAIDs) especially was thought be critical in the malignant transformation of prostatic cells, and selective COX-2 inhibitors were regarded as promising agents in the prevention of prostate cancer (Yoshimura et al., 2000). However, the side-effect profile of NSAIDs, and ultimately concerns about the cardiovascular risks associated with COX-2 inhibitors, have resulted in the discontinuation of most cancer prevention trials with this class of drugs (Bertagnolli et al., 2006).

The pharmacological prevention of prostate cancer may also use drugs that induce apoptosis and inhibit tumor growth. Statins are commonly used cholesterol-lowering drugs with apoptotic activity that may affect cancer risk (Bonovas et al., 2007). Laboratory data suggest that statins may have chemopreventive potential against cancer at various sites, including the breast and the prostate (Kotamraju et al., 2007). Conflicting evidence has been reported from epidemiological studies on the association of statins and risk of prostate cancer (Coogan et al., 2002; Shannon et al., 2005). Some evidence exists that statins are not associated with a risk of prostate cancer overall, but with a reduced risk of advanced prostate cancer (Platz et al., 2006). Again, plausible explanations for the conflicting evidence include, for example, differences in disease ascertainment between cases and controls (or study groups), or simply the lack of an association between statins and prostate cancer. Several dietary factors with possible influence on prostate cancer development include dietary fat, red meat, vegetables, phyto-estrogens, vitamins (D and E) and trace elements (calcium and selenium), as discussed earlier. Several studies are currently ongoing to ascertain whether any of these has potential for successful prostate cancer prevention. For example, a large trial (SELECT) involving some 32,000 men is in progress to investigate the role of selenium and vitamin E for prostate cancer prevention (Klein et al., 2001). The final results will be available at the earliest in 2013.

Interestingly, a large, prospective study reported last year found no association between the regular use of multivitamin supplements and the risk of early prostate cancer (Lawson et al., 2007). On the

contrary, the results suggested an increased risk of advanced and fatal prostate cancer in men regularly using multivitamins (Lawson et al., 2007).

Physical activity has been proposed as a modifiable risk factor for prostate cancer because of its potential effects on circulating hormones, but the findings have been inconsistent. No association was found in a Canadian study between total life-time activity and the risk of developing prostate cancer (Friedenreich et al., 2004). Nevertheless, the results suggested a decreased risk of prostate cancer in men with a history of regular vigorous activity, or activity during the first 18 years of life. A recent study has also suggested that high levels of physical activity may decrease the likelihood of aggressive prostate cancer, particularly in men aged 65 years or older (Giovannucci et al., 2005).

3. Diagnosis and management of prostate cancer

3.1. Diagnosis

The diagnosis of prostate cancer should always be based on the histological examination of tissue samples, most often obtained at a prostate biopsy, showing malignant transformation of prostatic cells. Sometimes prostate cancer may be found incidentally in a pathological specimen removed during surgery for benign prostatic hyperplasia or urothelial malignancy. Sometimes the diagnosis of prostate cancer may be suspected and confirmed only at autopsy. Neither clinical tests nor symptoms alone can fully confirm a diagnosis of prostate cancer.

3.1.1. Symptoms

Prostate cancer does not usually cause any signs or symptoms for many years. Lower urinary tract symptoms, often referred to as early prostate cancer symptoms, are more commonly due to benign prostatic hyperplasia (or some other benign urological disorder) than a cancerous condition (Godley & Carpenter, 2007). Nevertheless, the presence of prostate cancer cannot be excluded, and diagnostic work-up is commonly recommended to determine the underlying cause of such symptoms. By the time that more specific symptoms typically occur, the disease is likely to have spread beyond the prostate. Generally, symptoms suggestive of prostate cancer may include e.g., urinary problems (i.e., nocturia and weak flow), hematuria, hemospermia, and pain in the lower back, hips or upper thighs.

3.1.2. Digital rectal examination

Digital rectal examination (DRE) is a procedure in which the size, shape and the texture of the prostate can be palpated via the rectum. Most cancers are known to arise in the peripheral region adjacent to the rectum, and hence they may be found in DRE. It is usually recommended that a suspicious finding in DRE warrants further diagnostic work-up (including a biopsy). Although asymmetry, induration or nodules are regarded as suspicious for cancer, they are not specific. The positive predictive value of DRE is only 4-11% at PSA levels 3 µg/l and below, but increases up to 83% at PSA levels 10 µg/l or above (Schröder et al., 1998). However, pathological examination often reveals prostate cancer on the opposite side to that raising suspicion of cancer in DRE, especially at low PSA levels (Vis et al., 2002). In fact, men with a unilateral palpable nodule at DRE are as likely to have a positive biopsy (cancer) on the side opposite to the palpable lesion (McNaughton et al., 1997). Reproducibility of DRE has also been shown to be only fair, limiting its

value as a diagnostic method for prostate cancer (Smith & Catalona, 1995). Criticism has been also raised against the role of DRE for early detection of prostate cancer because a substantial proportion of cancers detected by DRE are pathologically advanced, and hence beyond cure (Chodak et al., 1989). It is also noteworthy that many men who ultimately die of prostate cancer may have a normal DRE at the time of diagnosis (Thompson & Zeidman, 1991).

3.1.3. Transrectal ultrasound

Transrectal ultrasound (TRUS) provides somewhat better means of assessing the prostate than DRE. It enables much more precise estimation of the size of the prostate, and also gives additional information on the various zones and the echogenic structure of the prostate (Watanabe et al., 1975). Initially, a biopsy guided to a hypoechoic lesion identified on TRUS was believed to be an effective way of diagnosing prostate cancer (Lee et al., 1985). However, the limitations of this approach became evident over time since the appearance of cancer on TRUS is variable and may be mimicked by a number of other conditions (Oyen et al., 1993). The lack of specificity and high costs are the major disadvantages associated with early detection of prostate cancer with TRUS (Torp-Pedersen et al., 1988; Lee et al., 1988).

3.1.4. Prostate-specific antigen

PSA is serine protease produced at high concentrations by the normal and malignant glandular cells of the prostate (Wang et al., 1981). It is abundant in seminal fluid, and its physiological function is to digest gel forming after ejaculation (Lilja, 1985). Minor amounts of PSA leak out into circulation from the normal prostate. In diseased conditions of the prostate, such as benign prostatic hyperplasia and cancer, the leakage of PSA is increased, presumably due to loss of normal tissue

architecture. The contribution of cancerous tissue to the serum concentrations of PSA is 10 to 30-fold compared to that of hypertrophic, or normal prostatic tissue respectively (Stamey et al., 1987). Therefore, increased levels of PSA may suggest the presence of prostate cancer. PSA was initially approved as a method to monitor disease progression, but was soon adopted to improve the early detection of prostate cancer. Serum bank studies suggest that a single PSA test is a strong predictor of prostate cancer diagnosed up to 25 years later (Vickers et al., 2007; Stenman et al., 1994). A numerous other conditions may also result in elevated PSA levels, which reduces its specificity as a tumor marker. For example, urinary tract infection, manipulation of the prostate (e.g., rigid cystoscopy or prostate biopsy), and even DRE may temporarily influence serum PSA levels (Stamey et al., 1987; Ornstein et al., 1997a). It is noteworthy that a biological variation of approximately 15% also occurs in measurements of total PSA concentration (Ornstein et al., 1997b).

There is an ongoing debate about an optimal PSA cutoff. The population-based estimate for a median level of PSA is approximately 0.5 µg/l before the age of 50 years, when the vast majority of men are likely to be free of prostate cancer and BPH (Hugosson et al., 2004). A PSA cutoff level of 4 µg/l was initially introduced on the basis of an analysis of the optimal sensitivity and specificity of PSA in a single report published by the manufacturer of the test (Myrtle et al., 1986). It has subsequently been argued that many important cancers may be missed at PSA levels below the traditional threshold of 4 µg/l. In the Prostate Cancer Prevention Trial, for example, a PSA cutoff of 4 µg/l would have corresponded to a sensitivity of approximately 20% and a specificity of 95% thus missing the majority of cancers detectable through biopsy (Thompson et al., 2005a). Therefore, lower cutoff levels have been strongly advocated. However, while increasing the chances of detecting prostate cancer (sensitivity), lower cutoffs would increase false positive test results (i.e., reduce specificity), and result in unnecessary diagnostic work-up among healthy individuals.

A common method to improve the performance of PSA is to use age-dependent threshold values for biopsy. Serum PSA levels are known to rise gradually with age, which is mostly attributable to the increasing prevalence of BPH in older men (Babaian et al., 1990). Age-specific PSA ranges have been proposed to improve cancer detection rates (or sensitivity) among younger men and to avoid unnecessary examinations among older (i.e., to enhance specificity) (Oesterling et al., 1995). However, the net benefit of this approach is not known. It has been argued that age-specific ranges could result in failure to detect clinically significant cancers in men who might benefit from early treatment (Bassler, Jr. et al., 1998).

Several ways have been suggested to improve the ability of PSA for distinguishing between malignant and benign conditions. The total PSA in circulation roughly corresponds to the sum of unbound PSA (free PSA, fPSA) and PSA bound to alpha-1-antichymotrypsin (complexed PSA, cPSA), which can be specifically measured by commercially available assays. The free PSA constitutes approximately 5-40% of the total PSA. Men free of cancer generally present with a higher percentage of free PSA (%FPSA) than men with prostate cancer (Chen et al., 1996). The frequency of false-positive results (and unnecessary biopsies) may be reduced, and specificity increased, by using %FPSA as a supplementary criterion for biopsy, particularly for men with PSA levels from 4 to 10 $\mu\text{g/l}$ (Catalona et al., 1998). A low proportion of FPSA also appears to be associated with more aggressive cancer, and may provide valuable information for identifying clinically relevant tumors (Raaijmakers et al., 2007). No decision limit for %FPSA has been agreed on, but generally %FPSA less than 0.07 is regarded as highly suspicious of cancer and a value above 0.25 as indicative of low risk (Chen et al., 1996). The need to validate the cutoff level for each free and total commercial PSA assay combination limits the applicability of %FPSA.

Several other composite measures have also been proposed to improve the specificity of a single PSA measurement for the early detection of prostate cancer. PSA density, PSA velocity and PSA doubling time have all been evaluated in this context (Benson et al., 1992; Carter et al., 1992;

Spurgeon et al., 2007). PSA density considers the relationship of total PSA value to the size of the prostate. The most important limitation of this method is the need for TRUS to measure the volume of the prostate. The higher the PSA density, the greater is the likelihood of prostate cancer (Benson et al., 1992). A PSA density of 0.15 has commonly been applied to differentiate between prostate cancer and benign conditions. Another method of improving the accuracy of PSA is called PSA velocity, which takes into account the change in PSA levels over time. The use of information that PSA levels are likely to rise more rapidly in men with prostate cancer than in men without the disease may improve the diagnostic accuracy of PSA (Carter et al., 1992). Evidence on PSA velocity is conflicting since it has been claimed to add only little (if any) to the diagnostic performance of a single PSA determination in a screening setting (Schröder et al., 2006; Etzioni et al., 2007). The PSA doubling time (defined as the time needed for a PSA concentration to double) has also been shown to be of limited value in the detection of prostate cancer in both screening and referral settings (Spurgeon et al., 2007). However, abundant evidence is available to support the prognostic value of PSA kinetics after therapy with curative intention (Zhou et al., 2005; D'Amico et al., 2005)

3.1.5. Prostate biopsy

A histological verification of prostate cancer is usually obtained at prostate biopsy. Ultrasound guidance was introduced in the late 1980's, and has since become a standard method for diagnosing prostate cancer. A random sextant biopsy was initially regarded as a sufficient method to discover most clinically significant tumors (i.e., minimize sampling error) (Hodge et al., 1989). Later, however, it emerged that a sextant biopsy may miss up to 20-30% of cancers (Rabbani et al., 1998). The technique was first refined by moving the biopsies more laterally to allow better sampling of the anterior horns of the peripheral zone (Stamey, 1995). Later, extended pattern biopsy schemes

were proposed to maximize the chances of finding prostate cancer detectable through biopsy (Presti, Jr., 2003). Extended pattern biopsy schemes have now become a widely accepted method to increase the detection rate. The evidence regarding the value of additional biopsies targeted at suspicious lesions identified in TRUS is contradictory (Onur et al., 2004). In fact, less than one in five suspicious lesions identified on TRUS contains cancer at histological examination (Eskew et al., 1997). On the other hand, more than half of nonpalpable cancers larger than 1 cm in diameter are not visualized by ultrasound (Carter, 1997). Saturation biopsies may be proposed, e.g., when PSA is highly suspicious or constantly rising in a man whose previous biopsies have not revealed cancer. The number of biopsy cores taken may vary from 20 to 40, depending on the size of the prostate. Saturation biopsies have found prostate cancer in up to 34% of men with a negative biopsy with a traditional scheme, yet the technique requires an outpatient surgical setting and intravenous sedation (Stewart et al., 2001). A concern also exists that extended pattern biopsy scheme may add to overdiagnosis of prostate cancer.

In future it may be possible to avoid unnecessary invasive examinations; prostate cancer gene 3 (PCA3) based testing is a novel method, which may aid in making biopsy decisions and reducing the number of unnecessary biopsies, especially in men with constantly elevated PSA levels and negative biopsy findings (Bussemakers et al., 1999; van Gils et al., 2007). The requirement of a urine sample collected after DRE (prostate massage) limits its usefulness in larger populations (e.g., screening purposes).

A prostate biopsy is generally regarded as a safe procedure. However, minor complications such as hematuria and rectal bleeding frequently occur. Discomfort and even pain may be also experienced during the procedure. Major complications, such as septicaemia or profuse bleeding, are uncommon (Rodriguez & Terris, 1998). Antibiotic prophylaxis is usually given orally prior to the procedure to prevent infectious complications. Various methods of anesthesia have been also developed to reduce pain experienced at prostate biopsy. A periprostatic injection of local anesthetics has been

shown to be efficient in preventing pain at biopsy, and has now become a standard of care (Alavi et al., 2001).

3.1.6. Grading

The Gleason score is the most frequently used grading system for prostate cancer (Gleason & Mellinger, 1974; Gleason, 1992). The Gleason score takes into account predominant and second most prevalent patterns of cancer, which are graded from 1 (most differentiated) to 5 (least differentiated). The Gleason score is the sum of the two grades, and ranges from 2 to 10. Hence a Gleason score of 10 describes an aggressive, undifferentiated prostate cancer. It is noteworthy that the Gleason score is not necessarily based on the highest grade within the surgical specimen. For biopsy specimens, however, both the primary pattern and the highest grade should be added to derive the Gleason score to overcome potential problems related to insufficient sampling of high-grade tumor within the prostate (Epstein et al., 2005). An expert panel has agreed that Gleason score 2-4 should not be assigned to cancer on prostate biopsy as most of these are actually graded 5 or more when reviewed by experts in urological pathology (Epstein et al., 2005). Gleason score 2-4 tumors exist, but they are usually found at TURP. It has been recognized that low-grade prostate cancers (i.e., Gleason score 2-4) are rarely seen at biopsy because of the anterior location and the small size of such tumors.

The Gleason score is a powerful predictor of prognosis. The major prognostic shift has been proposed to occur at Gleason score 7, which can be subclassified into 3+4 or 4+3, the latter being more aggressive (Kang et al., 2007). It is common to use terms well to moderately differentiated for Gleason score 2-6 tumors, moderately (3+4) to poorly (4+3) differentiated for Gleason score 7, and poorly differentiated for Gleason score 8-10 prostate cancers (DeMarzo et al., 2003). Recently a

tertiary pattern Gleason grade has been suggested to be of prognostic significance for prostate cancer (Mosse et al., 2004).

The most important limitation of the Gleason score determined at biopsy is that it may differ significantly from that found at radical prostatectomy (Freedland et al., 2007). Upgrading and downgrading cancers found at prostate biopsy commonly occur (27% and 11% respectively) in relation to a radical prostatectomy specimen given the critical role of tumor grade in treatment decisions (Freedland et al., 2007). Both the Gleason score determined in biopsy as well as in a radical prostatectomy specimen are highly predictive of prognosis (Albertsen et al., 2005b; Boorjian et al., 2007). Like any grading system, the Gleason system suffers from interobserver variability and requires expertise in urological pathology. In fact, it has been shown that urological pathologists agree on grouped Gleason score in no more than 70% of cases, and general pathologists do significantly worse (Allsbrook, Jr. et al., 2001a; Allsbrook, Jr. et al., 2001b).

The World Health Organization (WHO) classification by Mostofi is often applied together with the Gleason score system in Finland (Mostofi, 1975). The WHO classification uses a 3-grade scale of differentiation (I, II, or III) depending on the degree of cell anaplasia. The higher the grade, the lower the differentiation of cancer. In principle, the limitations of the WHO grade are the same as in the Gleason grading system.

3.1.7. Staging

The extent of prostate cancer predicts the natural course of the disease and provides valuable information which may greatly influence therapeutic decisions. The TNM classification system (T=primary tumor, N=lymph node status and M=distant metastasis) is a widely accepted method for staging prostate cancer (TNM Classification of Malignant Tumours 6th edn., 2002). The TNM system can be used in two kinds of circumstances: First, when the patient undergoes a clinical

evaluation (clinical TNM, cTNM) at the time of diagnosis, and secondly at the microscopic evaluation of an organ or a part of it (pathological TNM, pTNM) after surgery. Clinically, the extent of a primary tumor (T-stage) can be assessed by means of DRE, TRUS, and sometimes with the use of other imaging modalities. Stage T1 signifies a tumor found incidentally in TURP for BPH, or on the basis of an elevated PSA level in the absence of abnormalities at DRE or TRUS. Upper T-stages signify a tumor detectable through clinical examination. Histological examination of lymph nodes removed at surgery is a principle method for assessing N-staging. The yield of different imaging techniques for N-staging is considered to be of limited use due to their poor sensitivity, and also because of the slight risk of lymph node metastasis in prostate cancer in general (Akin & Hricak, 2007). Prostate cancer typically metastasizes to the bones, and therefore bone scan (scintigraphy) is usually performed to evaluate the presence of possible metastasis (M-stage). Because the bone scan is normal for the majority of men with PSA levels of 20 µg/l or less, it is considered superfluous for a subgroup of patients with low risk of suffering bone metastasis (Oesterling, 1993). In Finland, bone scan is not considered necessary for patients with PSA levels of 20 µg/l or below with well or moderately differentiated tumor without any signs or symptoms suggestive of distant metastasis (www.terveysportti.fi, 2007). The European Association of Urology (EAU) currently recommends bone scan for patients with PSA levels less than 10 µg/l only in the presence of poorly differentiated cancer, or symptoms suggestive of bone metastasis (European Association of Urology Guidelines 2007 edn., 2007). The latest TNM classification for prostate cancer (2002) is summarized in Table 3. In general, clinical T1-2M0 tumors are localized, T3-4M0 locally advanced, and T1-4M1 cancers have distant metastases. Unfortunately, clinical staging is inaccurate in a significant number of patients. Commonly used methods (i.e., DRE and TRUS) often fail to predict the presence of a localized disease (Ravery & Boccon-Gibod, 1997). At the beginning of the PSA era, more than half of men undergoing radical surgery for prostate cancer were eventually upstaged on the basis of microscopic evaluation (Bostwick et al., 1994).

Difficulties related to reliable prediction of the extent of the disease prevail especially in patients with high PSA levels (i.e., 20 µg/l or higher) (Gallina et al., 2007). Magnetic resonance imaging and other modern imaging studies are of limited value in enhancing the accuracy of staging (Akin & Hricak, 2007). PSA has been found to be a useful indicator of disease extent, but cannot be used alone for staging prostate cancer. Apart from T1, which does not have a pathological equivalent, clinical and pathological T-categories are comparable.

Table 3. TNM classification for prostate cancer (TNM Classification of Malignant Tumours 6th edn., 2002).

TNM Classification	Definition
T1	Clinically inapparent tumor (not palpable or visible)
T1a	Tumor found incidentally at TURP, $\leq 5\%$ of tissue cancerous
T1b	Tumor found incidentally at TURP, $> 5\%$ of tissue cancerous
T1c	Needle biopsy (e.g., because of elevated PSA)
T2	Tumor confined within the prostate
T2a	\leq half of one lobe
T2b	$>$ half of one lobe
T2c	Both lobes
T3	Tumor extends through prostatic capsule
T3a	Extracapsular extension
T3b	Seminal vesicles invasion
T4	Tumor is fixed to or invades adjacent structures
N1	Tumor involvement of regional lymph node(s)
M1	Distant metastases
M1a	Non-regional lymph node(s)
M1b	Bone(s)
M1c	Other site(s)

3.2. Treatment

The management of early-stage prostate cancer presents many challenges. The natural course of the disease is often difficult to predict at the time of diagnosis. It is widely recognized that as many as 50% of cancers detected on the basis of PSA testing may be attributed to overdiagnosis i.e., the disease progresses so slowly that it will not cause any morbidity or mortality during the individual's life-time (Draisma et al., 2003). This notwithstanding, more than half of all men with low-risk prostate cancer undergo a definitive therapy, which is likely to be indicative of potential overtreatment (Miller et al., 2006). A major challenge is to identify those patients with an early-stage prostate cancer who are most likely to benefit from active treatment. Conversely, it is equally important to avoid unnecessary therapies (overtreatment) and their possible side effects in men with slowly growing tumors.

In general, the treatment choice for patients with prostate cancer depends on both patient and tumor characteristics, both of which have been significantly influenced by the adoption of PSA testing. Patients are now younger and cancers are detected at an earlier stage than before. Therefore, the distribution of different treatment modalities, as well as practice patterns, have changed a great deal. In the United States, for example, most men currently diagnosed with prostate cancer undergo radical surgery or radiotherapy with a curative intent (Shaw et al., 2000). A similar trend has also been seen in Europe. In the Netherlands, the rate of radical prostatectomy as initial therapy rose from 11% in 1988-1990 to 33% in 1994-1996 among men aged 70 years or less (Post et al., 1999). Concurrently, the use of radiotherapy increased from 31% to 41% in the age group 70-74 years (Post et al., 1999).

An early-stage prostate cancer is usually managed with curative intent by radical surgery or radiotherapy, but randomized trials comparing different options for curative treatment over another are lacking. In theory, radical prostatectomy is likely to provide the best chance of a cure. However,

the benefit of radical surgery over expectant management in terms of reduced mortality was not shown until 2005. A Scandinavian trial of radical surgery versus watchful waiting (SPCG4) after an estimated 10 years of follow-up showed that the absolute risk of death from prostate cancer was 5.3% lower in men undergoing radical prostatectomy than in those who were managed expectantly (Bill-Axelsson et al., 2005). In terms of number needed to treat (NNT), nearly 20 operations were required to prevent one prostate cancer death. The major criticism of this trial, however, concerns the applicability of the results to contemporary patients. Only 5% of study subjects were diagnosed on the basis of PSA, whereas 75% had a palpable disease. Nevertheless, this study provided the first solid evidence of mortality reduction through radical surgery compared to expectant management; albeit with only modest benefit. It was also suggested that younger patients (i.e., under 65 years) would benefit most from active treatment.

Although potentially providing a cure for some patients, radical prostatectomy is often associated with significant complications such as urinary incontinence and impotence. A total loss of urinary control after radical prostatectomy is rare (1%), whereas frequent or occasional leakage respectively affects 5-33% of patients after surgery (Stanford et al., 2000). Up to 48% of men become incapable of sexual intercourse because of erectile dysfunction due to surgery. The risk of death attributable to radical prostatectomy is low (<1.5%), but still exists, as in any other major surgical procedure (Davidson et al., 1996). There is a trend towards robotic radical prostatectomy, which may allow a more precise and less invasive techniques reducing post-operative morbidity and possible side effects. However it will take years to find out whether this will translate into any survival benefit compared to a conventional open approach.

External beam radiotherapy has often been proposed for early-stage prostate cancer in men with extensive co-morbidities (European Association of Urology Guidelines 2007 edn., 2007). Men treated with radiotherapy are usually somewhat older than those undergoing radical surgery. Even though external beam radiotherapy is associated with a 10-year survival rate of $\geq 75\%$ overall,

ultimate eradication of the disease as defined by clinical or biochemical progression may fail in a significant proportion of men (Lu-Yao & Yao, 1997; Shipley et al., 1999). However, recent developments in radiotherapy make it possible to deliver a higher dose of radiation for cancer control without a substantial increase in side effects. High-dose radiotherapy is associated with a lower risk of biochemical failure, but the survival benefit has yet to be shown (Zietman et al., 2005). The side effects of radiotherapy include bladder (e.g., urgency and hematuria) and rectal morbidity (e.g., diarrhea). Radiation proctitis is seen in 2-39% of patients depending on the definition used and the technical aspects of delivering radiation (Hamilton et al., 2001). The irritative side effects are persistent in approximately 5% of patients, and their severity may even increase over time. Impotence may occur in up to 40-50% of men undergoing radiotherapy (Hamilton et al., 2001).

Brachytherapy represents a form of radiotherapy in which radioactive seeds are placed in the prostate to eradicate the disease. The use of brachytherapy for early-stage prostate cancer is increasing, but it still accounts a small proportion of treatment overall (Edwards et al., 2005). Currently, it may be regarded as an option for men with early-stage prostate cancer with favorable pathological findings at biopsy (Gleason score 3+4 or less) and only moderately elevated PSA levels (European Association of Urology Guidelines 2007 edn., 2007). Furthermore, patients should be relatively free of urinary symptoms because of increased risk of acute urinary retention due to tissue swelling immediately after seed placement. Otherwise, the side effect profile is similar to that with external beam radiotherapy. Despite favorable short-term results, the impacts of brachytherapy on long-term results are still insufficiently known, and again, comparative studies with other treatment modalities are lacking (Heysek, 2007).

Despite the emerging results in favor of radical prostatectomy over watchful waiting as well as improvements in radiotherapy, the management of early-stage prostate cancer remains controversial. As only a minority of men diagnosed with prostate cancer will eventually die of it

irrespective of the treatment chosen, the major challenge in the contemporary management of early-stage disease is to maintain an acceptable quality of life. Active surveillance is a novel approach in which therapy is determined by the biological behavior of prostate cancer (Klotz, 2002; Klotz, 2005). The aim of active surveillance is to observe selected men with prostate cancer expectantly with curative intent. By deferring curative treatment until the signs of progression occur, a significant number of men with a slowly growing tumor may be spared the side effects of active management. This is different from watchful waiting, in which therapy (usually without curative intent) is postponed until the symptoms of (advanced) prostate cancer occur (Schröder et al., 2003). It is critical for active surveillance to reliably identify those in whom the progression of disease occurs while a cure is still feasible. Patients need to accept and understand the concept of active surveillance in order to tolerate the anxiety and distress associated with a possible risk of disease progression and deferred therapy. Currently, active surveillance is regarded as an attractive approach for men with a favorable prognosis. Arguments for opting for active surveillance are mainly related to quality of life issues, although the ethical as well as economic consequences are not trivial either. Unfortunately, the criteria for selecting patients suitable to be managed safely with active surveillance remain arbitrary, but this issue is currently the focus of several trials (Carter et al., 2007; van den Bergh et al., 2007).

Apart from radical surgery and radiotherapy, early-stage prostate cancer can be managed locally, e.g., by cryotherapy and high-intensity focal ultrasound. However, given the limited experience available, they cannot so far be widely recommended (European Association of Urology Guidelines 2007 edn., 2007).

Despite increasing efforts at early detection of prostate cancer (or if therapy with curative intent initially fails), the disease may be seen as locally advanced or with distant metastasis. Such patients are best managed with hormonal therapy. In principle, the aim of endocrine therapy is to alleviate symptoms attributable to advanced disease, and to delay progression sufficiently so that patient will

die from some other cause than prostate cancer. After disease progression to a hormone-refractory stage, even the latest cytotoxic agents provide only a modest improvement in the prognosis of prostate cancer (Prezioso et al., 2007).

4. Screening for prostate cancer

4.1. Principles of screening

Controlling cancer may occur at several levels. Primary prevention should be given the highest priority whenever possible. However, a proven method for preventing the development of prostate cancer is still lacking. Extensive research is therefore currently ongoing for ways of controlling prostate cancer through screening (secondary prevention). The rationale for screening is to reduce mortality from prostate cancer through early diagnosis and management of the disease when a cure is still possible. The target population of screening consists of people of whom only a minority is likely to have the target condition, which has not so far become symptomatic. While the possible beneficial effects of prostate cancer screening (in terms of morbidity or mortality) are still unknown, negative side effects (such as psychological distress and complications caused by diagnostic tests initiated by screening or prostate cancer management) are inevitable. Thus, it is equally important to determine how the quality of life is affected by screening in addition to mortality assessment.

A decision to introduce a screening program has far-reaching consequences, and therefore, should be based on sound evidence. At a minimum, the overall benefit should outweigh the physical and psychological harm caused by screening. Judging the merits of screening is conventionally based on the WHO criteria published in 1968 (Table 4) (Wilson & Jungner, 1968). In the absence of mortality results, however, these conditions are insufficient indicators of the ultimate effect (or

benefit) (Hakama, 1991). Since geographical and temporal comparisons provide only inconclusive evidence, the preferred means of evaluating the effectiveness of a screening program is through randomized controlled trials (Hakama, 1991). Even though all the prerequisites of a successful screening program are fulfilled, a decision to screen is more complex, and is also likely to be affected by local economic and political conditions.

Table 4. Wilson and Jungner criteria of a successful screening program (Wilson & Jungner, 1968).

1. The condition sought should be an important health problem.
2. There should be an accepted treatment for patients with the disease.
3. Facilities for treatment and diagnosis should be available.
4. There should be a recognizable latent or early symptomatic stage.
5. There should be a suitable test or examination.
6. The test should be acceptable to the population.
7. The natural history of the condition should be adequately understood.
8. There should be an agreed policy of whom to treat as patients.
9. The cost should be balanced in relation to possible expenditure on medical care as a whole.
10. Case-finding should be a continuing process and not a once and for all project.

Due to the long natural history of prostate cancer, it may take years to observe a possible mortality benefit attributable to screening. Meanwhile the interim evaluation of a screening program relies on

process measures, which are, however, inconclusive for final decision-making on introducing screening.

First, the success of screening depends on the performance of the screening test itself (Cole & Morrison, 1980). Sensitivity and specificity are commonly used measures to determine test performance. Sensitivity describes the ability of a test to identify the target condition at a pre-clinical detectable phase, whereas specificity refers to the identification of healthy individuals among those tested (Table 5) (Hakama et al., 2007). The clinical performance of the test is often described in terms of a positive predictive value, which refers to the proportion of affected individuals among those with a positive test. Likewise, a negative predictive value refers to the proportion of healthy individuals among those with a negative test. The predictive values depend on the validity of the test and the prevalence of the target condition among those tested. In spite of a valid screening test (with high sensitivity and specificity), screening may still fail in its objective (Hakama et al., 2007).

Table 5. Sensitivity and specificity.

Test	Disease	
	Present	Absent
Positive	<i>A</i>	<i>B</i>
Negative	<i>C</i>	<i>D</i>

$$\text{Sensitivity} = A / (A + C)$$

$$\text{Specificity} = D / (B + D)$$

The second determinant of a successful screening program is the ability of the program as a whole to identify the disease in the target population (Cole & Morrison, 1980). Program validity is a summary measure of program sensitivity and specificity. Apart from test validity, program validity depends on the frequency of screening as well as on coverage of the target population (Hakama, 1991). Short screening intervals increase adverse effects, such as overdiagnosis and costs without necessarily improving efficacy in terms of advanced cancers prevented, whereas too long an interval fails to detect potentially lethal tumors at curable stages. The latter is closely related to compliance of the target population in attending both screening and diagnostic tests. Poor performance of diagnostic confirmation may also substantially impair program sensitivity, and potentially, the effectiveness of screening (Auvinen et al., 2004).

Third, the success of screening is determined by the ability of the program to improve the prognosis of the disease in the target population. An effective program should result in a favorable change in the stage of the disease compared to cases detected on a clinical basis, but that still does not guarantee lower death rates (Day & Walter, 1984). In general, the earlier prostate cancer is detected, the better is the outcome. It is still likely that screening will detect disproportionate numbers of slow-growing tumors compared to incident cases. Hence, an apparent improvement in the outcome of screen-detected cases does not necessarily result from earlier diagnosis and treatment, but different (more indolent) biological behavior. This phenomenon is known as length bias (Feinleib & Zelen, 1969). Overdiagnosis represents the utmost manifestation of length bias. Overdiagnosis can be defined as the detection of cancer that will not lead to death, or which would not otherwise have been diagnosed during a lifetime. Screening may also result in improvement in survival without actually postponing the time of death, which is known as lead time bias (Hutchison & Shapiro, 1968). Lead time is the amount of time by which the diagnosis is brought forward because of screening compared to the time at which cancer would have surfaced clinically.

Instead of wide coverage of the population, screening may be applied to only a part of the entire target population, which is assumed to be at elevated risk of the target condition. The purpose of selective screening of high-risk groups is to reduce the resources required, or sometimes to minimize the adverse effects of screening by leaving a substantial part of the population outside a (potentially harmful) intervention (Hakama, 1991). However, selective screening must identify a substantial proportion of the disease in the target population in order to prove successful. Selective screening influences program validity by improving program specificity, whereas program sensitivity is reduced. The validity of the screening test itself remains unchanged. Any factor related to the occurrence of the disease may be used for the identification of high-risk populations, given that a sufficient proportion of all cases in the population fall in the group defined on the basis of this criterion. However, potential benefits may be lost if the outlined group becomes too large. Almost without exception age and sex are taken into account as potential risk indicators when planning the allocation of screening and available resources. Often a familial background is also of great interest. In particular, family history selective screening has been strongly advocated lately for prostate cancer (Smith et al., 2006).

The ultimate outcome of a screening program is usually measurable only after several years of follow-up. In the absence of mortality data, the evaluation of a screening program often tends to be based on process measures as a surrogate for the final outcome. Surrogate indicators are still incapable of reliably distinguishing between effective and ineffective screening programs. Even if most (or all) of them are in favor of screening, a screening program may still prove inefficient (Marcus et al., 2000). Therefore, mortality from the target condition provides the only valid indicator of the effectiveness of a screening program, and should be assessed preferably by means of a randomized controlled trial with a balanced distribution of confounding factors (Hakama, 1991).

4.2. Screening with prostate-specific antigen

So far, no conclusive evidence is available to prove (or disprove) mortality reduction from prostate cancer through screening. Several ecological (i.e., comparisons of aggregated mortality and incidence data with the rate of PSA testing) and observational studies have addressed this issue, but the findings have been conflicting (Table 6) (Roberts et al., 1999; Merrill & Stephenson, 2000; Skarsgard & Tonita, 2000; Bartsch et al., 2001; Vutuc et al., 2001; Perron et al., 2002; Lu-Yao et al., 2002; Coldman et al., 2003; Weinmann et al., 2004; Weinmann et al., 2005; Kopec et al., 2005; Oberaigner et al., 2006; Concato et al., 2006; Agalliu et al., 2007; Etzioni et al., 2008; Marcella et al., 2008). No randomized controlled trial has so far demonstrated the effectiveness of PSA screening. Two large-scale trials are currently in progress in Europe and in the United States, but their follow-up is still insufficient for mortality analysis (de Koning et al., 2002). A trial in Quebec has reported a reduction in prostate cancer mortality in screened men, but fundamental limitations related to poor compliance and analytical procedures make the results at present uninterpretable (Labrie et al., 1999).

Table 6. Overview of non-randomized studies on PSA screening.

Author(s) and year	Setting	Study design	Study subjects	Mortality impact	Comment
Marcella et al., 2008	New Jersey, USA	Case-control	380 case subjects	None	Exposure to PSA assessed in the scale ever/never
Etzioni et al., 2008	USA	Ecological (mathematical modeling/time trend)	SEER data	45-70% of observed decline in PC mortality attributable to PSA	PSA may account for much, but not all observed mortality decline
Bergstralh et al., 2007	Minnesota, USA	Case-control	74 case subjects	Beneficial (adjusted odds ratio 0.35, 95% CI 0.17-0.71)	DRE commonly performed together with PSA
Agalliu et al., 2007	Washington, USA	Case-control	706 case subjects	Beneficial (adjusted odds ratio 0.38, 0.19-0.77)	Screening with PSA and/or DRE.
Concato et al., 2006	New England, USA	Case-control	501 case subjects	None (adjusted odds ratio 1.08, 0.71-1.64)	
Oberaigner et al., 2006	Tirol, Austria	Ecological (geographical)	Austrian males	Beneficial (risk ratio of 0.81, 0.68-0.98 for PC mortality in Tirol)	PC mortality assessed in Tirol offering free PSA testing in contrast to rest of country
Kopec et al., 2005	Toronto, Canada	Case-control	236 case subjects	Odds ratio of 0.65 (0.45-0.93) for metastatic PC	Metastatic disease used as a surrogate for PC mortality
Weinmann et al., 2005	Four health care organizations, USA	Case-control	769 case subjects	Beneficial in white (odds ratio 0.65, 0.48-0.88) but not in black men (0.86, 0.53-1.4)	Screening primarily with DRE

Author(s) and year	Setting	Study design	Study subjects	Mortality impact	Comment
<i>Continue (Table 6)</i>					
Weinmann et al., 2004	Nonprofit health care organization, USA	Case-control	171 case subjects	None (adjusted odds ratio 0.70, 0.46-1.10)	Screening primarily with DRE
Coldman et al., 2003	British Columbia, Canada	Ecological (geographical)	Men aged 50-74 in British Columbia	None	Intensity of PSA testing not related to mortality decline
Lu-Yao et al., 2002	Seattle-Puget Sound and Connecticut, USA	Cohort	215,521	None	No decline in PC mortality over 11 years of follow-up despite >5-fold difference in use of PSA in Seattle vs. Connecticut
Perron et al., 2002	Quebec, Canada	Cohort	Birth cohorts of men ≥ 50 in Quebec	None	Intensity of PSA testing not related to mortality decline
Vutuc et al., 2001	Austria	Ecological (time trend)	Austrian males	None	PC incidence increased, but no impact on mortality observed
Bartsch et al., 2001	Tirol, Austria	Ecological (geographical)	Austrian males	Beneficial	
Skarsgard & Tonita 2000	Saskatchewan, Canada	Ecological (time trend)	Men in Saskatchewan	None	Mortality remained unchanged from 1970 to 1997
Merrill & Stephenson 2000	USA	Ecological (time trend)	SEER data	Beneficial	Decrease in PC mortality after 1992 attributed to PSA testing
Roberts et al., 1999	Minnesota, USA	Ecological (time trend)	Men in Olmsted County	Mortality lower than before PSA testing	Mortality declined quite early to be attributed to PSA (alone)

The European Randomized Study of Screening for Prostate Cancer (ERSPC) is a major effort launched in 1994 to shed light on the dilemma concerning the impact of PSA screening on prostate cancer mortality (Auvinen et al., 1996). It involves more than 200,000 men aged 45-74 years at entry from eight European countries including Finland. All the centers use PSA as a principal screening test, but the cutoffs vary between the PSA of 2.5 to 4.0 µg/l. The trials also diverge in recruitment strategy (volunteer versus population-based approach) and interval of screening (from 2 to 7 years). The first mortality results from the ERSPC are expected within a few years. In addition to the European study, another large-scale trial (the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial, PLCO) is currently ongoing in the United States to assess the impact of PSA screening on prostate cancer mortality (Kramer et al., 1993). These two trials have common characteristics, and a joint analysis is planned (de Koning et al., 2002). The key characteristics of these two trials are summarized in Table 7.

Even though PSA screening has not yet been proven to save lives, opportunistic (non-organized) screening has become common practice in many industrialized countries. The extent of opportunistic PSA testing is likely to be greatest in the United States, where up to 75% of men aged 50 years or older have been tested for PSA (Sirovich et al., 2003). Even in men older than 75 years up to a third undergo PSA testing despite an average life-expectancy of less than 10 years (Scales, Jr. et al., 2006). In Finland, the rate of opportunistic screening was modest (7-14%) during the first years of our trial, but it is likely to have increased over time (Ciatto et al., 2003).

Table 7. Key characteristics of the study protocols in the ERSPC and PLCO trials.

	ERSPC								PLCO
	Finland	Netherlands	Sweden	Belgium	Italy	Spain	Switzerland	France	
Age at entry	55/59/63/67	55-74	51-66	55-74	55-70	45-70	55-70	55-69	55-74
Screening interval	4	4	2	7	4	4	4	2	1
Recruitment	Population-based	Volunteers	Population-based	Volunteers	Population-based	Volunteers	Population-based	Population-based	Volunteers
Randomization	Before consent	After consent	Before consent	After consent	Before consent	After consent	After consent	Before consent	After consent
Target sample size*	80,000	42,000	20,000	10,000	15,000	4,300	10,000	101,000	74,000
PSA threshold (µg/l) [†]	4.0	3.0	2.54	3.0	4.0	3.0	3.0	3.0	4.0
Supplemental screening criteria [‡]	%FPSA	-	-	DRE	DRE/ TRUS	%FPSA	%FPSA	-	DRE

* Crude. [†], [‡] Current protocol.

At present, the recommendations issued by a number of authoritative organizations on the use of PSA for prostate cancer screening are highly controversial (Table 8). The European Union and the World Health Organization, for example, conclude that PSA screening cannot be recommended as health care policy before a possible advantage is shown in randomized trials (Lynge, 2000; www.who.int/cancer/detection/prostatecancer/en/index.html, 2008). By contrast, both the American Urological Association and the American Cancer Society advocate beginning PSA testing at the age of 50 years, or even earlier in the case of positive family history (American Urological Association (AUA), 2000; Smith et al., 2006). According to the Finnish Urological Society the evidence is still insufficient to recommend screening routinely, but the PSA test should not be denied if requested because of symptoms indicative of prostate cancer (www.terveysportti.fi, 2007).

Table 8. Overview of recommendations on PSA screening worldwide.

World Health Organization¹ European Union² European Association of Urology³	Not recommended before effectiveness is shown in randomized trials.
U.S. Preventive Services Task Force⁴ National Cancer Institute⁵	Evidence insufficient for or against PSA screening.
American Cancer Society⁶ American Urological Association⁷	<p>PSA test (and DRE) should be offered annually starting at age 50 years for men with life expectancy of ≥ 10 years (or from age 40 if at high risk).</p> <p>Need for discussion of potential benefits, limitations, and drawbacks of PSA testing.</p>
Finnish Urological Association⁸	<p>Not recommended before effectiveness is shown in randomized trials.</p> <p>PSA test should not be withheld from men with symptoms.</p>

References: ¹(www.who.int/cancer/detection/prostatecancer/en/index.html, 2008), ²(Lynge, 2000), ³(European Association of Urology Guidelines 2007 edn., 2007), ⁴(Harris & Lohr, 2002), ⁵(www.cancer.gov/cancertopics/pdq/screening/prostate/healthprofessional, 2008), ⁶(Smith et al., 2006), (American Urological Association (AUA), 2000) and ⁸(www.terveysportti.fi, 2007).

AIMS OF THE THESIS

The general aim of this thesis is to assess the program performance and early outcome measures of PSA screening in the Finnish component of the European Randomized Study of Screening for Prostate Cancer (ERSPC). The specific aims are:

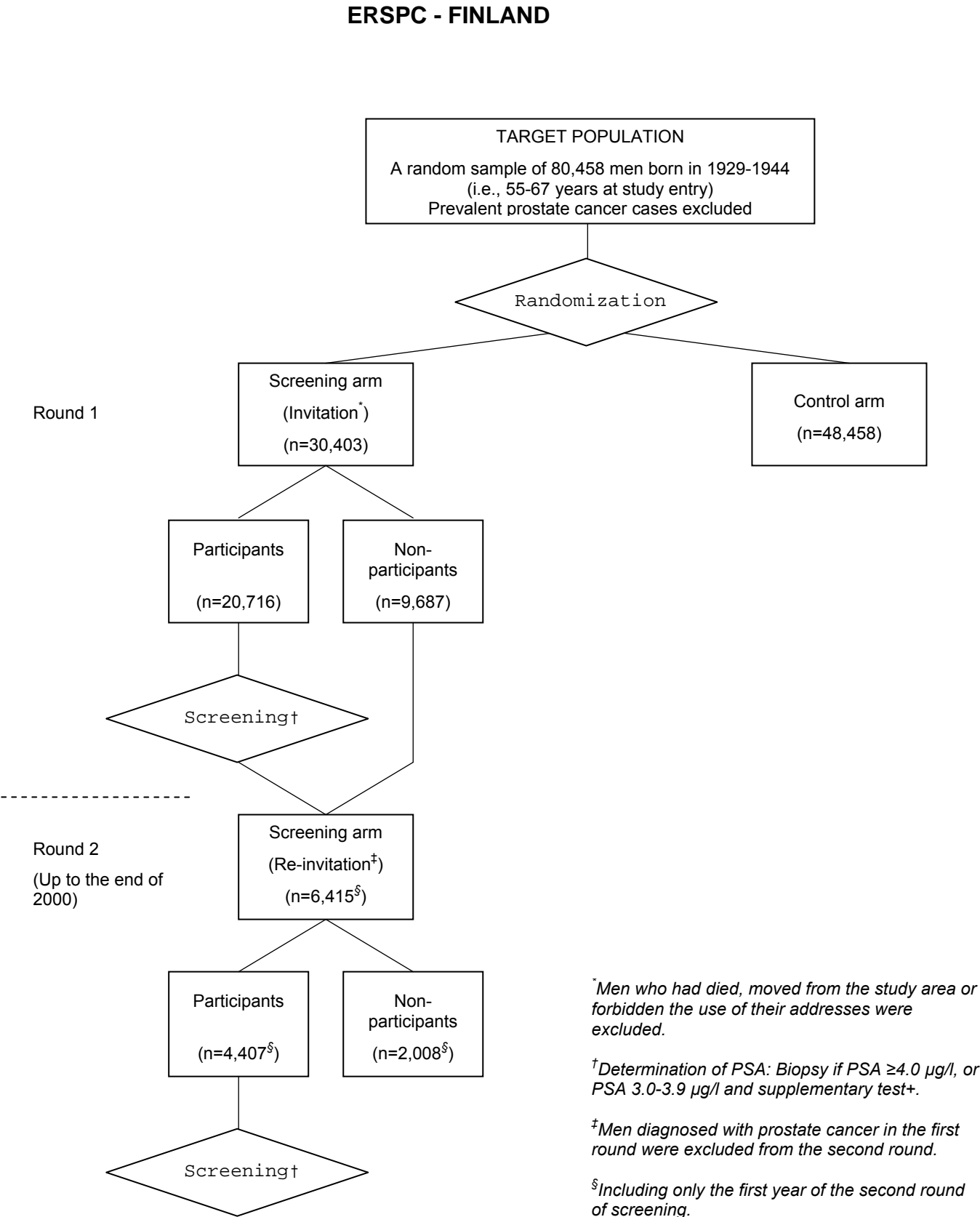
1. To assess the feasibility of PSA screening in terms of participation in the intervention arm of the trial and the acceptance of prostate biopsy following a positive screening test (I-V).
2. To compare the program performance of PSA screening in the first and second rounds in terms of compliance with screening, cancer detection rate and positive predictive value of PSA (II-V).
3. To evaluate the impact of PSA screening on the clinical characteristics of prostate cancer in the target population of screening (II-V).
4. To compare digital rectal examination (DRE) and percentage of free PSA (%FPSA) as a supplementary screening test within the PSA range of 3.0-3.9 µg/l (III).
5. To assess the feasibility of selective screening with PSA on the basis of family history (IV).

MATERIALS AND METHODS

1. Target population of the Finnish Population-based Prostate Cancer Screening Trial

The Finnish trial is a part of the European Randomized Study of Screening for Prostate Cancer (ERSPC) covering more than 200,000 men from eight European countries (www.erspc.org, 2008). The Finnish study was initiated in May 1996, and involves a comprehensive population sample of 80,458 men in the cities of Tampere and Helsinki with their respective surrounding municipalities of Kangasala, Lempäälä, Nokia, Pirkkala and Ylöjärvi, likewise Espoo, Kauniainen and Vantaa. The study subjects were born 1929-1944, and enrolled from the Population Register of Finland. Men with a previous diagnosis of prostate cancer were excluded prior to randomization. The first round of screening was undertaken 1996-1999, and each year a random sample of 8,000 men aged 55, 59, 63 or 67 years was allocated to the screening arm. Simple randomization was employed without stratification by age or place of residence (i.e., each man in the study population had an equal chance of being allocated to the intervention arm). By the end of the first screening round, a total of 32,000 men were randomized to the intervention arm, whereas the remaining 48,458 men formed the control arm. Men who had died, moved outside the study area by the time of invitation, or refused the use of their address for any purpose were considered ineligible and not invited for screening. The men randomized to the control arm were not contacted. The second round of screening began in 2000 after a screening interval of 4 years. Again, men diagnosed with prostate cancer, as well as those who had died, moved outside the study area, or forbidden the use of their addresses before the second round of screening were excluded. (Figure 2)

Figure 2. Flowchart of the Finnish Population-based Prostate Cancer Screening Trial.



2. Laboratory methods

A venous blood sample of 15 ml was drawn from screening participants after written informed consent. After separation, frozen serum was sent for analysis of both total and free PSA at the Department of Clinical Chemistry, Helsinki University Central Hospital. The serum concentration of total PSA was determined primarily with the Hybritech Tandem-E method (Hybritech, BeckmanCoulter, San Diego, CA), but also with the Delfia PSA Free/Total assay (PerkinElmer) calibrated against the Hybritech method. The calibrated value was occasionally used, if technical problems occurred in the primary method. Determination of the percentage of free PSA (%FPSA) was based on the Delfia Free/Total assay (PerkinElmer).

3. Screening algorithm

The total concentration of serum PSA was used as a principal test of screening. All men with PSA 4.0 µg/l or higher were regarded as screening positives, and were referred for diagnostic examination including a digital rectal examination, transrectal ultrasound and sextant biopsies of the prostate supplemented by a directed biopsy if a focal finding was found in either DRE or TRUS. In addition, a supplementary screening test was offered to men with intermediate PSA levels (i.e., 3.0-3.9 µg/l). During the first three years of the trial in 1996-1998, a supplementary DRE was available for those with a PSA level of 3.0-3.9 µg/l, and prostate biopsies were indicated if nodularity, induration or asymmetry was present. The screening algorithm was changed for the last year of the initial round of screening in 1999 by substituting DRE with %FPSA within the PSA range of 3.0-3.9 µg/l. Diagnostic examinations were performed if %FPSA was <16%. Otherwise, the core protocol remained unchanged.

4. Diagnostics

Diagnostic workup initiated by the screening test was carried out on an outpatient basis. The prostate biopsies were taken by a senior-level urology resident or an attending urologist. An antibiotic prophylaxis was routinely used before biopsy without pre-biopsy bowel preparations. In Study I, 500 mg ciprofloxacin was given orally 30 to 60 minutes prior to the biopsy. Local anesthetics were not used. Random sextant biopsies were taken under ultrasound guidance (supplemented by an additional biopsy if a focal lesion was found in TRUS or DRE) using a spring-loaded biopsy gun with an 18-gauge needle.

All of the prostate cancer diagnoses were histologically confirmed. Both the Gleason score and the WHO system were used in tumor grading (Mostofi, 1975; Gleason, 1992). So far, a systematic central pathology review of tumor grades was undertaken only for a random sample of cases. Clinical staging was conducted according to the TNM classification using primarily DRE, TRUS and bone scan to evaluate possible extracapsular extension and distant metastases of prostate cancer (TNM Classification of Malignant Tumours 6th edn., 2002). Generally, bone scanning was not conducted at PSA levels less than 20 µg/l with well or moderately differentiated disease because of the low risk of bone metastases (Oesterling, 1993).

5. Follow-up

Follow-up for the study subjects started from randomization. Information on incident cases of prostate cancer in both arms of the trial (including non-participants) was collected prospectively at the participating hospitals. To ensure complete identification of the subjects with prostate cancer, record-linkage was conducted with the discharge database of hospitals in the study area, likewise with the Finnish Cancer Registry, a nationwide population-based cancer registry with virtually

complete coverage of solid cancer cases in Finland (Teppo et al., 1994). Cases found in the screening arm were regarded as screen-detected if diagnosed in accordance with the study protocol within 12 months of drawing the blood sample.

6. Study subjects and data analyses

In general, Studies I-IV were based on the first round results of the Finnish trial in 1996-1999. Study V involved the cohort of 8,000 men randomly assigned to the screening arm in 1996, and invited for re-screening after an interval of 4 years in 2000. (Figure 2)

6.1. Acceptance and adverse effects of prostate biopsy (Study I)

The assessment of biopsy effects on men attending PSA screening was based on a comparison of 100 consecutively recruited screenees in the first round of the Finnish trial with 100 consecutive, hospital-referred symptomatic patients in the same age groups (born 1929-1944) in Tampere University Hospital 1997-2000. Immediate complications were recorded by the urologist at the time of diagnostic workup. Psychological aspects of biopsy, as well as possible late (up to two weeks) complications were assessed using a self-administered questionnaire with a set of intervention-specific questions. The acceptability of biopsy, as well as the perception of adverse effects, were assessed using a three-point verbal rating scale with options no/minor, moderate, and severe. Information on adverse effects, their duration and possible treatment was collected using structured questions. The amount of bleeding from the urethra and rectum or blood in semen was subjectively evaluated using a similar three-point scale. The men were asked to complete and return the questionnaire within two weeks of biopsy (i.e., before a definitive diagnosis was known). Ninety-seven screenees and eighty-four controls returned the questionnaire.

6.2. Occurrence and characteristics of prostate cancer (Study II)

The impact of PSA screening on tumor characteristics and detection in the initial round was evaluated on the basis of the first three-year results of the Finnish trial (1996-1998) with 60,211 men in the total target population. Those with prevalent prostate cancer (n=238) were identified through record-linkage with the Finnish Cancer Registry and excluded from the study before randomization. Of the 22,732 men eligible for screening, 15,685 (69%) eventually participated. The 35,973 men comprising the control arm of the trial were not contacted.

The occurrence and characteristics of prostate cancer were compared between the screening and the control arm of the trial. The detection rate was defined as the prevalence of the disease, i.e., the number of cancers detected as a result of screening among all men screened (tested). Cases found in the screening arm were regarded as screen-detected if diagnosed in accordance with the study protocol within 12 months of drawing the blood sample. Among non-participants and controls, all prostate cancer cases detected during the first post-randomization year were included in the analyses. The medical records were reviewed to obtain comparable information on stage and grade for patients detected outside the organized screening, i.e., in the control population and the non-participants of screening. Cumulative incidence was calculated for non-local cancers, and was defined as the number of cases detected during the follow-up period (i.e., 12 months) relative to the number of men within a study group.

6.3. DRE and %FPSA as supplementary screening tests (Study III)

Study III assessed the use of supplementary screening tests at intermediate PSA levels in the first round of screening. Of the 20,716 first-round participants, 1,071 (5.2%) screenees had PSA between 3.0 and 3.9 $\mu\text{g/l}$ (i.e., below the PSA cutoff of 4.0 $\mu\text{g/l}$ used as the principal criterion for screening

positivity). A supplementary DRE was offered to 801 men with PSA 3.0-3.9 µg/l during 1996-1998, and those with a suspicious DRE finding were referred for biopsy. The screening algorithm was modified by substituting DRE with %FPSA (cutoff point 16%) as a biopsy criterion among 270 men with PSA levels of 3.0-3.9 µg/l in 1999. The performance of DRE and %FPSA was evaluated in terms of the cancer detection rate, biopsy per cancer ratio, specificity and the clinical characteristics of cancers detected (i.e., histological grade and clinical stage) in men with intermediate PSA levels. The specificity of the screening program was defined as the proportion of men with a negative test in screening among all screened men without prostate cancer 12 months after the screening test.

6.4. Family history and prostate cancer screening (Study IV)

The impact of family history on PSA screening was assessed on the basis of the first round results of the Finnish trial. Analyses were based on 20,716 participants in the screening arm in 1996-1999. The study population was formed at baseline, with exposure contrast defined on the basis of family history. Information on family history was obtained by questionnaire at the time of invitation. If a subject reported one or more first-degree relatives (i.e., father or brother) diagnosed with prostate cancer, the family history was regarded as positive. Due to reasons of confidentiality, the affected relatives could not be identified and it was therefore not possible to confirm the self-reported diagnoses from medical records or the cancer registry.

The ratio of detection rates (rate ratio, RR) was calculated for men with an affected family member(s) relative to those without such family history. The 405 men with missing information concerning family history were excluded from the analyses. The risk of prostate cancer was analyzed separately for screenees below and above 60 years of age, as well as by the age of an affected relative at diagnosis excluding those 74 (0.4%) men for whom the age of an affected

relative was unavailable. For comparison of tumor characteristics, patients with unavailable Gleason score at biopsy (n=5) or unavailable clinical stage (n=3) were excluded. The specificity of the PSA test was given separately for men with and without family history of prostate cancer, and corresponded to the proportion of men with PSA levels below 4.0 µg/l among all healthy screening participants with corresponding family history. The approximation of program sensitivity for family history as a supplementary screening criterion indicated the proportion of cancers detectable by selective screening policy in the screened target population with missing information on interval cancers. In other words, it represents the proportion of screen-detected cases with a family history among all screen-detected cancers (with information on family history available). Specificity of family history as a supplementary screening criterion indicated the proportion of men correctly identified to be free of prostate cancer by a negative test combination of family history and PSA among all screening participants with known family history remaining disease-free for one year after screening. In addition, the program specificity for a family history selective screening was estimated as the proportion of healthy screenees correctly identified as free of cancer by negative family history alone.

6.5. Second round results of screening (Study V)

Study V covered 8,000 men randomly assigned to the screening arm in 1996 and invited for re-screening after an interval of four years in 2000. Men diagnosed with prostate cancer during the first round of screening, men who had died, moved outside the study area, or forbidden the use of their addresses were excluded. Eventually, a total of 6,415 men were invited for re-screening at the ages of 59, 63, 67 or 71 years during the first year of the second screening round in 2000.

The detection rates by total PSA, age, Gleason score and clinical stage of cancers found were calculated. The risk of prostate cancer at round 2 was estimated in relation to the first-round PSA

values. The risk was calculated in terms of the ratio of detection rates using men with PSA levels below 3.0 µg/l at round 1 as a reference.

6.6. Statistics

Pearson's chi-square test was used to assess the statistical significance of the difference in the clinical characteristics and detection rates of detected tumors between the study groups (II-V). The statistical significances of the differences in the perception of prostate biopsy were also calculated using Pearson's chi-square test and Fischer's exact test (I). Patients with clinical grade or stage unavailable, as well as non-respondents to the biopsy questionnaire were excluded from the analysis. Pearson's chi-square test was also used to compare compliance with re-screening in relation to baseline PSA levels. Student's t-test was used for comparison of the mean ages in men with and without a family history for prostate cancer (IV). Wilcoxon signed rank test was used for comparisons of PSA concentrations (II, IV). All the main outcome measures were reported with 95% confidence intervals.

Statistical analyses were performed on CIA version 1.1 (Martin J. Gardner and British Medical Journal) and S-PLUS version 4.0 (MathSoft Inc., Cambridge, MA).

7. Ethics

The ethical committee of each participating hospital approved the protocol of the Finnish Population-based Prostate Cancer Screening Trial. Permission to access medical records was obtained from the Ministry of Social Affairs and Health and for the use of cancer registry data from the Research and Development Center for Welfare and Health (STAKES). Study I assessing the

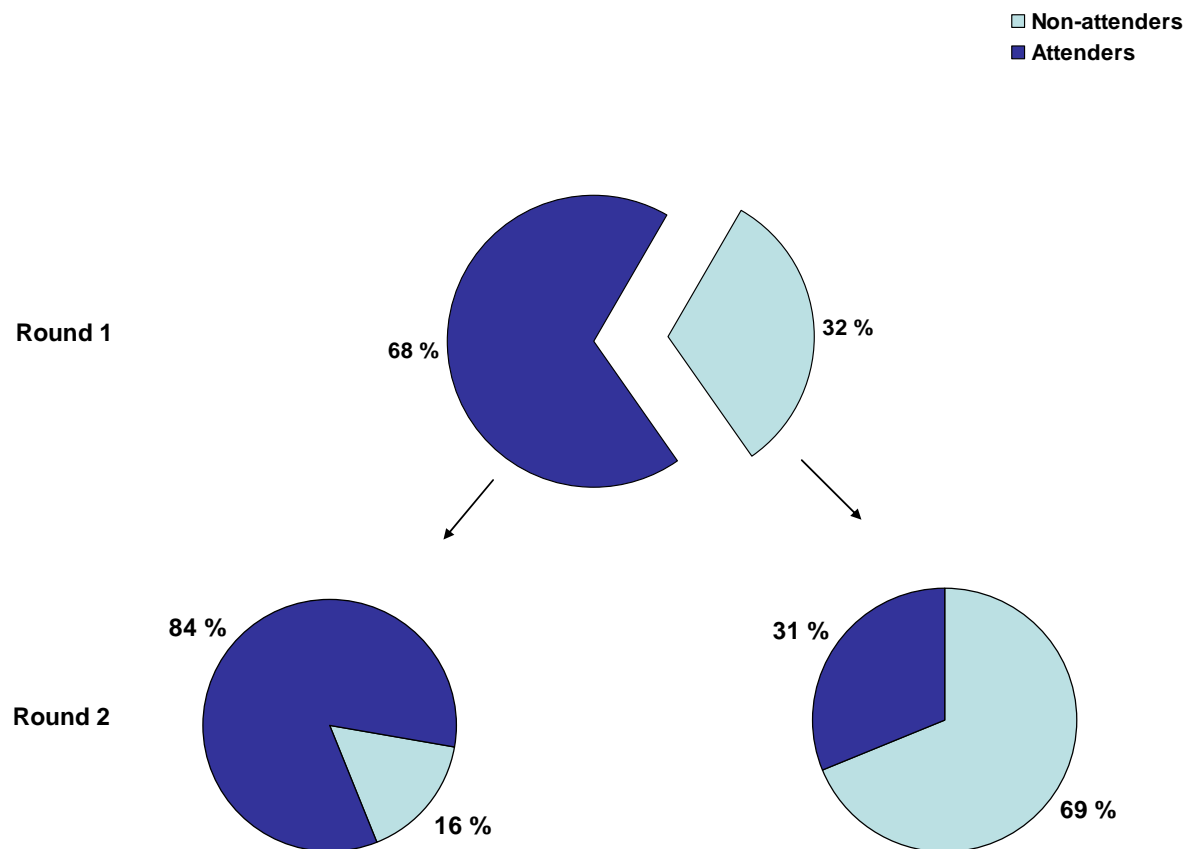
acceptability and complications of prostate biopsy was also approved separately by the ethical committee of Tampere University Hospital.

RESULTS

1. Participation in screening

Overall, 68% (20,716/30,403) of eligible men participated in screening during the first round of the Finnish Population-based Prostate Cancer Screening Trial 1996-1999. The overall attendance at re-screening remained virtually unchanged at the beginning of the second round in 2000. Of the cohort of 4,556 men who participated in the initial screening round in 1996, 84% (3,833) attended for repeat screening after an interval of four years (Figure 3). Of the 1,859 first-round non-attenders, only 31% (574) participated in the second round of screening ($p<0.001$). Attendance was also higher among first round participants with negative screening results (PSA of <4.0 $\mu\text{g/l}$) than among those with false positive results, i.e., with a PSA 4.0 $\mu\text{g/l}$ or higher, but no cancer at biopsy (85% vs. 64%; $p<0.001$).

Figure 3. Participation rate in men invited to the first and second screening rounds of the Finnish Population-based Prostate Cancer Screening Trial in 1996 and 2000.



2. PSA distribution

A total of 8% (1,592/20,716) of participants were defined as screening positive on the basis of serum PSA of 4.0 µg/l or higher in the first screening round (Table 9). After an interval of four years, PSA levels of 4.0 µg/l or higher were seen among 10% (461/4,407) of men invited for re-screening during the first year of the second screening round. A supplementary screening test was offered to 5% (1,071/20,716) of men on the basis of serum PSA of 3.0-3.9 µg/l in the first round, compared to 7% (314/4,407) in the second round in 2000. An overview of screening results per PSA range is shown in Figure 4.

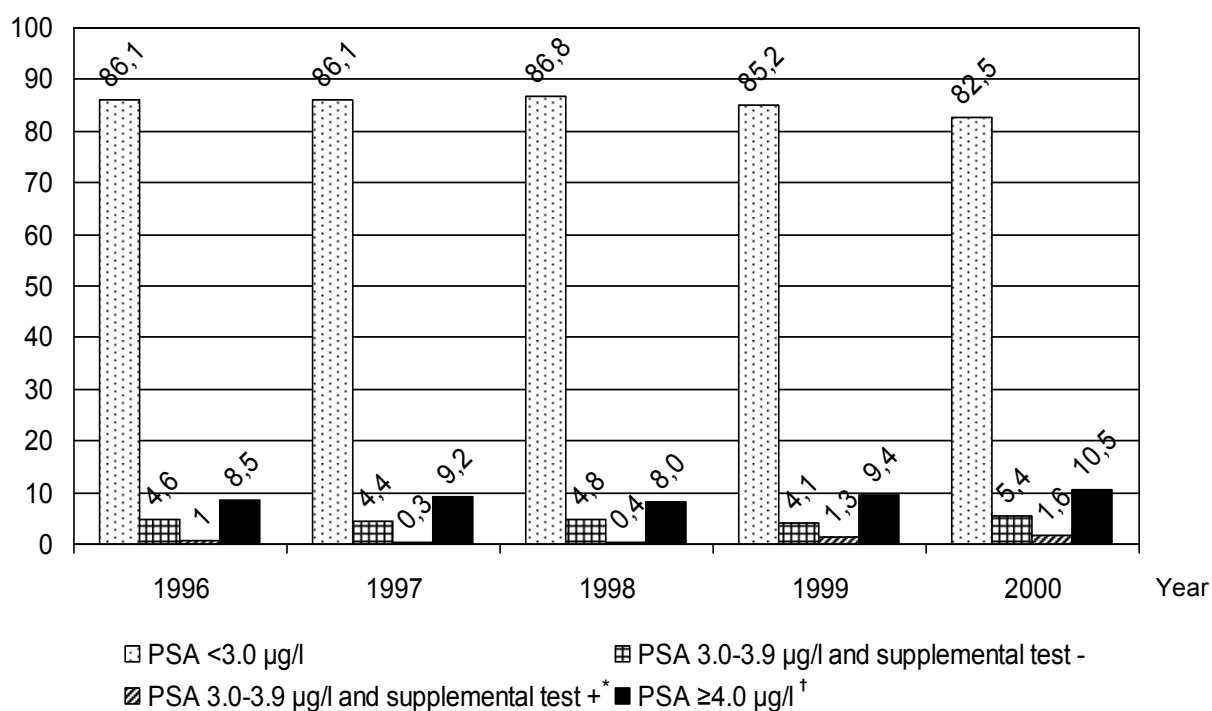
Table 9. Distribution of screening participants by serum PSA concentration in the first and second rounds of the Finnish Population-based Prostate Cancer Screening Trial in 1996-1999 and 2000.

	Round	
	1	2*
	N (%)	N (%)
PSA (µg/l)		
0-2.9	18,053 (87)	3,632 (82)
3.0-3.9	1,071 (5)	314 (7)
4.0-9.9	1,293 (6)	413 (9)
≥10.0	299 (1)	48 (1)
Total	20,716 (100)	4,407 (100)

*Including only the first year of the second round of screening.

Figure 4. Overview of screening results per PSA range in the first and second round of screening in the Finnish Population-based Prostate Cancer Screening Trial in 1996-1999 and 2000, respectively.

% of screening participants



* † All men with PSA ≥4.0 µg/l as well as those with PSA 3.0-3.9 µg/l and a supplementary screening test positive were referred for prostate biopsies.

3. Acceptability and adverse effects of prostate biopsy

No major complications occurred among the 100 consecutive screen-positive men referred for sextant biopsy, although minor adverse effects were common (Table 10). More than half of the men experienced rectal hemorrhage at biopsy and a few (3%) had bleeding from the urethra. Afterwards, hematuria was reported by two thirds of screenees, and in up to 25% it persisted for more than two days. More than half of the men also had persistent rectal bleeding. Signs and symptoms suggestive of infectious complications, such as high temperature and dysuria, were somewhat less frequent, affecting respectively 8 and 17% of biopsied men. No differences were seen in either immediate or late adverse effects of prostate biopsy between the screenees and the 100 men referred for other reasons (Table 10).

The biopsy procedure was considered moderately or very unpleasant by 69% (67/97) of screenees compared to 61% (51/84) of the hospital-referred controls ($p=0.31$). Correspondingly, 52% (50/97) and 63% (53/84) reported moderate pain at biopsy ($p=0.16$), while a few experienced severe pain (3 vs. 5% respectively; $p=0.71$).

Of the screening-positive men, most (82%, 80/97) would undergo a biopsy again if recommended. Only 2% (2/97) of them would decline in future, while 14% (14/97) were uncertain. Willingness to undergo biopsies again did not differ from that among the hospital-referred patients, of whom 86% (72/84) would attend prostate biopsy in future if necessary, 10% (8/84) being uncertain and 2% (2/84) refusing ($p=0.70$).

Table 10. Immediate and late adverse effects of prostate biopsy among 100 consecutive screening-positive men and 100 hospital-referred controls.

Adverse effect	Screening group (%)	Control group (%)
Immediate		
Any adverse effect	58 (58)	52 (52)
Rectal bleeding	57 (57)	51 (51)
Urethral bleeding	3 (3)	2 (2)
Vasovagal episode	1 (1)	1 (1)
Total	100 (100)	100 (100)
Late*		
Any adverse effect	84 (87)	79 (94)
Hematuria	65 (67)	62 (74)
Rectal bleeding	54 (56)	52 (62)
Hematospermia	52 (54)	45 (54)
Difficult voiding	27 (28)	34 (40)
Diarrhea	21 (22)	28 (33)
Dysuria	17 (18)	17 (20)
High temperature	8 (8)	6 (7)
Total	97 (100)	84 (100)

*Three screenees and sixteen controls did not respond to the questionnaire.

No significant difference was found between the groups in any of the variables.

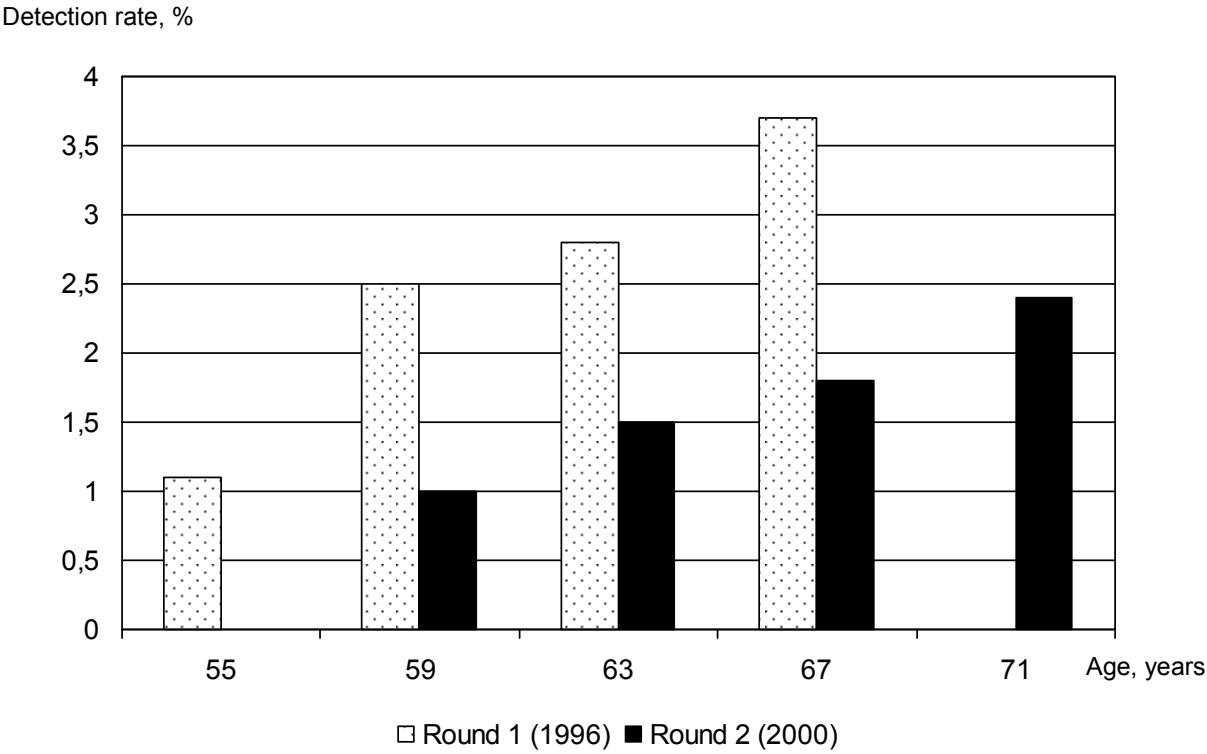
4. Occurrence of prostate cancer

During the first three years (1996-1998), a total of 377 screen-detected prostate cancers were seen among the 15,685 screening participants corresponding to a detection rate of 2.4% (95% CI, 2.2-2.6%). Meanwhile, forty prostate cancers were seen among the 7,047 non-participants of screening and 112 cases among the 35,973 men in the control arm, corresponding to a respective cumulative incidence of 0.6% (95% CI, 0.4-0.7%) and 0.3% (0.3-0.4%) within 12 months of randomization.

The overall prostate cancer detection rate in the first screening round was 2.6% (95% CI, 2.3-2.8%; 530/20,716). A total of 491 tumors were found on the basis of serum PSA of 4.0 µg/l or higher, corresponding to a detection rate of 2.4% (95% CI, 2.2-2.6%). Thirty-six cancers were detected through a supplementary screening test (i.e., DRE or %FPSA) within a PSA range of 3.0-3.9 µg/l, contributing 0.2% to the overall detection rate. Three cancers were found at a PSA level of 2.0-2.9 µg/l through DRE before its use was discontinued at such low PSA levels.

During the first year of the second screening round, 97 prostate cancers were detected among the 4,407 second-round participants, corresponding to an overall detection rate of 2.2% (95% CI, 1.8-2.6%). Of these, 79 cancers were found in the 3,833 men attending screening for the second time and 18 cancers among the 574 men screened for the first time (delayed first screen). These figures correspond to respective detection rates of 2.1% (95% CI, 1.6-2.6%) and 3.1% (1.9-4.9%). The overall rate of prostate cancer detection by age was substantially lower at incidence (2nd) than at prevalence (1st) screen as shown in Figure 5.

Figure 5. Overall rate of prostate cancer detection by age in the first and second rounds of screening in 1996 and 2000.



5. Positive predictive value of PSA

Of the 530 prostate cancers detected in the first round, 491 had PSA above the cutoff level of 4.0 µg/l, corresponding to a positive predictive value (PPV) of 27% (95% CI, 25-29%; 491/1,815), or 3.7 biopsies per cancer. Overall, the PPV of 18% (95% CI, 15-22%; 84/461) was somewhat lower in the second round of screening in 2000. The loss of predictive value was also demonstrated by the PPV of 17% (95% CI, 14-21%; 67/389) among the 3,833 second-time screenees compared to 24% (14-35%, 17/72) observed for 574 men screened for the first time. A reduction in PPV after the initial round was also shown for the PSA cutoff of 10.0 µg/l as evinced by the PPV of 47% (95% CI, 23-72%; 8/17) among the first-time attenders compared to the PPV of 32% (17-51%, 10/31) in the second-time participants.

The PPV for the PSA threshold of 4.0 µg/l at baseline (i.e., in the first round of screening in 1996) was 11% in second-time screening participants after an interval of 4 years. Men with an initially elevated PSA level (i.e., 3.0 µg/l or higher) but free of cancer in the first round of screening in 1996 were at increased risk of prostate cancer in re-screening in 2000. The risk was approximately 6-fold (95% CI, 3.2-10.1%; ratio of detection rates) with fourteen cancers found in the 191 men with baseline PSA levels 3.0-3.9 µg/l compared to 45 cancers detected among the 3,459 men at PSA levels less than 3.0 µg/l in the first round of screening. The risk was 8.6-fold (95% CI, 5.1-14.4; 19 cancers per 170 men) for those with baseline PSA level between 4.0 and 9.9 µg/l.

6. Tumor characteristics

PSA screening resulted in a significant increase in the number prostate cancer cases detected as clinically localized. The detection rate of organ-confined tumors was 2.0% (95% CI, 1.8-2.3%; 319/15,685) compared to the cumulative incidence of 0.2% (0.2-0.2%, 72/35,973) among the controls or 0.3% (0.2-0.5%, 23/7,047) among the non-participants of screening (Table 11). Of the screen-detected cancers, 85% (319/377) were clinically localized (T1-2NxM0) and 15% (58/377) advanced (T3-4NxM0/T1-4NxM1) in the first round of screening 1996-1998. Among non-attenders, 58% (23/40) of cancers were organ-confined and 43% (17/40) advanced. Thus, the overall proportion of localized prostate cancers in the screening arm was 82% (342/417) compared to 64% (72/112) in the control arm ($p<0.001$). However, the cumulative incidence of non-local cancers was higher in the screening than the control arm of the trial (0.3% vs. 0.1%). The median PSA was substantially lower among the screen-detected cases (PSA 7.1 $\mu\text{g/l}$) than among the non-attenders (15.7 $\mu\text{g/l}$, $p<0.001$) and the controls (13.2 $\mu\text{g/l}$, $p<0.001$).

An improvement was observed in clinical stage between the first and second rounds of screening. Of the screen-detected cancers in the first screening round in 1996, 87% (95% CI, 80-93%; 91/105) were clinically localized compared to 94% (87-98%, 91/97) in the second round in 2000 (Table 12). The number of non-local cancers relative to the number of screening participants also decreased from 0.3% to 0.1% ($p<0.001$).

Table 11. Clinical stage of prostate cancers diagnosed in the first round of the Finnish trial 1996-1998.

Stage	Screening arm		Control arm [‡]			
	Participants [*]		Non-participants [†]			
	No. of cancers (%)	Detection rate, %	No. of cancers (%)	Cumulative incidence, % [§]	No. of cancers (%)	Cumulative incidence, % [§]
T1NxM0	176 (47)	1.1	12 (30)	0.2	35 (31)	0.1
T2NxM0	143 (38)	0.9	11 (28)	0.2	37 (33)	0.1
T3-4NxM0/ T1-4NxM1	58 (15)	0.4	17 (43)	0.2	38 (34)	0.1
Unknown	-	-	-	-	2 (2)	0.0
Total	377 (100)	2.4	40 (100)	0.6	112 (100)	0.3

^{*}, [†], [‡] A total of 22,732 were eligible for screening. Of these, 15,685 participated and 7,047 men declined to be screened. A total of 35,973 men were randomized to the control arm of the trial 1996-1998.

[§] Within 12 months of randomization

Table 12. Clinical stage of prostate cancers detected in the first and second rounds of the Finnish trial in 1996 and 2000.

Stage	Round 1*		Round 2			
			Re-screen [†]		Delayed first screen [‡]	
	No. of cancers (%)	Detection rate, %	No. of cancers (%)	Detection rate, %	No. of cancers (%)	Detection rate, %
T1NxM0	42 (40)	0.8	43 (54)	1.1	10 (56)	1.7
T2NxM0	49 (47)	1.0	31 (39)	0.8	7 (39)	1.2
T3-4NxM0/ T1-4NxM1	14 (13)	0.3	5 (6)	0.1	1 (6)	0.2
Total	105 (100)	2.1	79 (100)	2.1	18 (100)	3.1

*A total of 7,821 men invited, of whom 5,050 participated in screening in 1996.

^{†, ‡}A total of 6,415 men invited, of whom 4,407 participated in 2000. Of them, 3,833 men were re-screened (i.e., second-time screenees) and 574 men were screened for the first time (defined here as delayed first screen).

More than nine out of ten screen-detected cancers were well or moderately differentiated (WHO grade I or II) during the first three years of the trial (Table 13). The grade distribution of screen-detected tumors did not differ from that of cases diagnosed among the non-participants in screening or in the control arm ($p=0.17$ and $p=0.71$ respectively). The Gleason score distribution is shown in Table 14 for the subgroup of men forming the intervention arm in 1996 and 2000 (i.e., 1st vs. 2nd round). At first round (in 1996), 81% of the screen-detected tumors were defined respectively as well (Gleason score 2-6), 10% moderately (Gleason score 7) and 7% poorly (Gleason score 8-10) differentiated compared to 74%, 18% and 4% found after an interval of four years (in 2000).

Table 13. Clinical grade (WHO) of prostate cancers diagnosed in the first round of the Finnish Population-based Prostate Cancer Screening Trial 1996-1998.

	Screening arm		Control arm [‡]			
	Participants [*]		Non-participants [†]			
	No. of cancers (%)	Detection rate, %	No. of cancers (%)	Cumulative incidence, % [§]	No. of cancers (%)	Cumulative incidence, % [§]
Grade						
I	139 (37)	0.9	20 (50)	0.3	45 (40)	0.1
II	209 (55)	1.3	16 (40)	0.2	56 (50)	0.2
III	28 (7)	0.2	4 (10)	0.1	8 (7)	0.0
Unknown	1 (0)	0.0	-	-	3 (3)	0.0
Total	377 (100)	2.4	40 (100)	0.6	112 (100)	0.3

^{*}, [†], [‡] A total of 22,732 were eligible for screening. Of them, 15,685 participated and 7,047 men declined to be screened. A total of 35,973 men were randomized to the control arm of the trial in 1996-1998.

[§] Within 12 months from randomization

Table 14. Gleason score of prostate cancers detected in the first and second rounds of the Finnish trial in 1996 and 2000.

	Round 1 [*]		Round 2			
			Re-screen [†]		Delayed first screen [‡]	
	No. of cancers (%)	Detection rate, %	No. of cancers (%)	Detection rate, %	No. of cancers (%)	Detection rate, %
Gleason						
2-6	85 (81)	1.7	57 (72)	1.5	15 (83)	2.6
7	10 (10)	0.2	15 (19)	0.4	2 (11)	0.3
8-10	7 (7)	0.1	3 (4)	0.1	1 (6)	0.2
Unknown	3 (3)	0.1	4 (5)	0.1	-	-
Total	105 (100)	2.1	79 (100)	2.1	18 (100)	3.1

^{*}A total of 7,821 men were invited, of whom 5,050 participated in screening in 1996.

^{†, ‡}A total of 6,415 men invited, of whom 4,407 participated in 2000. Of these, 3,833 men were re-screened (i.e., second-time screenees) and 574 men were screened for the first time (defined here as delayed first screen).

7. DRE and %FPSA as supplementary screening tests

A supplementary screening test (DRE in 1996-1998 or %FPSA in 1999) was offered to 5% (1,271/20,716) of men with a serum PSA of 3.0-3.9 µg/l in the first screening round. Of the 801 men with a PSA of 3.0-3.9 µg/l during the first three years of the trial, 81 (10%) had a suspicious finding in DRE and were referred for prostate biopsies (Table 15). A total of 23 cancers were found corresponding to the detection rate of 2.9% (95% CI, 1.8-4.3%; 23/801) and the positive predictive value of 28% (19-40%, 23/81) within the PSA range of 3.0-3.9 µg/l. Thus, 32 DREs or 3.5 biopsies were required to detect one prostate cancer. The application of DRE as a supplementary test of screening contributed 0.1% (23/15,685) to the overall detection rate of 2.6% (412/15,685) for the original (initial) screening protocol (Table 16).

The screening algorithm was changed in 1999 by substituting %FPSA for DRE within the PSA range of 3.0-3.9 µg/l. A total of 270 screening participants had a PSA of 3.0-3.9 µg/l in the last year of the first round, and 64 (24%) of them were referred for prostate biopsies on the basis of %FPSA less than 16% (Table 15). Thirteen cancers were found, corresponding to a detection rate of 4.8% (95% CI, 2.6-8.9%; 13/270) and a positive predictive value of 22% (12-34%; 13/60), or 4.6 biopsies per cancer. The overall detection rate of the screening program was 2.6% according to the modified protocol. The contribution of the %FPSA within the PSA range of 3.0-3.9 µg/l to the overall detection rate was 0.3% (Table 16).

Table 15. DRE and %FPSA as supplementary screening tests within the PSA range 3.0-3.9 µg/l in the Finnish Population-based Prostate Cancer Screening Trial in 1996-1998 (Protocol I) and 1999 (Protocol II).

	PSA 3.0-3.9 µg/l	
	Protocol I	Protocol II
Indication for biopsy	<i>DRE+</i>	<i>%FPSA <16</i>
No. of men (%)	<i>801 (5.1)</i>	<i>270 (5.4)</i>
No. of biopsy referrals (%)	<i>81 (10)</i>	<i>64 (24)</i>
No. of biopsies	<i>81</i>	<i>60</i>
No. of cancers (%)	<i>23 (2.9)</i>	<i>13 (4.8)</i>
Biopsy-to-cancer ratio	<i>3.5 : 1</i>	<i>4.6 : 1</i>

The specificity of the screening program based on supplementary DRE was 93.4% (95% CI, 93.0-93.8%; 14,262/15,276) compared to 88.6% (88.1-89.2, 13,542/15,276) for the PSA threshold of 3.0 µg/l alone (Table 16). In other words, respectively 93.4% and 88.6% of men free of cancer were correctly classified as test negatives. Correspondingly, the specificity of the screening program was increased from 87.5% (95% CI, 86.5-88.4%; 4,288/4,902) for the PSA threshold of 3.0 µg/l alone to 91.7% (90.9-92.5%, 4,494/4,902) using the algorithm based on the %FPSA.

The Gleason score and clinical stage of cancers detected within the PSA range of 3.0-3.9 µg/l are shown in Table 17.

Table 16. Overview of screening results by PSA level in the first round of the Finnish trial.

	Protocol I [*]			Protocol II [†]		
	No. of men (%)	No. of cancers (%)	DR, %	No. of men (%)	No. of cancers (%)	DR, %
PSA (µg/l)						
0-2.9	13,542 (86.3)	3 (0.7) [‡]	0.0	4,288 (85.2)	-	-
3.0-3.9 and supplementary test negative	720 (4.6)	-	-	206 (4.1)	-	-
3.0-3.9 and supplementary test positive	81 (0.5)	23 (5.6)	0.1	64 (1.3)	13 (10.1)	0.3
≥4.0	1,342 (8.6)	386 (93.7)	2.5	473 (9.4)	116 (89.9)	2.3
Total	15,685 (100)	412 (100)	2.6	5,031 (100)	129 (100)	2.6

^{*}*DRE as a supplementary test of screening.*

[†]*%FPSA as a supplementary test of screening.*

[‡]*A supplementary DRE resulted in the diagnosis of three cancers in the PSA range 2.0-2.9 µg/l before the practice was discontinued.*

Table 17. Gleason score and clinical stage of the cancers detected on the basis of DRE and %FPSA as supplementary screening tests within the PSA range 3.0-3.9 µg/l.

	PSA 3.0-3.9 µg/l	
	Protocol I [*]	Protocol II [†]
	No. of cancers (%)	No. of cancers (%)
Gleason score		
2-6	18 (78)	9 (69)
7	4 (17)	3 (23)
8-10	-	-
Unknown	1 (4)	1 (8)
Total	23 (100)	13 (100)
Clinical stage		
Localized	22 (96)	12 (92)
Locally advanced	1 (4)	1 (8)
Metastatic	-	-
Total	23 (100)	13 (100)

^{*}DRE as a supplementary test of screening.

[†]%FPSA as a supplementary test of screening.

8. Family history and prostate cancer screening

Self-reported information on family history was available for 98% (20,311/20,716) of the men who participated in the first screening round. A total of 964 out of 20,311 (4.7%) men reported one or more affected first-degree relative(s). Detailed information on family history is shown in Table 18.

Of the 964 men with a positive family history, 105 had a PSA of 4.0 µg/l or higher. Twenty-nine tumors were diagnosed corresponding to a detection rate of 3.0% (95% CI, 2.0-4.3%; 29/964) and a PPV of 28% (19-36%, 29/105). The specificity of the PSA threshold of 4.0 µg/l was 91.9% (95% CI, 89.9-93.5%; 859/935) among men with a positive family history of prostate cancer. Correspondingly, 1,487 of 19,347 (7.7%) men with no such family history had a PSA of 4.0 µg/l or higher and 462 cancers were found. The detection rate was 2.4% (95% CI, 2.2-2.6%; 462/19,347) and the PPV was 31% (95% CI, 29-33%; 462/1,487). The specificity of the PSA threshold of 4.0 µg/l was 94.6% (95% CI, 94.2-94.9%; 17,860/18,885) among men without a family history of prostate cancer.

The risk of prostate cancer was not materially increased among the men with a positive family history [ratio of detection rates (RR), 1.3; 95% CI 0.9-1.8] (Table 18). Similar findings were also obtained for features commonly associated with an inherited susceptibility to prostate cancer, e.g., for men with an affected relative on the maternal side of the family (RR 1.1, 95% CI, 0.6-2.1), or with a family member diagnosed before the age of 60 (RR 1.4, 0.5-4.3; data not shown).

Table 18. Number of men and screen-detected prostate cancers with the ratio of detection rates (RR) for prostate cancer (PC) by family history in the first round of the Finnish Population-based Prostate Cancer Screening Trial 1996-1999.

	Family history				RR* (95% CI)
	Yes		No		
	No. of men	No. of PC	No. of men	No. of PC	
Affected first-degree relatives					
Any first-degree relative(s)	964	29	19,347	462	1.3 (0.9-1.8)
Father	708	20	19,603	471	1.2 (0.8-1.8)
Brother(s)	266	10	20,045	481	1.6 (0.9-2.9)
Any first-degree relative(s), age of screenee <60 years	539	10	11,208	171	1.2 (0.7-2.3)
Affected second-degree relatives					
Any second-degree relative(s)	685	18	19,626	473	1.1 (0.7-1.7)
Maternal grandfather or uncle(s)	365	10	19,946	481	1.1 (0.6-2.1)
Paternal grandfather or uncle(s)	340	8	19,971	483	1.0 (0.5-1.9)
Any affected first- or second-degree relative(s)	1,558	47	18,753	444	1.3 (1.0 [†] -1.7)

*The ratio of detection rates (RR) was calculated with those reporting no corresponding family history as a reference. [†]Non-significant (exact value 0.95)

The sensitivity of family history as a supplementary screening criterion (or selective screening based on family history) was 5.9% [95% CI, 4.0-8.4%; $29/(29+462)$] in the absence of information on interval cancers (Table 19). In other words, restriction of screening to men with a positive family history only would have missed 94.1% of all prostate cancers detectable through PSA screening. Correspondingly, the specificity for a family history as a supplementary screening criterion was 99.6% [95% CI, 99.5-99.7%; $(1,025+859+17,860)/(76+1,025+859+17,860)$] (Table 19). The program specificity for a family history selective screening was 95.3% [95% CI, 95.0-95.6%; $(1,025+17,860)/(76+1,025+859+17,860)$], i.e., limiting screening to men with a positive family history only would have correctly identified more than 95% of men without prostate cancer (Table 19).

No differences were observed in the characteristics (i.e., Gleason score and stage) of screen-detected tumors for men with and without a family history of prostate cancer (data not shown). The mean age at diagnosis was 61 years in both groups, and the median PSA values were also comparable in men with or without a familial background of prostate cancer (i.e., 6.2 $\mu\text{g/l}$ and 7.5 $\mu\text{g/l}$, respectively; $p=0.24$).

Table 19. Number of men by PSA level and family history in the first round of the Finnish trial.

PSA (µg/l)	Family history	Prostate cancer		Total
		Yes	No	
≥4.0				
	<i>Positive</i>	29	76	105
	<i>Negative</i>	462	1,025	1,487
	<i>Unknown</i>	11	25	36
0-3.9*				
	<i>Positive</i>	-	859	859
	<i>Negative</i>	-	17,860	17,860
	<i>Unknown</i>	-	369	369
Total		502	20,214	20,716

*Tumors below a PSA cutoff of 4.0 µg/l were regarded as non-detectable through screening, and such patients were here defined as healthy.

DISCUSSION

Few issues in health care are as controversial as prostate cancer screening. The best way to resolve this issue is through randomized controlled trials. So far, no mortality results are available from randomized trials, apart from early and inconclusive findings from the Quebec trial (Labrie et al., 1999). The Finnish Population-based Prostate Cancer Screening Trial, a part of the European Randomized Study of Screening for Prostate Cancer (ERSPC), was launched in 1996 to assess the impact of PSA screening on disease-specific mortality and quality of life (Auvinen et al., 1996). The final outcome of the ERSPC is not to be expected until around 2010, and the Finnish trial does not have sufficient power on its own. Although mortality results are not yet available, the ERSPC has already vastly increased knowledge about the use of PSA for early detection and screening for prostate cancer, likewise about the epidemiological aspects of the disease. The articles constituting this thesis are based on the Finnish contribution to the ERSPC with the focus on both the performance and the early outcome measures of screening. A change for the better in these provides necessary, although still inconclusive evidence for potential mortality reduction attributable to PSA screening.

1. Acceptability of PSA screening

The Finnish Prostate Cancer Screening Trial is population-based and thus allows estimation of the effects in general population, i.e., screening implemented as a part public health policy. High attendance (68%) was achieved in the first round of screening, and it was maintained in the second round. The participation rate in Finland compares favorably with those at other centers of the ERSPC with randomization of subjects from population registries, but was somewhat lower than that in the centers recruiting volunteers (de Koning et al., 2002). Compared to the experiences from cervical and breast cancer screening, a participation rate of close to 70% in the prostate cancer

screening trial can be regarded as acceptable (Anttila & Nieminen, 2000; Anttila et al., 2002). High coverage of the target population is of great importance for screening as a part of public health policy, since it forms an important determinant of program sensitivity (i.e., the ability of a screening program to identify the target condition in the population) and is a prerequisite for effectiveness (Hakama et al., 2007).

Although the overall attendance in the second round of screening remained acceptable (69%), the proportion of men dropping out of re-screening was substantially higher among the screen-positive men with no cancer found at prostate biopsy in the first round (i.e., with a false-positive screening result) than among screen negatives at baseline (36% vs. 15%). Plausible explanations for this difference include the possibility that a negative biopsy may give (false) assurance of a low future risk of cancer, but also refusal because of discomfort and pain experienced during earlier biopsies, or even fear of cancer. Irrespective of individual reasons, poor compliance with screening after a false-positive result seems to be particularly relevant for program sensitivity (and ultimately the effectiveness of screening) because the risk of cancer at repeated screening was, in fact, higher among the false-positives than in the men with a prior negative screening test.

It is widely agreed that the screening test must be acceptable to the population. In prostate cancer screening, this should also cover the subsequent diagnostic examinations including prostate biopsy after a positive PSA test. In attending or refusing prostate cancer screening, urological complaints (or their absence), attitudes and socio-demographic factors, but also anticipated pain or discomfort may play an important role (Nijs et al., 1997). There is no doubt that undergoing a prostate biopsy is at best an uncomfortable, and at times, even a painful experience. Nevertheless, only 2% of the screening-positive men responding to the questionnaire indicated an unwillingness to undergo a prostate biopsy again if recommended, whereas 14% were uncertain. The acceptance of biopsy is of great importance, since it may substantially impair the results of screening as evinced by the results of the PLCO trial. Of the men referred to biopsy in that study, only 31% complied, yielding an

overall detection rate of 1.4%, i.e., substantially lower than that in our trial with more than 90% compliance with a biopsy referral (Andriole et al., 2005). Given the higher background incidence of prostate cancer in the United States, the difference in detection rates is likely to be (at least to some extent) related to biopsy compliance.

Our study assessing the feasibility of prostate biopsy in PSA screening (as well as the other articles in this thesis), was based on sextant biopsy. Therefore, the acceptability of biopsy remains to be established for the current practice of a 10 to 12-core biopsy regimen adopted in 2002. In addition to a presumable increase in the rate of prostate cancer detection (and possible overdiagnosis), this change may reduce the tolerability of the biopsy procedure. On the other hand, the use of local anesthetic has improved patient toleration of the more extensive procedure (Alavi et al., 2001). The acceptance of biopsy was evaluated in the early years of our trial, when biopsies were performed without analgesia. It is now self-evident that the use of local anesthetics should be advocated to improve the acceptability of prostate biopsy.

2. Effects of screening on prostate cancer detection

Screening is likely to have a substantial impact on the occurrence of the disease in population. Initially, the number of cancers detected temporarily increases, because of the earlier diagnosis as a result of screening (Hakama, 1991). This was also observed in the Finnish trial with an approximately 6-fold difference in the occurrence of prostate cancer between the screening and the control arm of the trial on initial (prevalence) screening within the first year after randomization. If compared only between the participants in screening and the control population the difference was as high as 8-fold. Prostate cancer was found in the 2.4% of first-round participants in screening compared to a cumulative incidence of 0.3% among controls and 0.6% among non-attenders at screening. These figures confirm that PSA screening is able to detect a substantial number of new prostate cancer cases. However, an acceptable level of prostate cancer detection providing the

optimal balance of avoiding the risk of missing significant cancers, but also ignoring clinically insignificant disease (i.e., overdiagnosis defined here as tumors that would otherwise remain clinically unrecognized until the individual died from other causes) remains to be established.

The Finnish trial represents a conservative (low-intensity) screening program, i.e., the PSA cutoff is higher and the screening interval longer than in most other studies (de Koning et al., 2002; Krumholtz et al., 2002). The advantages of a conservative screening strategy include the possibility to minimize the costs and to avoid potential adverse effects of screening (such as false positive results and overdiagnosis). On the other hand, the major potential drawback of a less aggressive approach is the risk of missing cancers that might pose a threat to the individual's health. In the absence of mortality results, however, this disadvantage cannot yet be evaluated, whereas the aforementioned advantages are undeniable. Likewise the potential benefit of higher detection rates observed for trials using a more intensive screening regimen still cannot be determined.

Although the overall detection of prostate cancer in the second round of the Finnish trial was comparable to that in the first round, a substantial reduction was found in age-specific rates. Moreover, the cumulative incidence of 4.6% in the two screenings has so far remained substantially lower than the lifetime risk of 6.8% observed for Finnish men aged 55-74 years in 1993-1997, i.e., when the prevalence of opportunistic screening in the population was estimated to be low (www.cancerregistry.fi/eng/, 2008; Ciatto et al., 2003). It is generally assumed that after an initial screening, the number of cancers detected will drop in successive rounds to a level, which is usually higher than the level without screening. This was also true for the Finnish trial. Such a reduction is dependent on both the biological properties of the disease and the aggressiveness of the screening program (Hakama, 1991). Failure to achieve this drop may indicate too long a screening interval, but may also be attributable to overdiagnosis. Interestingly, both a reduction, but also an increase in the detection rate of prostate cancer between the study rounds has been reported for PSA screening

in the ERSPC trial (Hugosson et al., 2004; Hoedemaeker et al., 2001). Because of frequent protocol changes undertaken for subsequent screens, these observations should be interpreted with caution.

3. Stage shift and tumor characteristics

A shift in tumor stage represents a surrogate measure of the effectiveness of screening, because the cure is potentially available only for cases detected early enough (Day & Walter, 1984). Hence, a shift towards earlier clinical stages attributable to PSA screening as shown here provides a necessary but not sufficient indication of mortality reduction. To our knowledge, our study was the first intention-to-screen analysis demonstrating the favorable impact of PSA screening on tumor characteristics in general population, and has been subsequently confirmed by others (Postma et al., 2006; Aus et al., 2007). A randomized controlled trial allows a balanced distribution of confounding factors (e.g., self-selection driven by different motives to attend screening), given that the representativeness of the population is ensured by sufficient attendance at screening. Contrary to ecological analyses based on temporal and geographical trends, our findings are likely to be free of the effects of contemporary changes in other factors affecting tumor stage. However, important sources of bias are known for tumor stage (most importantly overdiagnosis) making it unsuitable for conclusive evaluation of the effectiveness of screening (Hakama, 1991). False inference may be due to both lead-time and length bias. Lead-time refers to the earlier time of diagnosis by screening, defined as the time from screening detection to the hypothetical diagnosis in the absence of screening (Hutchison & Shapiro, 1968). Because of lead-time, the survival time with disease may be increased even if death is not postponed. The mean lead-time in PSA screening has been estimated as 5 to 12 years (Auvinen et al., 2002; Draisma et al., 2003; Törnblom et al., 2004). Another source of bias limiting the use of tumor stage as a surrogate for the effectiveness of screening is known as length bias, which refers to a higher likelihood of detecting slow-growing as against aggressive cancers (Feinleib & Zelen, 1969). Detection of such less aggressive tumors may

artefactually improve stage distribution and apparent survival. Overdiagnosis represents the extreme manifestation of length bias. Indeed, the natural course may be so slow that death occurs from other causes before the disease progresses to a life-threatening condition even without any attempt at cure (Johansson et al., 2004; Albertsen et al., 2005b). This issue is particularly relevant for prostate cancer due to its slow natural course.

To be effective, screening should reduce the incidence of advanced disease (for which no cure is available), or in some opinions, to delay the progression sufficiently so that men would die from some other cause. However, the one-year cumulative incidence of advanced cancers in the screening arm at initial (prevalence) screen exceeded that in the control arm. Presumably, the lack of reduction in advanced cancer does not indicate a failure of screening, first because of the preliminary nature of this finding with only a short, one year follow-up from randomization. Second, it is possible that some advanced tumors would not have surfaced (and/or resulted in death) in the absence of screening, suggesting that overdiagnosis may occur for advanced disease as well. Third, because of the estimated mean lead-time of 5-12 years for prostate cancer, the difference in cumulative incidence should be diminished, or even reversed in due course. The second round results were in line with this assumption, since the rate of advanced cases was substantially lower at repeat screening. These, together with a low rate of interval cancers reported later, suggest that a screening interval of four years is likely to be sufficient to prevent the development of advanced and potentially fatal prostate cancer (Auvinen et al., 2004). The reasoning is still limited because of the lack of information on cancers detected outside organized screening during follow-up. This shortcoming was overcome in the recent report of the Swedish branch of the ERSPC trial showing that biennial PSA screening reduces metastatic prostate cancer (Aus et al., 2007).

Our results are in line with other studies showing a significant improvement in major prognostic factors of prostate cancer, i.e., tumor stage, involvement of biopsy by tumor and PSA levels after successive screens (Aus et al., 2007; Postma et al., 2007). Not all the changes observed for repeated

screening have been positive. The reduction of advanced disease was shown to occur at the price of a 1.8-fold risk of being diagnosed with prostate cancer in the Swedish trial (Aus et al., 2007). According to the Dutch results, minimal cancer (defined as tumor with a volume less than 0.5 ml, organ confined and no Gleason pattern 4 or 5 at radical prostatectomy) increased from 31.6% in men undergoing surgery in the first round to 42.6% in the second round of screening (Postma et al., 2007). These findings indicate that potential overdiagnosis is likely to increase in the setting of repeated screening.

Tumor grade is of major importance for the ultimate outcome of prostate cancer screening, as survival of patients with highly-differentiated tumors is comparable to that of age-matched controls, whereas those with an aggressive disease have substantially reduced life expectancy (Chodak et al., 1994). Most of the cancers detected through PSA screening in our trial were well-differentiated (i.e., Gleason score 2-6), and hence, suggestive of potential overdiagnosis. Furthermore, the cumulative incidence of well-differentiated (defined here as WHO grade I) cases was significantly higher in the screening than in the control arm during the first three years of our trial (0.7% vs. 0.1%). Even though the natural course of the disease is difficult to predict for an individual patient, overdiagnosis is most likely present among cases with the most favorable prognostic factors. On the other hand, screening was also able to detect aggressive, Gleason score 7-10 cancers, as evinced by a detection rate of 0.5% for such tumors in both the first and second round of our trial. However, the lack of experience with the use of the Gleason score system in the initial phase of our trial may attenuate the comparability between the rounds. It is possible that changes in the interpretation of grading criteria (such as abandoning the use of Gleason scores 2-4 for biopsy specimens) may have altered the grade distribution in the absence of true biological change (Epstein et al., 2005). In fact, a reduction of low-grade tumors reported after the introduction of PSA screening has been suggested to be at least partly artifactual, constituting a so-called “Will Rogers” phenomenon (Albertsen et al., 2005a). This phenomenon may have contributed to a shift toward the Gleason

score 7 tumors also observed in our trial, with a concomitant decrease in Gleason score 2-6 cases at re-screening. In this study, Gleason score 7 was not divided into two components in order to follow the original classification used in the ERSPC, and thereby to maintain comparability with other participating centers.

4. PSA and supplementary screening tests

Serum prostate-specific antigen was shown to be a powerful predictor of prostate cancer when the test was first introduced for purposes of early detection of prostate cancer (Stamey et al., 1987). Up to one third of men with a PSA of 4.0 µg/l or higher were diagnosed with prostate cancer at biopsy during the early years of PSA testing (Catalona et al., 1991). In the first round of our trial, the positive predictive value of a PSA cutoff of 4.0 µg/l was 27%, (i.e., 3.7 biopsies per cancer). In the second round of screening, however, the positive predictive value dropped to 18% (5.6 biopsies per cancer). A similar change has also been observed in other trials, indicating that PSA is more predictive at initial screen than later (Labrie et al., 1996; Hoedemaeker et al., 2001). This is presumably due to a change in the ratio of prostate cancer to other conditions causing elevated PSA levels, i.e., most commonly benign prostatic hyperplasia. A large proportion of the prevalence pool (men harboring prostate cancer) is ‘harvested’ at prevalence screen, while those with other prostatic diseases remain in the target population. Because of this, the positive predictive value is likely to be diminished in successive rounds, which is related to the fact that the positive predictive value is not determined only by the test itself, but also by the prevalence of the target condition in the source population. The loss in the predictive value of PSA is also likely to have important clinical implications. Indeed, it has been recently suggested that PSA is no longer an indicator of prostate cancer, but only benign prostatic hyperplasia (due to widespread and intensive PSA testing) (Stamey et al., 2004).

As discussed earlier, a PSA cutoff of 4.0 µg/l was chosen in the Finnish trial to reduce the costs and possible side effects of screening inevitable with lower cutoff values. It was conceded, however, that this approach may miss some tumors, and some of these may surface as interval cancers, whereas others would be detected at subsequent screening rounds. Therefore, it was decided to incorporate an ancillary test (at first DRE, and later, %FPSA) for detecting such cases within the PSA range of 3.0-3.9 µg/l, and still to maintain acceptable specificity (i.e., frequency of false-positives). As a consequence of reducing PSA cutoff from 4.0 µg/l to 3.0 µg/l, the number of men referred to biopsy (i.e., screening positives) would have increased by more than two thirds in the first round of the Finnish trial. The supplementary tests yielded 4-5% improvement in the program specificity, i.e., the proportion of men free of prostate cancer correctly identified. In other words, the use of supplementary screening tests may potentially spare 4,000-5,000 men an unnecessary biopsy in the target population of 100,000 men (per screening round). However, the use of DRE and %FPSA as a supplementary screening test contributed only modestly (0.1-0.3%, respectively) to the approximate overall detection rate of 2.4%.

The respective detection rates attributable to DRE and %FPSA were substantially lower (i.e., 2.9% and 4.8%) than the 26.9% found when all the men within a PSA range of 3.0-3.9 µg/l were biopsied in the Prostate Cancer Prevention Trial (Thompson et al., 2004). It is obvious that a substantial number of cancers remained undetected in our trial because of the decision to use a supplementary screening test instead of biopsying all men within this PSA range, but the implications of a resultant loss in sensitivity remain to be established. It is possible that potentially significant tumors initially missed within the PSA range of 3.0-3.9 µg/l would be still detectable at a curable stage during subsequent screens. If this is true, and the number of indolent tumors at low PSA levels is by far greater than that of aggressive tumors, these cases may add to overdiagnosis without substantially improving the mortality impact of screening. However, the findings are still too tentative for conclusive evaluation of this issue.

DRE was replaced by %FPSA after three years of screening, because of the disproportionate effort (and costs) required relative to the small number of cancers found. In fact, 32 men had to undergo DRE to detect one cancer at PSA levels between 3.0-3.9 $\mu\text{g/l}$, although the ratio of 3.5 biopsies per cancer may be regarded as reasonable. However, the resources required for a DRE approach those needed for biopsy. Our findings confirm earlier results indicating that DRE is of little value in screening for prostate cancer (Schröder et al., 1998; Chodak et al., 1989). The use of %FPSA resulted in a slight, but not statistically significant increase in prostate cancer detection compared to DRE. However, the gain in the detection of prostate cancer was accompanied by a similar increase in the number of biopsies. This notwithstanding, the latter protocol may be regarded as less labor-intensive than the initial practice in which a clinical examination (DRE) was required for all men with the PSA levels between 3.0-3.9 $\mu\text{g/l}$.

The decision to incorporate DRE, and later %FPSA, in our screening program was to some extent influenced by an assumption that cancers so detected might be more aggressive than tumors detected otherwise. The evidence related to DRE remains conflicting, whereas the relation of a low %FPSA with unfavorable tumor characteristics is more convincing (Raaijmakers et al., 2007; Gosselaar et al., 2007; Shariat et al., 2006). Our results were also interpreted first as supporting the association between a low %FPSA and aggressive prostate cancer, but this interpretation was based on a different classification of tumor grade in the original paper (i.e., the Gleason score 5 or higher tumors were regarded as aggressive, whereas Gleason scores 2-4 were classified as indolent) as currently recommended (Epstein et al., 2005). When reassessed, Gleason score 7 or higher cases indicating an aggressive tumor, were detected with similar frequency through DRE and %FPSA (i.e., approximately 1%). However, the lack of knowledge of tumor characteristics for cancers potentially missed within this PSA range and the small number of cases limit the conclusions. The lack of experience with the Gleason score system in the initial phase of our trial also adds uncertainty to our results, as discussed earlier.

5. Selective screening by family history

The Finnish trial provided no support for selective screening in men with a family history of prostate cancer. We found no difference in the process measures of screening between men with and without a familial background suggesting a similar impact on the final outcome (i.e., mortality). Nevertheless, it is a common belief that men with a family history of prostate cancer should be offered regular PSA testing. At present, several recommendations rely on the assumption that screening is effective, and therefore, selective screening is justifiable, and of particular importance for high risk populations (American Urological Association (AUA), 2000; Smith et al., 2006). In theory, selective screening may improve program performance in terms of lower costs and adverse effects of screening, given that a sufficient proportion of all cancers in the population occur in the high-risk group (Hakama, 1991).

Our results demonstrated that selective screening based on family history would have improved specificity (i.e., a vast majority of healthy men in the target population would have been classified as free of cancer). However, the program sensitivity would have been only 5.9%, i.e., a selective approach would have failed to identify most cancers in the population detectable through PSA screening. The program sensitivity was only slightly higher (i.e., 10.5%) in the volunteer-based Dutch ERSPC trial, but may still be regarded as unacceptably low (Roemeling et al., 2006). The somewhat higher program sensitivity in the Dutch trial may be partly attributable to a different recruitment strategy (volunteer-based) applied because of possible selection bias affecting participation (i.e., men with affected relatives are more likely to attend screening than those without a family history). Indeed, the proportion of men reporting a positive family history was higher in the Netherlands than in Finland (6.8% vs. 4.7%), but the impact of possible difference in genetic susceptibility for prostate cancer between these populations cannot be ruled out. However, a lack of genetic predisposition to prostate cancer in the Finnish population is an unlikely explanation for the failure (in terms of cancers missed) of the possible use of a family history selective screening in our

trial (Schleutker et al., 2000). Although several candidate susceptibility loci (or genes) have been identified among high-risk families, their prevalence either alone, or even together may be insufficient to be of importance at population level (Zheng et al., 2008). In other words, the program sensitivity of selective screening based on hereditary factors may be too low to be effective in public health policy.

We do not dispute the significance of family history as a risk factor of prostate cancer, even though in our trial statistical significance was not achieved for this association. Familial risk estimates may be diluted because of the detection of incidental tumors at biopsy (i.e., overdiagnosis) as a result of PSA screening. In contrast to the results of our study, increased risks of prostate cancer associated with family history have usually been observed for clinically detected cases (Pienta & Esper, 1993). A modest impact of family history in screening may be explained if the majority of screen-detected tumors, especially among men without a family history, are attributable to overdiagnosis. However, we were not able to show any difference in major prognostic factors between cases with family history and sporadic tumors detected as a result of PSA screening, which is in line with recent findings from other PSA studies (Kupelian et al., 2006; Roemeling et al., 2006; Kiemeny et al., 2008). Even so, it is not known whether differences would occur if cases were diagnosed years later on a clinical basis. Family history may still be important in determining prognosis for selected individuals (or families), even though the prognostic impact of familial background seems to become minimal (or non-existent) at population levels in the PSA era. Indeed, both good and poor prognosis has been observed for prostate cancer patients with familial background (Hemminki et al., 2008). So far, the lack of difference in prognostic factors implies that for an individual screenee the potential benefit (if any) of screening is not likely to differ from that for the population overall.

6. Benefits and drawbacks of PSA screening

Screening may provide a means of disease control in populations with only a small proportion harboring a pre-clinical prostate cancer limiting the frequency of tolerable side effects. The overall benefit of prostate cancer screening must outweigh the adverse effects inherent in any screening program. The effectiveness of screening is estimable only in population terms i.e., the difference in prostate cancer mortality in the presence of screening compared to the death rate observed for the situation in which screening is not offered. For an (asymptomatic) individual participating in a screening program, the benefits are likely to be minimal (in terms of a potential reduction of the risk of dying from prostate cancer) apart from the possible assurance of being free of cancer (whether justified or not). Due to a low risk of death from an early-stage disease even without any attempt at cure, the potential benefit of screening also remains modest for those with screen-detected prostate cancer (Albertsen et al., 2005b; Johansson et al., 2004). While reflecting this against the fact that a substantial risk of prostate cancer death also exists for men with PSA levels less than 4.0 µg/l at the time of diagnosis, the number of screenees to benefit from screening is likely to represent only a fraction of the overall number of men with a screen-detected tumor (Thompson et al., 2005b). Furthermore, it generally takes years to observe a mortality benefit (if any) attributable to screening, whereas most of the adverse effects are immediate and directly observable on an individual basis.

The assessment of the adverse effects of screening must cover the entire chain of events from the screening test itself to diagnostics, and finally the management of prostate cancer. We demonstrated here that adverse effects related to sextant biopsies of the prostate are common, but relatively well tolerated. This is in line with the results from the Dutch trial showing no significant impact on short-term quality of life resulting from the screening or biopsy procedure itself (Essink-Bot et al., 1998). Most side effects observed in our study were minor (e.g., hematuria and rectal bleeding), whereas more serious complications (such as severe bleeding or infections) were rare. Overall, prostate biopsy may be regarded as a relatively safe and acceptable procedure in the context of

screening. As long as a histological verification is required to make a prostate cancer diagnosis, significant improvements are unlikely to occur to improve the safety of prostate biopsies. Rather, the focus should be on improving the performance of screening tests or decision algorithms given that more than three biopsies out of four are negative (i.e., either due false-positive screening result or false negative biopsy).

Screening also involves several other side effects, but their assessment was beyond the scope of this thesis. Overdiagnosis is perhaps the most serious adverse effect of screening (apart from lethal complications induced by screening). Estimates of overdiagnosis range from 15% up to 200-250% when defined as detection of cases not diagnosed in the absence of screening (Zappa et al., 1998; Etzioni et al., 2002; Draisma et al., 2003). Because of an inability to reliably distinguish clinically significant cancers from indolent tumors, extensive research is ongoing to define optimal strategies for active surveillance to avoid overtreatment and its adverse effects. Quality of life aspects are also of great importance in evaluating the impact of screening. Quality of life reflects the psychological effects of participating in a screening program. Even though the short-term quality of life effects attributable to PSA screening have been suggested to be only minor, the psychological impact of screening is not negligible, especially among anxiety-prone individuals (Essink-Bot et al., 1998). The potential sources of anxiety are numerous including false-positive screening results, a negative perception of mental as well as overall health after prostate cancer diagnosis, and depression associated with treatment related side-effects (i.e., sexual, urinary and bowel dysfunction).

Despite numerous studies describing the impact of PSA screening on prostate cancer mortality, the evidence so far remains inconclusive and conflicting (Labrie et al., 1999; Roberts et al., 1999; Merrill & Stephenson, 2000; Skarsgard & Tonita, 2000; Bartsch et al., 2001; Vutuc et al., 2001; Perron et al., 2002; Lu-Yao et al., 2002; Coldman et al., 2003; Weinmann et al., 2004; Weinmann et al., 2005; Kopec et al., 2005; Oberaigner et al., 2006; Concato et al., 2006; Agalliu et al., 2007; Bergstralh et al., 2007; Etzioni et al., 2008; Marcella et al., 2008). It is now extremely important to

be able to resist the enthusiasm and pressure created by the general public and also some professional medical organizations advocating the adoption of screening until sufficient evidence from properly designed randomized trials becomes available. Once screening is started, it would be extremely difficult to discontinue it (even if the later evidence were against such practice). So far, several findings (although not all) obtained from randomized studies are encouraging, but still inconclusive. Even if a reduction of prostate cancer mortality attributable to PSA screening were shown in the future, its adoption as a part of public health policy is more complex involving far-reaching value and economic judgments. Therefore, strategies to reduce screening-related costs and potential side effects are likely to be of great relevance in the future (given that mortality benefit will be shown).

SUMMARY AND CONCLUSIONS

The Finnish Population-based Prostate Cancer Screening Trial has met several preconditions required for a successful screening program. Wide coverage of the target population was achieved in the Finnish trial as evinced by the participation rate of close to 70% in both the first and second rounds of screening. However, compliance with re-screening was substantially lower among men with false-positive screening results in the first round of screening compared to screen-negative men. Plausible explanations include (false) assurance after a negative biopsy of a low future risk of cancer, but also pain and discomfort experienced at biopsy at initial screen, or even fear of cancer. Although individual motives for refusing remain unclear, low compliance after a false-positive test result may substantially impair the outcome of a screening program.

The first round results confirmed that the adoption of PSA screening dramatically increases the detection of early stage prostate cancer in the population. This is of great importance because a cure is potentially only available for cases detected early enough. Although this finding is consistent with the potential beneficial effect of screening, it may also result from both lead-time and length biases. It is possible that the survival time with the disease will be increased, even if death is not postponed because of earlier diagnosis (lead-time bias). It is also known that screening generally detects more slow-growing than aggressive cancers (length bias), and therefore stage shift does not necessarily imply decreased mortality. In fact, most cancers detected through PSA screening in our trial were well-differentiated, but a substantial number of aggressive cancers (defined as Gleason score 7 or higher) were also detected in both the first and second rounds of screening. Although an improved stage distribution is a necessary prerequisite for an effective screening program, lead-time and length bias make it an invalid indicator of the ultimate effect (i.e., a change in prostate cancer mortality). This notwithstanding, the second round results were indicative of a shift towards lower clinical stages, and, more importantly, of a reduction in the detection of advanced cancer compared

with the initial round. This, together with a low rate of interval cancers, suggests that a screening interval of four years is likely to be sufficient to prevent the development of advanced and potentially fatal prostate cancer.

This thesis provided no support for family history selective screening compared with a comprehensive population approach, mainly because the cases detectable through PSA screening were too numerous among those without affected relatives. The program sensitivity (in terms of the number of cancers detected by family history selective screening in screened population) was inadequate and not balanced by an improvement in program specificity to justify a selective approach. Moreover, no difference was observed in prognostic factors between those with and without a family history of prostate cancer, suggesting a similar potential for effectiveness.

The use of DRE and %FPSA as supplementary tests in PSA screening was evaluated in the first round of our trial. We found that the adverse effects of screening may be reduced (i.e., program specificity improved) with either ancillary tests at intermediate PSA levels instead of lowering the PSA cutoff criteria, but the contribution to prostate cancer detection was only modest. DRE proved to be an inefficient method for improving the validity of a screening program as evinced by the need to clinically examine 32 men to detect one prostate cancer. The usefulness of %FPSA remains to be established, even though the yield (in terms of cancer detected) was somewhat higher than that for DRE. Overall, the significance of cancer detection at these low PSA levels remains unclear, since potentially significant tumors that are initially missed may still be detectable at a curable stage during subsequent screens. If this is true, it is possible that most tumors found at low PSA levels only add to the rate of overdiagnosis without necessarily improving the effectiveness of screening.

Finally, our results confirmed that PSA is a powerful predictor of biopsy outcome in previously unscreened populations as demonstrated by 3.7 biopsies required per cancer in the first round of screening above a PSA cutoff of 4.0 $\mu\text{g/l}$. The number of biopsies per cancer increased from 3.7 to 5.6 for the second-time participants in screening demonstrating the loss in positive predictive value

over successive screens. A previous history of PSA screening thus constitutes an important determinant regarding the immediate implications (i.e., cancer risk) of a positive test result for the screenee.

In conclusion, the Finnish Population-based Prostate Cancer Screening Trial with PSA achieved favorable findings in several process measures of screening, i.e., intermediate indicators of the final outcome. Although such indicators are still inconclusive for demonstrating the effectiveness of PSA screening, they support the continuation of the Finnish trial. Ultimately, the benefit of PSA screening (measured in terms of quality of life and prostate cancer mortality) should outweigh the (inevitable) drawbacks to justify its use as a means of public health policy.

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ORIGINAL COMMUNICATIONS

ACCEPTABILITY AND COMPLICATIONS OF PROSTATE BIOPSY IN POPULATION-BASED PSA SCREENING VERSUS ROUTINE CLINICAL PRACTICE: A PROSPECTIVE, CONTROLLED STUDY

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ABSTRACT

Objectives. To compare both the acceptability and the complications of prostate biopsy between men attending screening and hospital-referred symptomatic patients. A screening program cannot be successful unless the screening and diagnostic examinations are well tolerated and the willingness to participate is high.

Methods. A total of 200 men, comprising 100 participants in the Finnish prostate cancer screening trial and 100 hospital-referred patients with signs or symptoms suggestive of prostate cancer, were consecutively recruited and underwent transrectal ultrasound-guided prostate biopsies. Immediate complications were recorded at the time of examination. Acceptance and possible late complications of biopsy were requested through a self-administered questionnaire, which was returned by 97% of those screened and 84% of the hospital-referred controls.

Results. No major complications were seen immediately after biopsy, but one half of the men had minor rectal hemorrhage and, in a few cases, bleeding from the urethra. Most screened (58%) and hospital-referred (65%) subjects felt no distress before biopsy. The procedure was considered unpleasant by 69% of those screened and 61% of the controls. Correspondingly, 52% and 63% of men reported moderate pain at biopsy, but only 3 of those screened (3%) and 4 controls (5%) experienced severe pain. Nevertheless, a great majority of men in both the screening (82%) and the control (86%) groups would be willing to undergo a repeated biopsy if needed. Persistent rectal bleeding and hematuria were common (13% to 35%, respectively), but less than one fourth considered this disturbing. No significant differences were seen either in complications or acceptability between the groups.

Conclusions. The results of our study demonstrated that minor complications are equally frequent among men undergoing prostate biopsy for screening and other men. Despite the complications, prostate biopsy was regarded as acceptable. Nevertheless, such complications may impair the acceptability, and eventually, the effectiveness of screening. UROLOGY 60: 846–850, 2002. © 2002, Elsevier Science Inc.

Large, randomized trials are currently ongoing to assess the impact of prostate-specific antigen (PSA)-based screening on mortality from prostate cancer.^{1,2} An essential element in these trials is to show that screening measures are acceptable to the target population, a basic requirement for a suc-

cessful screening program. A venous puncture to determine the serum PSA level is a safe procedure causing very little pain, but more invasive diagnostic examinations, including prostate biopsy, are required among PSA-positive men. A PSA cutoff level of 4 ng/mL identifies approximately 10% of the

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male population aged 55 years or older as screening positive, but histologically defined malignancy is eventually revealed in only one fourth of them at biopsy.³ A large number of biopsies are thus done in the healthy population, setting high requirements for the safety and acceptability of prostate biopsy. Studies in other settings have shown a low rate of major complications such as sepsis or profuse bleeding attributable to prostate biopsy.⁴ The procedure has been regarded as acceptable and safe when undertaken on a clinical basis despite its frequent but relatively harmless minor complications, including hematuria and rectal bleeding. The applicability of these findings to the screening setting is unclear, because men examined in screening trials tend to be younger and likely to have fewer prior complaints than other patients. Little is known regarding the physical and psychological effects of prostate biopsy done for screening purposes in the general population.⁵⁻⁷ We therefore compared prospectively the effects of prostate biopsy on healthy men attending population-based PSA screening with outpatient patients referred on the grounds of clinical suspicion of prostate cancer.

MATERIAL AND METHODS

STUDY POPULATION

The Finnish trial of the European Randomized Study of Screening for Prostate Cancer began in 1996. Subjects aged 55 to 67 years were identified from the Population Register of Finland in 1996 to 1999 and randomized to either the screening or the control arm. Men with a previous diagnosis of prostate cancer were excluded before randomization. A blood sample was drawn from the men randomized to the screening arm, and those with PSA levels of 4 ng/mL or greater (Hybritech Tandem-E) were regarded as screening positive and were referred for diagnostic examinations, including a prostate biopsy. A supplementary screening test (digital rectal examination in 1996 to 1998 and proportion of free PSA of 16% or less from 1999 onward) was used as a biopsy criterion within the PSA range of 3.0 to 3.9 ng/mL. The assessment of biopsy effects on men attending PSA screening was based on a comparison of 100 consecutively recruited participants in the Finnish screening trial with 100 consecutive, hospital-referred symptomatic men belonging to the same age groups in the Tampere University Hospital in the period 1997 to 2000.

BIOPSY PROCEDURE

Diagnostic examinations were carried out on an outpatient basis, and the biopsies were taken by a senior-level urology resident or an attending urologist. Ciprofloxacin 500 mg was given orally 30 to 60 minutes before the biopsy as antibiotic prophylaxis. Random sextant biopsies were taken under ultrasound guidance supplemented by an additional biopsy if a focal lesion was found on transrectal ultrasonography or digital rectal examination using a spring-loaded biopsy gun with an 18-gauge needle. The biopsy protocol was similar for both screening participants and controls. Four men had fewer biopsies because of the small size of the prostate. The median number of biopsies was 6 (range 4 to 10) for both the screening and the control groups (mean 6.1 and 6.5, respectively).

TABLE 1. Immediate adverse effects of prostate biopsy among participants in PSA screening and hospital-referred symptomatic patients

Adverse Effect	Screening Group (%)	Control Group (%)
Any adverse effect	58 (58)	52 (52)*
Rectal bleeding	57 (57)	51 (51)*
Urethral bleeding	3 (3)	2 (2) [†]
Vasovagal episode	1 (1)	1 (1) [‡]
Total	100 (100)	100 (100)

Key: PSA = prostate-specific antigen.

Numbers in parentheses are the numbers of participants.

* $P > 0.4$.

[†] $P > 0.9$.

[‡] $P = 1$.

No prebiopsy bowel preparations, cleansing enemas, or local anesthetic agents were used.

ETHICS

The study was approved by the local ethics committee. All study participants provided written informed consent.

DATA COLLECTION

Immediate complications were recorded by the urologist at the time of examination. The psychological aspects of biopsy and possible late complications were assessed using a self-administered questionnaire with a set of intervention-specific questions. The acceptability of biopsy, as well as the perception of adverse effects, was assessed using a verbal rating scale with the options no or minor, moderate, and severe. Information on adverse effects and their duration and possible treatment were collected using structured questions. The amount of bleeding from the urethra and rectum or blood in the semen was subjectively evaluated using a similar three-point scale. The men were asked to complete and return the questionnaire within 2 weeks after their biopsy (before a definitive diagnosis).

STATISTICAL ANALYSIS

The statistical significance of the differences between the study groups was calculated using Pearson's chi-square test and Fisher's exact test. Nonrespondents were excluded from analysis.

RESULTS

The screening participants and the hospital-referred men were of a similar age (mean 63.2 and 63.4 years, respectively). No major complications were seen at biopsy in either group. However, one half of the men in both groups had rectal hemorrhage, and 5 men had bleeding from the urethra immediately after biopsy. Two vasovagal episodes were observed (Table 1).

The self-administered questionnaire was returned by 97% (97 of 100) of those screened and 84% (84 of 100) of the controls. The nonrespondents were somewhat younger than those responding (mean 62.0 and 63.5 years, respectively). Fewer of those screened (58%) than controls

TABLE II. Discomfort, pain, and willingness to undergo repeated biopsy among study participants

Variable	Screening Group (%)	Control Group (%)
Discomfort at biopsy		
None or mild	31 (30)	39 (33)
Moderate	64 (62)	56 (47)
Severe	5 (5)	5 (4)
Pain at biopsy		
None or mild	45 (44)	32 (27)
Moderate	52 (50)	63 (53)
Severe	3 (3)	5 (4)
Willingness to undergo repeat biopsy		
Yes	82 (80)	86 (72)
No	2 (2)	2 (2)
Uncertain	14 (14)	10 (8)
Total	100 (97)	100 (84)

Numbers in parentheses are numbers of participants.

No significant difference was found between any of the variables.

(65%) reported no distress before biopsy, but the difference was not statistically significant ($P = 0.36$). The procedure was considered moderately or very unpleasant by 69% of those screened and 61% of the controls ($P = 0.31$). Correspondingly, 52% and 63% reported moderate pain at biopsy ($P = 0.16$), but only three of those screened (3%) and four controls (5%) experienced severe pain ($P = 0.71$). Nevertheless, most men in both the screening (82%) and the control group (86%) were willing to undergo a repeated biopsy if recommended ($P = 0.70$). Some were uncertain, but few (2 of those screened and 2 controls) would refuse a similar procedure in the future (Table II).

No differences were observed in the frequency of late complications between the screening participants and the hospital-referred controls. Hematuria occurred among 70% and rectal bleeding among 59% of the respondents within 2 days of the biopsy. Up to 25% complained of blood in the urine, and 8% still experienced rectal bleeding after the second postoperative day (Table III). One screening participant was admitted to a hospital for loss of consciousness due to bleeding, but was discharged the following day without specific treatment. Fourteen men (8%) were febrile, but only three had a fever of 38.5°C or greater. Seven men consulted a physician, and antibiotics were prescribed for four (Table III).

Hematuria and rectal bleeding were regarded as disturbing by only a minority of the study participants, and most considered the amount of bleeding modest. Hematuria caused some disturbance for 12 of those screened (18%) and 17 controls (27%, $P = 0.32$), and rectal bleeding disturbed 7 of those

TABLE III. Delayed adverse effects of prostate biopsy among study participants

Adverse Effect	Screening Group (%)	Control Group (%)
Any adverse effect	87 (84)	94 (79)*
Hematuria	67 (65)	74 (62) [†]
Rectal bleeding	56 (54)	62 (52) [†]
Hemospermia	54 (52)	54 (45) [‡]
Difficult voiding	28 (27)	40 (34)*
Diarrhea	22 (21)	33 (28)*
Dysuria	18 (17)	20 (17) [§]
Fever	8 (8)	7 (6) [§]
Total	100 (97)	100 (84)

Numbers in parentheses are numbers of participants.

* $P > 0.1$.

[†] $P > 0.4$.

[‡] $P > 0.9$.

[§] $P > 0.7$.

screened (13%) and 10 controls (19%, $P = 0.54$). Almost two thirds with hemospermia (29 of those screened and 29 controls, $P = 0.51$) regarded this as disturbing (Table IV).

COMMENT

The benefit of screening must outweigh the adverse effects inherent in any early detection program. In a screening program, the benefits for the individual are likely to be modest, and the risks involved should therefore also be kept to a minimum. The large number of men who undergo diagnostic examinations and the small proportion of these diagnosed with cancer also limit the tolerable frequency of side effects. For prostate cancer screening, evidence of mortality reduction or improved quality of life is still lacking and will not be available until the completion of the current extensive screening trials in North America and Europe.^{1,2} Meanwhile, adverse effects of screening, such as anxiety due to false-positive test results, complications of diagnostic tests, and possible over diagnosis, should be carefully evaluated for future decision-making on the implementation of PSA-based prostate cancer screening as public health policy. The screening trials also provide the best opportunity to evaluate adverse effects, because they provide a comparable control population and a rigorous protocol for the assessment of complications. The acceptability of the screening procedure and the diagnostic examinations should be high to achieve a high participation rate.

Little information is available on biopsy experiences among screened men, although the acceptance of prostate biopsy is a basic requirement for screening. We report what is to our knowledge the first controlled study of prostate biopsy experiences in a screening setting. Our results suggest

TABLE IV. Disturbance due to hematuria, rectal bleeding, and hematospermia among study participants

Adverse Effect	Disturbance			Total (%)
	Minor (%)	Moderate (%)	Severe (%)	
Hematuria				
Screening group	82 (53)	18 (12)	—	100 (65)
Control group	73 (45)	27 (17)	—	100 (62)
Rectal bleeding				
Screening group	87 (47)	11 (6)	2 (1)	100 (54)
Control group	81 (42)	17 (9)	2 (1)	100 (52)
Hematospermia				
Screening group	44 (23)	44 (23)	12 (6)	100 (52)
Control group	36 (16)	62 (28)	2 (1)	100 (45)

Numbers in parentheses are numbers of participants.

No significant difference was found between any of the variables.

that the current biopsy procedure does not substantially reduce the willingness to participate in screening. Despite a high proportion of men reporting discomfort and pain, most screening participants would undergo a prostate biopsy again if recommended. This finding is consistent with that of a descriptive study conducted in conjunction with the Dutch screening trial.⁷ Their results showed that nearly 95% of all screened men would return for repeated screening, but only a minority of the subjects had undergone a prostate biopsy.

The complication rate, as well as the pain and discomfort experienced, were similar among screened men and hospital-referred symptomatic patients. This finding is consistent with those in studies conducted in a clinical setting, indicating that prostate biopsy is safe, although minor adverse effects occur frequently.^{4,8–15} Hematuria and rectal bleeding are the most common adverse effects of prostate biopsy, but treatment is rarely required. In our study, overnight hospitalization because of rectal bleeding was needed for 1 participant of 97. Major complications requiring hospital treatment were not encountered.

A limitation of our results was a lower response rate among the hospital-referred controls than of those screened, nearly all of whom responded. No reminders or other means of contact were used afterward to assess their perception of the biopsy. The nonrespondents were somewhat younger, which may have biased the results because of a negative association between increasing age and discomfort experienced at biopsy, as suggested by earlier studies.^{4,13} The possible bias is in favor of screening in this study, because most nonrespondents were hospital-referred controls. However, the target population of screening is generally younger than those undergoing biopsy on clinical basis and may thus affect the tolerability of the procedure for screening. Another shortcoming of

our study is the lack of a validated questionnaire in the assessment of pain. Hence, suboptimal validity may attenuate the comparisons between the groups.

More aggressive biopsy protocols are being progressively integrated in the current clinical practice. The applicability of our findings using sextant biopsy remains to be established in the context of 10 or 12-core biopsies, although recent studies on more intensive biopsy protocols in a clinical setting have suggested that increasing cores does not reduce the acceptability or increase the complications of biopsy.^{16,17} We are currently planning a study of a sextant versus 12-core biopsy protocol to confirm these findings, also in a screening setting.

Even though the complication rates of prostate biopsy were comparable in the screening and clinical setting, the negative consequences of biopsy are likely to be more extensive in the target population of the screening program. First, significantly more men will be examined on the basis of screening than of symptoms. Second, in screening, a larger number of biopsies are needed to detect lesions that fulfill the histologic criteria of malignancy, and such lesions represent over diagnosis more often than those detected because of clinical symptoms. In other words, a loss in the predictive value and over diagnosis account for the differences at the population level in a screening setting even if the complication rates are identical with those in men undergoing a prostate biopsy because of symptoms. Because evidence of mortality reduction through screening is lacking, the balance between the benefits and the disadvantages of screening cannot yet be fully assessed.

Low attendance may substantially impair the results of a screening program, as demonstrated by a Canadian screening trial.¹⁸ In our study, a minority of men (2%) indicated an unwillingness to undergo a repeated biopsy. As men with positive

screening results, however, these men represent a high-risk group, and hence their attendance for repeated screening may have a larger impact on the effectiveness of screening than their relatively small number suggests. Moreover, the 14% of those screened who indicated uncertainty pertaining to the acceptability of a repeated biopsy may further impair the effectiveness of screening. Adequate counseling should thus be given before biopsy, and possibly local anesthetics should be used to improve the compliance in undergoing repeated screening and eventually prostate biopsy in the future.

CONCLUSIONS

Prostate biopsy is a safe and well-tolerated procedure for the diagnosis of prostate cancer in both screening and clinical practice, despite minor complications. Nevertheless, such complications may impair, but not substantially affect, the acceptability, and eventually, the effectiveness of screening.

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Tumor Characteristics in a Population-based Prostate Cancer Screening Trial with Prostate-specific Antigen¹

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ABSTRACT

Purpose: Early diagnosis of prostate cancer is a necessary, but not sufficient, prerequisite for an effective screening program aiming at mortality reduction. We compared tumor characteristics between the screening and control arms in the Finnish population-based screening trial.

Experimental Design: The Finnish trial is the largest component in the European Randomized Study of Screening for Prostate Cancer. A total of 24,000 men aged 55–67 years were randomized to the screening arm, whereas 35,973 men formed the control arm during the first three screening years. At the time of invitation, 22,732 men were eligible for screening, and 15,685 (69%) participated. A prostate-specific antigen (PSA) concentration of ≥ 4 $\mu\text{g/liter}$ was defined as a screening-positive finding.

Results: The detection rate among screenees was 2.4% (377 of 15,685), whereas 0.6% (40 of 7,047) of nonparticipants in the screening arm and 0.3% (112 of 35,973) of the controls were diagnosed with prostate cancer during the first postrandomization year in the absence of screening. In the screening arm, 82% of the cancers were clinically organ confined compared with 65% in the control arm. Yet, both the absolute number and cumulative incidence of advanced cancer were higher in the screening arm. No differences were seen in the WHO grade distribution between the study

groups. The median PSA was substantially lower among screen-detected cases (7.1 $\mu\text{g/liter}$) than among nonattenders (15.7 $\mu\text{g/liter}$) and controls (13.2 $\mu\text{g/liter}$).

Conclusions: Our findings on intermediate indicators of PSA screening provide encouraging, yet inconclusive evidence for eventual mortality reduction.

INTRODUCTION

The aim of prostate cancer screening is to reduce mortality through curative treatment of early stage disease. A decrease in prostate cancer mortality has been reported from the United States after adoption of widespread PSA³ testing (1). However, similar changes have been reported from other countries with less aggressive use of PSA, which suggests that mortality reduction may be also attributable to other factors, such as concurrent changes in treatment, *e.g.*, early endocrine treatment (2). No mortality results are available from randomized trials, apart from early and inconclusive findings from the Quebec trial (3).

The Finnish population-based screening trial, with a total sample size of $\sim 80,000$ men, forms the largest component of the European Randomized Study of Screening for Prostate Cancer (4). Although the importance of randomized PSA screening trials has been well recognized, the present study provides to our knowledge the first intention-to-screen analysis of tumor characteristics in a prostate cancer screening trial.

MATERIALS AND METHODS

Study Population. The Finnish component of the European Randomized Study of Screening for Prostate Cancer was started in 1996. A total of 60,211 men aged 55–67 years (born 1929–1944) were enrolled from the Finnish Population Register in the period between 1996 and 1998. Men with prevalent prostate cancer ($n = 238$) were identified through record linkage with the Finnish Cancer Registry and excluded from the study before randomization. Annually, 8,000 men aged 55, 59, 63, and 67 years were randomized to the screening arm, and the remaining $\sim 12,000$ men formed the control arm. Men deceased, moved outside the study area by the time of invitation, or refusing the use of their address for any purpose were considered ineligible and not invited for screening ($n = 1,268$). Of the 22,732 men eligible for screening, 15,685 (69%) eventually participated. The 35,973 men comprising the control arm of the trial were not contacted (Fig. 1).

Information on prostate cancer in the control population and among nonparticipants was obtained through a record linkage with the Finnish Cancer Registry, which is a nationwide population-based cancer registry with virtually complete cover-

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³ The abbreviations used are: PSA, prostate-specific antigen; DRE, digital rectal examination; TNM, Tumor-Node-Metastasis; TRUS, transrectal ultrasound.

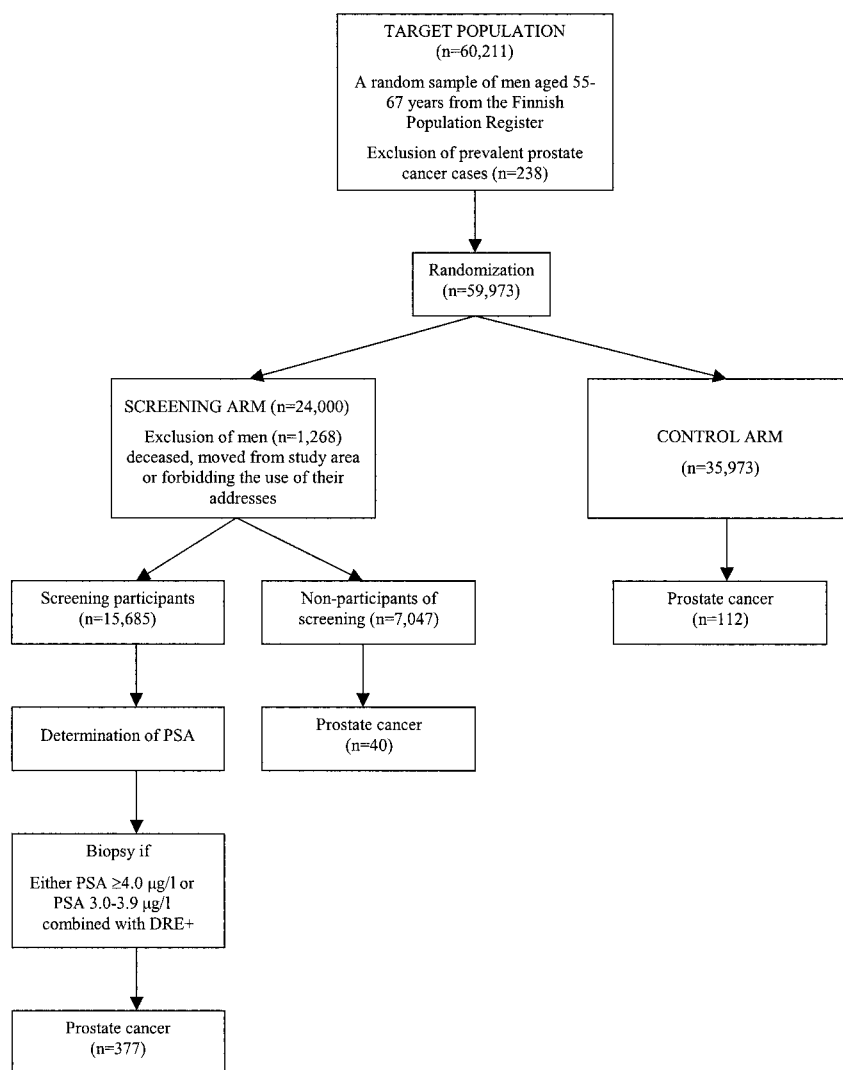


Fig. 1 Study protocol of the Finnish screening trial for prostate cancer from 1996 to 1998.

age of solid cancer cases in Finland (5). Information on cases among the screening participants was collected prospectively at participating hospitals. To ensure completeness of information, a record linkage with the discharge database of hospitals in the study area was conducted. The medical records were reviewed to obtain comparable information on stage and grade for patients detected outside the organized screening, *i.e.*, in the control arm and among the nonparticipants. Causes leading to a diagnosis of prostate cancer were retrieved to assess the extent of PSA testing in the unscreened population. Opportunistic PSA screening was defined as a PSA determination in asymptomatic men during a general health checkup or at a physician's appointment unrelated to any urological symptoms. One prostate cancer found at autopsy in the control arm was excluded.

Screening Algorithm. On informed consent, a blood sample was drawn from the screenees, and the serum PSA concentration was determined (Hybritech Tandem-E). All screening participants with a PSA of ≥ 4 µg/liter were referred for diagnostic examinations, including DRE, TRUS, and prostate sextant biopsies. A directed biopsy was taken if a focal

finding in either DRE or TRUS was noted. A supplemental DRE was offered for those with a PSA level of 3–3.9 µg/liter, and prostate biopsies were indicated if nodularity, induration, or asymmetry was present.

Diagnostics. All diagnoses were based on histological examination. Clinical staging at diagnosis was conducted according to the TNM classification primarily with TRUS and bone scan, but when necessary, other modalities were also used (6). The histological characteristics of detected tumors at biopsy were graded according to the WHO system (7).

Statistics. Screen-detected cancers were diagnosed in accordance with the study protocol within 12 months from drawing the blood sample. Among nonparticipants and controls, all prostate cancer cases detected during the first postrandomization year were included in the analyses. Clinical grade and stage of tumors detected in the screening and control arms were compared using Pearson's χ^2 test. Patients with unavailable clinical grade or stage were excluded from analyses. The proportions of organ-confined tumors and clinical grades were given with 95% confidence intervals. Cumulative incidence was defined as the

Table 1 PSA level in patients with prostate cancer in the Finnish screening trial

	Screening arm				Control arm	
	Participants		Nonparticipants			
	No. of PC ^a	(%)	No. of PC	(%)	No. of PC	(%)
PSA (μg/liter)						
<4	24	(6)	1	(3)	8	(7)
4–9.9	223	(59)	9	(23)	30	(27)
≥10	130	(34)	30	(75)	74	(66)
Total	377	(100)	40	(100)	112	(100)

^a PC, prostate cancer.

Table 2 Clinical stage and grade of prostate cancers diagnosed in the Finnish screening trial

	Screening arm				Control arm	
	Participants		Nonparticipants			
	No. of PC ^a	(%)	No. of PC	(%)	No. of PC	(%)
Stage						
T ₁ N _x M ₀	176	(47)	12	(30)	35	(31)
T ₂ N _x M ₀	143	(38)	11	(28)	37	(33)
T ₃₋₄ N _x M ₀ /T ₁₋₄ N _x M ₁	58	(15)	17	(43)	38	(34)
Unknown					2	(2)
Grade						
I	139	(37)	20	(50)	45	(40)
II	209	(55)	16	(40)	56	(50)
III	28	(7)	4	(10)	8	(7)
Unknown	1	(0)			3	(3)
Total	377	(100)	40	(100)	112	(100)

^a PC, prostate cancer.

number of cases detected during the follow-up period (*i.e.*, 12 months) relative to the number of men within a study group. The Wilcoxon signed rank test was used for comparison of PSA concentrations. Statistical analyses were performed on CIA version 1.1 (Martin J. Gardner and British Medical Journal) and S-PLUS version 4.0 (MathSoft, Inc., Cambridge, MA).

Ethics. The study protocol was approved by the ethical committee in each participating hospital. Permission to retrieve medical records was acquired from the Ministry of Social Affairs and Health and for cancer registry data from the Research and Development Center for Welfare and Health (STAKES).

RESULTS

A total of 377 prostate cancers were detected among the 15,685 screening participants, corresponding to a detection rate of 2.4%. Forty prostate cancers were diagnosed among the 7,047 nonparticipants (0.6%) in the screening arm and 112 cases among the 35,973 men (0.3%) in the control arm during the first postrandomization year.

More than half of the tumors outside the organized screening program were detected on the basis of lower urinary tract symptoms. Opportunistic PSA screening contributed to the diagnosis in 13% (5 of 40) of cases among the screening nonparticipants and in 21% (23 of 112) of the patients in the control arm.

Two-thirds of the screen-detected cases had a PSA level < 10 μg/liter, as compared with one-fourth of the cases detected otherwise (Table 1). The median PSA was substantially lower among screen-detected cases (7.1 μg/liter) than among nonattenders (15.7 μg/liter, $P < 0.001$) and controls (13.2 μg/liter, $P < 0.001$). Overall, the difference between the screening and control arms was also substantial (medians 7.7 *versus* 13.2 μg/liter, $P < 0.001$).

Of the screen-detected prostate cancers, 85% (95% confidence interval 81–88%) were clinically organ confined, compared with 58% (41–73%, $P < 0.001$) among the nonattenders and 65% (57–74%, $P < 0.001$) in the control arm (Table 2). The overall proportion of organ-confined tumors in the screening arm was 82% (78–86%) based on intention-to-screen analysis ($P < 0.001$). Yet, both the absolute number (75 *versus* 38 cases) and number of nonlocal cancers relative to the number of men (cumulative incidence 0.3 *versus* 0.1%) were higher in the screening than control arm of the trial.

WHO grade I cancers comprised 37% (32–42%), grade II 55% (50–61%), and grade III 7% (5–11%) of the screen-detected tumors. The grade distribution of cases diagnosed among nonparticipants ($P = 0.17$) and controls ($P = 0.71$) was not different from that of the screen-detected tumors (Table 2). However, the number (32 *versus* 8 cases) as well as cumulative incidence (0.1 *versus* 0.02%) of poorly differentiated cancer were higher in the screening arm than among controls.

DISCUSSION

The aim of our study was to compare stage and grade of cancers detected in the screening and control arms of a randomized PSA-based screening trial. Previous studies on screening have reported a drift toward earlier stages using historical or otherwise selected hospital-referred patients as a control population (8, 9). However, analyses of time trends are not particularly informative in view of the lack of comparability (contemporaneous changes in factors other than screening, *e.g.*, staging procedures or classifications), relatively low coverage of screening (reducing contrast and, hence, statistical power), as well as possible overdiagnosis (detection of indolent cases; Ref. 10). The same limitations also apply to geographical comparisons. Our results were obtained in a randomized, population-based screening trial. The participation rate was high, which is an essential requirement for a population-based (effectiveness) trial based on a study cohort representative of the general (source) population. The advantages of this experimental design include comparability of screening and control arms, *i.e.*, balanced distribution of other factors ensured by randomization. This avoids the selection bias inherent in screening programs recruiting volunteers, *e.g.*, participation affected by education, health insurance, and family history influencing the likelihood of prostate cancer diagnosis and death (11). Such selection was also evident in our results, as witnessed the large proportion of advanced cases among the nonparticipants. The advantages of randomization are lost if the analysis is not based on the intention-to-screen principle. An example of this is the Quebec trial, with mortality comparisons between screened and unscreened men irrespective of the result of the randomization (*i.e.*, the trial arm to which they were allocated; Ref. 3).

Our results revealed a substantially smaller proportion of advanced prostate cancer in the screening than in the control arm (18 *versus* 35%) but no reduction in cumulative incidence of advanced prostate cancer. Although cancers in nonparticipants were more frequently advanced than screen-detected cases, this did not substantially affect the overall stage distribution in the screening arm because of their relatively small number. Stage of prostate cancer represents a surrogate measure of the effectiveness of screening, because curative treatment is available only for patients with organ-confined disease. Hence, a larger proportion of organ-confined cases is a prerequisite for effectiveness of screening. Although effective screening requires case detection at an earlier stage, a favorable shift in stage distribution is not sufficient evidence of mortality reduction. Screening is likely to cause lead-time bias because of the slow development of prostate cancer, *i.e.*, only the survival time with disease is extended even if death is not postponed. Furthermore, detection of indolent cancers may artifactually improve stage distribution and apparent survival. It also remains to be shown that rapidly growing aggressive cancers can be detected by screening at a curable stage. To reduce deaths from prostate cancer, screening will not only have to achieve detection at an early stage but also prevent deaths by altering the course of the disease.

A larger number and higher cumulative incidence of advanced cancer were seen in the screening than control arm, despite the fact that no information was available on interval

cancers in the screened group. If screening succeeds in early detection and advancing the time of cancer diagnosis (as intended), it should be followed by a reduction in incidence in screened population. Therefore, the difference between the arms should diminish over the entire 4-year screening interval. We do not think that the lack of reduction in advanced cancer represents a failure of the screening, because of the fact that the lead time (*i.e.*, advancement of diagnosis in time by screening) for clinically significant prostate cancer may be up to 10 years (12), allowing ample time for the control arm to catch up the difference in cumulative incidence. Rather, increased detection of advanced cancer may indicate that because of differences in natural course of the diseases, *e.g.*, growth rate, the same process measures that are useful in breast cancer screening (13, 14) are probably not useful in prostate cancer screening.

How much can be inferred from these findings as to the effectiveness of screening also depends on the extent to which PSA, clinical stage, and grade predict mortality (predictive validity). They are the most powerful prognostic factors but, nevertheless, do not accurately predict the outcome (15). This limitation is most evident in clinically localized disease, because many cases are eventually upstaged and upgraded based on examinations of radical prostatectomy specimens (16). It is also unclear how applicable findings based on clinically detected cases are in the context of screen-detected cancer. A marked discrepancy has been observed between the prevalence of autopsy tumors and clinically detected cases, which suggests a strong possibility of overdiagnosis in screening (17). The detection of slow-growing, indolent tumors exposes the target population to unnecessary therapy and resultant morbidity and increases the costs of screening disproportionately. Previous screening studies have, however, suggested that the majority of screen-detected tumors are clinically significant in regard to tumor grade and stage (18). This notwithstanding, no method is currently available for reliable prediction of the significance of screen-detected tumors.

Information on screen-detected cancers was obtained prospectively, unlike those detected outside the organized screening program. However, a record linkage both with the Finnish Cancer Registry and discharge databases of hospitals in the study area ensured a high completeness of case ascertainment in both study arms. Yet, a higher completeness in the screening arm is possible, but it is unlikely to affect our conclusions unless very selective in terms of tumor characteristics. A limitation of our results is the fact that the cases did not undergo a central, blinded pathological evaluation. Yet, the same pathologists evaluated cancers in both arms using identical criteria. However, stage and grade were classified without blinding in regard to screening history. Hence, both misclassification and information bias are possible. With this in mind, we are planning a blinded central review of the histological specimens.

A potential source of bias in randomized screening trials is contamination, *i.e.*, the use of PSA testing for opportunistic screening in the control population. Early detection with PSA has become a common practice especially in the United States, and hence, an unscreened control population is difficult to enroll for studies on prostate cancer screening. One of the strengths of our study is that PSA screening has been opposed as a public health policy in Finland. During the first three screening years,

only approximately a fifth of tumors in the control arm were attributable to contamination. This has to be taken into account when evaluating the long-term effects of screening.

Our results pertain to the first years of a screening program. Although the stage characteristics of tumors discovered in the control arm would not be expected to change with time, stage distribution among screen-detected tumors at subsequent screening rounds is likely to shift further to earlier stages (19, 20). Unless PSA-based case finding increases dramatically in the control arm, it is therefore likely that the difference in tumor stage between the screening and control arm will increase with time.

In conclusion, the Finnish screening trial with PSA provides encouraging evidence in terms of stage reduction, but definitive conclusions on the effectiveness of a screening program must be based on a comparison of prostate cancer mortality between screening and control arms during longtime follow-up.

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PROSTATE CANCER SCREENING WITHIN A PROSTATE SPECIFIC ANTIGEN RANGE OF 3 TO 3.9 NG./ML.: A COMPARISON OF DIGITAL RECTAL EXAMINATION AND FREE PROSTATE SPECIFIC ANTIGEN AS SUPPLEMENTAL SCREENING TESTS

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ABSTRACT

Purpose: Performing biopsy in all men with a serum prostate specific antigen (PSA) of 3 to 3.9 ng./ml. increases the sensitivity of prostate cancer screening compared with a PSA cutoff of 4 ng./ml. but decreases specificity and may contribute to over diagnosis. Therefore, we evaluated the detection rate and specificity attributable to digital rectal examination and percent free PSA within the PSA range of 3 to 3.9 ng./ml.

Materials and Methods: Serum PSA was determined in 20,716 participants in the Finnish population based screening trial. Supplementary digital rectal examination was offered to men with a PSA of 3 to 3.9 ng./ml. during 1996 to 1998 (protocol 1). Those with a suspicious digital rectal examination finding were referred for biopsy. The screening algorithm was modified by substituting percent free PSA for digital rectal examination with a cutoff of 16% as a biopsy criterion in 1999 (protocol 2). In addition, biopsies were performed in all men with PSA 4 ng./ml. or greater.

Results: A total of 23 cancers (2.9%) were detected by digital rectal examination among 801 men, while percent-free PSA resulted in the diagnosis of 13 cases (4.8%) among 270 men with a PSA of 3 to 3.9 ng./ml. The detection rate of tumors with a Gleason score of 5 or greater increased from 1.6% (13 of 801 cases) to 4.4% (12 of 270) in the modified screening program. The PSA cutoff of 3 ng./ml. alone showed 88.6% and 87.5% specificity in protocols 1 and 2 but specificity increased to 93.3% and 91.7% using digital rectal examination and percent free PSA, respectively.

Conclusions: Using percent free PSA increased the detection rate of aggressive disease compared with digital rectal examination and provided higher specificity than PSA alone.

KEY WORDS: prostate, prostatic neoplasms, prostate-specific antigen, mass screening, sensitivity and specificity

Serum prostate specific antigen (PSA) testing is widely done for the early detection of prostate cancer. At a PSA cutoff of 4 ng./ml. prostate cancer is detected in 25% to 30% of men with positive screening results.¹ A fairly high detection rate of 13% to 22% has been reported at a PSA of 3 to 3.9 ng./ml. but lowering the cutoff to 3 ng./ml. significantly increases the number of screening positive cases.^{2,3}

A PSA cutoff of 3 ng./ml. exposes more men to the negative effects of screening, such as psychological distress caused by false-positive test results and over diagnosis, than screening with higher PSA cutoffs. This aggressive strategy also increases screening costs, which may be a major obstacle for screening as a public health policy. It is also unclear whether cancer diagnosed at PSA 3 to 3.9 ng./ml. would be detectable at a localized stage during subsequent screening. Furthermore, the effectiveness of prostate cancer screening, namely mortality reduction, remains to be established. Thus, a more selective screening method that improves the specificity of screening without compromising sensitivity is urgently

needed. Various strategies based on supplementary tests have been used to decrease the frequency of false-positive tests with lower cutoffs.^{4–7}

Our study was based on the Finnish prostate cancer screening trial, which is the largest component in the European Randomized Study of Screening for Prostate Cancer. We compared the performance of digital rectal examination and percent free PSA at a PSA of 3 to 3.9 ng./ml. for prostate cancer screening. The main outcome measures reported are the prostate cancer detection rate, screening program specificity and the histological characteristics of detected tumors.

MATERIAL AND METHODS

Subjects. The Finnish prostate cancer screening trial was initiated in May 1996. Our study was based on prevalence screening done in 1996 to 1999. A total of 59,973 men who were 55 to 67 years old were enrolled from the Population Register of Finland during years 1 to 3 up to the end of 1998 (protocol 1). Men diagnosed with prostate cancer before randomization were excluded from study. A total of 24,000 men were randomly allocated to the screening arm and the remaining 35,973 comprised the control arm, which was not contacted. Those who had died, moved outside of the study area by the time of invitation or refused the use of their addresses for any purpose were also excluded from analysis.

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Thus, at the time of invitation 22,732 men were eligible for screening, of whom 15,685 (69%) participated.

A total of 20,485 men were enrolled from the Population Register in 1999, including 8,000 randomized to the screening arm after modification of the screening algorithm (protocol 2). The remaining 12,485 men comprised the control arm. Of the 7,671 men eligible for screening 5,031 (66%) eventually participated.

Laboratory methods. After informed consent was obtained a blood sample was collected. Serum total PSA was determined by the Hybritech Tandem-E assay (Beckman Coulter, San Diego, California). Percent free PSA was measured with the ProStatus free-to-total PSA assay (EG&G Wallac, Turku, Finland). All analyses were done at the Department of Clinical Chemistry, Helsinki University Central Hospital.

Screening algorithm. According to protocol 1 supplementary digital rectal examination performed by a urologist was offered to men in the screening arm with PSA between 3 and 3.9 ng./ml. Only these initial digital rectal examinations were assessed in our analysis. Participants with a suspicious digital rectal examination finding were further referred for transrectal ultrasound and sextant biopsies supplemented with directed biopsy if there was a focal finding on digital rectal examination or transrectal ultrasound. Digital rectal examination findings were considered suspicious when nodularity, induration or asymmetry was noted. All men with a PSA of 4 ng./ml. or higher were referred for diagnostic examination, including digital rectal examination, transrectal ultrasound and prostate sextant biopsies supplemented with directed biopsy when indicated. The screening algorithm was changed after the initial 3 years by substituting percent free PSA for digital rectal examination within the PSA range of 3 to 3.9 ng./ml. In this protocol 2 biopsy was done at less than 16% free PSA. Otherwise the core protocol remained unchanged.

Diagnostics. All diagnoses were based on histological examination. Clinical staging was performed according to the TNM classification using primarily transrectal ultrasound and bone scan but also other modalities when necessary.⁸ Histological characteristics at biopsy were graded according to the Gleason score system.⁹ Gleason score was unavailable in 3 cases due to insufficient biopsy material but they were graded as well differentiated according to the WHO system. All cancers detected as a result of screening (on diagnostic examinations initiated by a positive screening test) were considered screening detected regardless of the interval since the initial PSA test.

Data analysis. Evaluation of the diagnostic tests was limited to participants with a PSA of 3 to 3.9 ng./ml. during 1996 to 1998, including 801 in protocol 1, and during 1999, including 270 in protocol 2. The statistical significance of the difference in the 2 protocols in terms of the detection rate, histological characteristics and clinical stage of tumors detected was calculated using Pearson's chi-square test. The specificity of the screening program was defined as the proportion of men with a negative test on screening of all those screened without prostate cancer. The 3 patients with an unavailable Gleason score were included in analysis except for the chi-square statistic related to the histological characteristics of detected tumors. Statistical analysis was per-

formed using S-PLUS, version 4.0 (MathSoft, Inc., Cambridge, Massachusetts).

Ethics. The ethics committee at each participating hospital approved the trial. Permission to obtain medical records was granted by the Ministry of Social Affairs and Health. Permission to obtain cancer registry data was obtained from the STAKES Research and Development Center for Welfare and Health.

RESULTS

Overall 32,000 men were randomized to the screening arm during screening round 1. During years 1 to 3, 15,685 of the 22,732 eligible men (69%) were screened using protocol 1, while 5,031 of 7,671 (66%) participated during year 4 in protocol 2. A total of 2,143 men (13.7%) were referred for further examination according to protocol 1 due to PSA 3 ng./ml. or higher, of whom 801 had a PSA of 3 to 3.9 ng./ml. and 23 were diagnosed with prostate cancer (detection rate 2.9%). Under protocol 2 a serum PSA of 3 ng./ml. or higher was detected in 743 participants (14.8%). In 270 participants with PSA 3 to 3.9 ng./ml. 13 cancers (detection rate 4.8%) were detected. Thus, modifying the screening algorithm within the PSA range of 3 to 3.9 ng./ml. resulted in a slight but not statistically significant increase in the detection rate ($p = 0.18$). The detection rate of 17% to 20% after biopsy in all men was markedly higher at the PSA level of 4 to 4.9 ng./ml. in protocols 1 and 2 (table 1).

Based on supplementary digital rectal examination specificity of the screening program was 93.4% (95% confidence interval [CI] 93.0 to 93.8) or 14,262 of 15,276 men. That is, 93.4% of cases without prostate cancer were classified as test negative, while the specificity of the PSA threshold of 3 ng./ml. alone would have been 88.6% (95% CI 88.1 to 89.2) or 13,542 of 15,276 men. Correspondingly the screening algorithm based on percent free PSA increased specificity to 91.7% (95% CI 90.9 to 92.5) or 4,494 of 4,902 men from 87.5% (95% CI 86.5 to 88.4) or 4,288 of 4,902 calculated for the PSA threshold of 3 ng./ml. in protocol 2 (table 2).

The positive predictive value of a suspicious digital rectal examination finding was 28% in men with a PSA of 3 to 3.9 ng./ml. Overall 32 digital rectal examinations and 3.5 biopsies were performed to detect 1 case of cancer. With the introduction of protocol 2 based on free PSA less than 16% as an indicator for biopsy, a positive predictive value of 22% was achieved, corresponding to 4.6 biopsies per each cancer case detected in the same PSA range. The biopsy-to-cancer ratio in the PSA range of 4 to 4.9 ng./ml. was approximately 5:1 (table 1). Within the PSA range of 4 to 4.9 ng./ml. applying percent free PSA with a cutoff of 16% would have missed 30 of 88 cancers (34%) in protocol 1 and 14 of 27 (52%) in protocol 2.

The proportion of Gleason score 5 or greater disease associated with a PSA of 3 to 3.9 ng./ml. was 59% (13 of 22 patients) in protocol 1 and 100% (all 12) in protocol 2, implying the detection of more aggressive cancer in the latter ($p = 0.01$). The detection rate of Gleason score 5 or greater tumors was 1.6% (13 of 801 patients) in the PSA range of 3 to 3.9 ng./ml. with the algorithm based on digital rectal examination but it increased significantly to 4.4% (12 of 270) with the

TABLE 1. Results of the Finnish prostate cancer screening trial in 1996 to 1998

	Protocol 1		Protocol 2	
	PSA 3–3.9 Ng./Ml.	PSA 4–4.9 Ng./Ml.	PSA 3–3.9 Ng./Ml.	PSA 4–4.9 Ng./Ml.
Biopsy indication	Pos. digital rectal examination	All biopsied	Free PSA less than 16%	All biopsied
No. pts. (%)	801 (5.1)	435 (2.8)	270 (5.4)	157 (3.1)
No. biopsy referrals (%)	81 (10)	435 (100)	64 (24)	157 (100)
No. biopsies	81	396	60	135
No. Ca (%)	23 (2.9)	88 (20.2)	13 (4.8)	27 (17.2)
Biopsy-to-Ca ratio	3.5:1	4.5:1	4.6:1	5.0:1

TABLE 2. Overview of screening results per PSA range in round 1 of the Finnish trial

PSA (ng./ml.)	Protocol 1		Protocol 2	
	No. Pts. (%)	No. Ca (%)	No. Pts. (%)	No. Ca (%)
0-2.9	13,542 (86.3)	3 (0.7)*	4,288 (85.2)	
3-3.9:				
Neg. supplementary test	720 (4.6)		206 (4.1)	
Pos. supplementary test	81 (0.5)	23 (5.6)	64 (1.3)	13 (10.1)
4 or Greater	1,342 (8.6)	386 (93.7)	473 (9.4)	116 (89.9)
Totals	15,685 (100)	412 (100)	5,031 (100)	129 (100)

* Supplementary digital rectal examination resulted in the diagnosis of 3 cancers before this practice was discontinued.

introduction of percent free PSA at the PSA level of 3 to 3.9 ng./ml. ($p = 0.02$). Furthermore, a slightly higher proportion of Gleason score 5 or greater disease was detected at PSA 3 to 3.9 ng./ml. than at 4 to 4.9 ($p = 0.09$). More than 90% of screening detected tumors were clinically organ confined in PSA ranges 3 to 3.9 and 4 to 4.9 ng./ml. (table 3).

DISCUSSION

We evaluated 2 screening algorithms in the Finnish prostate cancer screening trial at the PSA level of 3 to 3.9 ng./ml., that is in the gray zone of prostate cancer screening. In the age range of 50 to 74 years the number of men with PSA 3 to 3.9 ng./ml. almost equals that of men with PSA 4 to 9.9 ng./ml. but the prevalence of cancer is substantially lower.^{7, 10, 11} Performing biopsy in all men within this PSA range would considerably impair the efficacy of the screening program by increasing the cost per participant or cancer detected. The aim of the screening program is the diagnosis of cancer that would present clinically in the absence of screening and, furthermore, the prevention of death from prostate cancer by effective treatment of early disease. There is likely to be a trade-off in terms of tolerable harm (adverse quality of life effects) and benefit gained (decreased mortality). To our knowledge the cutoff providing the optimal balance of detecting significant cancer and ignoring clinically insignificant disease remains to be established. Detecting tumors that would not present during the lifetime of the screened individual negatively affects quality of life in terms of over treatment and possible complications. In Finland the lifetime risk of prostate cancer in 55 to 74-year-old men was 6.8% in 1993 to 1997 according to Finnish Cancer Registry data. This rate is only 10% to 15% of the corresponding prevalence of latent tumors since 1 of every 2 men in this age group has indolent prostate cancer at autopsy.¹² The optimal detection rate of the screening program is likely to approach the cumulative risk in an unscreened population but probably not exceed it. Correspondingly 90% or greater specificity is likely to be almost optimal. Below that value screening costs, the psychological distress caused by false-positive test results and over diagnosis are likely to increase disproportionately.

Using digital rectal examination or percent free PSA as a supplementary test in men with PSA 3 to 3.9 ng./ml. essen-

tially decreased the number of biopsies compared with the PSA cutoff of 3 ng./ml. alone as a biopsy criterion in the Finnish screening trial. Only 10% of men with a PSA of 3 to 3.9 ng./ml. were referred for biopsy based on digital rectal examination and 24% were referred based on free PSA less than 16%. The supplementary tests provided 4% to 5% improvement in specificity, decreasing the number of biopsies by 4,000 to 5,000/100,000 men screened. Cancer was detected in approximately 1 in 4 biopsies based on digital rectal examination and percent free PSA, which was similar to the positive predictive value of the 4 ng./ml. PSA cutoff.¹ Unfortunately we cannot evaluate the loss in sensitivity due to these policies compared with performing biopsy in all men with a PSA of 3 to 3.9 ng./ml. but the 0.1% to 0.3% contribution to the overall 2.6% detection rate in the Finnish screening program was modest. The detection rate was 3% to 5% at PSA 3 to 3.9 ng./ml. in our study compared with 13% when all men with PSA in this range underwent biopsy in the Swedish screening trial.² In the Rotterdam trial a 12% detection rate was extrapolated from higher PSA levels.¹⁰ These values are about 4-fold the rate in our study, while the background incidence rates of prostate cancer are comparable. Over diagnosis and missing significant disease remain plausible interpretations for the differences in the detection rates. This issue may only be solved through followup and mortality analysis in these trials.

The detection rate of aggressive disease was increased using percent free PSA at a PSA of 3 to 3.9 ng./ml., although the overall rate was not materially higher than with digital rectal examination. Interestingly no Gleason score 2 to 4 tumors were detected in this PSA range. The risk of advanced disease increases only slightly in the PSA range of 2.5 to 6 ng./ml., which implies that the effectiveness of prostate cancer screening in terms of decreased mortality does not necessarily require detecting disease at PSA 3 to 3.9 ng./ml. if it is detected at 4 to 6.0 ng./ml. at subsequent screening.¹³

When the Finnish trial commenced, digital rectal examination was done to detect tumors in men with PSA below 4 ng./ml. Hence, digital rectal examination was offered not only to those with PSA between 3 and 3.9 ng./ml., but also to those with PSA 2 to 2.9 ng./ml. This practice was soon discontinued due to the low detection rate and substantial cost. The effort

TABLE 3. Histological characteristics and clinical stage of screening detected cancers in 1996 to 1998 and 1999

	No. Protocol 1 (%)		No. Protocol 2 (%)	
	PSA 3-3.9 Ng./Ml. and Pos. Digital Rectal Examination	PSA 4-4.9 Ng./Ml.	PSA 3-3.9 Ng./Ml. and Free PSA Less Than 16%	PSA 4-4.9 Ng./Ml.
Gleason score:				
2-4	9 (41)	33 (38)		8 (30)
5 or Greater	13 (59)	54 (62)	12 (100)	19 (70)
Totals	22 (100)	87 (100)	12 (100)	27 (100)
Clinical stage:				
Organ confined	22 (96)	82 (93)	12 (92)	26 (96)
Extracapsular, distant metastasis	1 (4)	6 (7)	1 (8)	1 (4)
Totals	23 (100)	88 (100)	13 (100)	27 (100)

Gleason score was unavailable for 3 cases which were excluded from the table.

needed to diagnose prostate cancer by digital rectal examination at PSA 3 to 3.9 ng./ml. was also considerable, requiring the clinical examination of 32 men to detect 1 cancer. The results confirm earlier results showing that digital rectal examination is a fairly inefficient screening test and cannot be recommended in a population based screening program.¹⁰

The diagnostic value of percent free PSA has been studied in volunteer based screening programs and clinical case series but remains controversial at low PSA levels.^{6, 14-16} To our knowledge no agreement on an appropriate cutoff has been reached. This issue is further confounded by substantial variations among commercial kits used for determining percent free PSA. However, a model based on percent free PSA has been suggested for identifying men at higher risk for prostate cancer at PSA 4 ng./ml. or less who have a normal digital rectal examination.⁶ On the other hand, the value of adding percent free PSA to PSA based screening has been questioned based on a serum bank study.¹⁷ In our trial adding percent free PSA in the screening algorithm increased the detection rate of aggressive Gleason score 5 or greater disease at PSA 3 to 3.9 ng./ml. Since ongoing screening programs reveal only a small minority of prevalent tumors, the important question is whether we detect cancer in time that must be cured. In this respect the degree of differentiation of prostate cancer is crucial. Studies of the natural history of prostate cancer have shown that the survival of patients with a well differentiated tumor is similar to that of age matched controls, whereas those with more aggressive disease have substantially decreased life expectancy.¹⁸ Thus, percent free PSA seems to result in the detection of tumors that are clearly relevant for prostate cancer screening. Comparing tumors detected in the PSA range of 3 to 3.9 ng./ml. with those diagnosed at 4 to 4.9 ng./ml. also supports the concept of the increased detection of aggressive disease with percent free PSA in our study. Low percent free PSA has been associated with aggressive prostate cancer in several studies, although some controversy still exists.^{19, 20} Thus, invasive and costly examinations may be limited to men at higher risk for aggressive disease at low PSA. However, information on interval cancers and cancers detected at subsequent screening is needed to evaluate the value of percent free PSA as a part of the screening program. A decrease in advanced disease and eventual prostate cancer death is required in men with a PSA of 3 to 3.9 ng./ml.

CONCLUSIONS

Digital rectal examination is an inefficient screening method at a PSA of 3 to 3.9 ng./ml. The algorithm based on percent free PSA did not increase the detection rate but the detection of aggressive cancer increased. Furthermore, unnecessary biopsies were avoided by supplementary digital rectal examination and percent free PSA, and specificity of the screening program was enhanced compared with the PSA threshold of 3 ng./ml. as a biopsy criterion.

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Family History and Prostate Cancer Screening With Prostate-Specific Antigen

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Purpose: Early detection of prostate cancer has been recommended for men with affected first-degree relatives despite the lack of evidence for mortality reduction. We therefore evaluated the impact of family history in the Finnish prostate cancer screening trial.

Patients and Methods: Approximately 80,000 men were identified from the population register for the first screening round. Of the 32,000 men randomized to the screening arm, 30,403 were eligible at the time of invitation. A blood sample was drawn from the participants ($n = 20,716$), and serum prostate-specific antigen (PSA) was determined. Men with a PSA level ≥ 4.0 ng/mL were referred for prostate biopsy. Information on family history was obtained through a self-administered questionnaire at baseline.

Results: A total of 964 (5%) of the 20,716 screening participants had a positive family history, and 105 (11%) were screening-positive. Twenty-nine tumors

were diagnosed, corresponding to a detection rate of 3.0% (29 of 964) and a positive predictive value of 28% (29 of 105). Of the 19,347 men without a family history, 1,487 (8%) had a PSA level ≥ 4.0 ng/mL. The detection rate was 2.4% (462 of 19,347) and the positive predictive value was 31% (462 of 1,487). The risk associated with a positive family history was not substantially increased (rate ratio, 1.3; 95% confidence interval, 0.9 to 1.8). The results were not affected by the age of the screenee or age at diagnosis of the affected relative. The program sensitivity was 6% (29 of 491) (ie, selective screening policy would have missed 94% of cancers in the population). No differences were seen in the characteristics of screen-detected cancers by family history.

Conclusion: Our findings provide no support for selective screening among men with affected relatives.

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PROSTATE CANCER screening is now common practice despite the lack of evidence for mortality reduction. One of the few established risk factors for prostate cancer is a family history of the disease, particularly for men with a family history of an early-onset prostate cancer.¹ In the United States, prostate-specific antigen (PSA)-based screening has been recommended by the American Urological Association and the American Cancer Society, especially for men with affected first-degree relatives.^{2,3} Little is known, however, about the impact of PSA screening among men with a family history of prostate cancer. Selective

screening of subgroups of the population with an increased risk of prostate cancer may improve program performance, that is, increase the detection rate in the high-risk population and program specificity in the target population (effectively identify men free of cancer), but has the disadvantage of low program sensitivity (only a small proportion of cancers in the target population are detected).⁴

In the first round of the Finnish prostate cancer screening trial (1996 through 1999), we compared the process measures of screening (ie, detection rate, positive predictive value, and specificity of PSA testing) between men with and without a family history. A family history was defined as positive if any first-degree relative was affected; however, the information of second-degree relatives was also collected. The importance of a family history at the population level was assessed in terms of program sensitivity and specificity.

PATIENTS AND METHODS

Subjects

The Finnish prostate cancer screening trial was initiated in May 1996. It is the largest component in the European Randomized Study of Screening for Prostate Cancer.⁵ Approximately 80,000 men aged 55 to 67 years (born 1929 to 1944) were enrolled from the population register during the first round in 1996 to 1999. Men with a diagnosis of prostate cancer before randomization were excluded. A total of 32,000 men were randomized onto the screening arm, and the remaining men formed the control arm. Persons who had died or moved outside the study area by the time of invitation or had forbidden the use of their

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addresses in the national population database for any purpose were excluded. At the time of invitation (an average of 6 months after randomization), 30,403 men were eligible for screening and 20,716 (68%) eventually participated. Our report is derived from cross-sectional data collected within a randomized screening trial. The study population was formed at baseline, with exposure contrast defined on the basis of family history.

Baseline Questionnaire

Information on family history was obtained by means of a questionnaire at the time of invitation. If a subject reported one or more first-degree relatives (ie, father or brother) diagnosed with prostate cancer, the family history was regarded as positive. Because of confidentiality reasons, we were not able to identify the affected relatives or confirm reported diagnoses from medical records.

Laboratory Methods

After informed consent, a blood sample was drawn. The serum concentration of total PSA was determined by the Hybritech Tandem-E assay (Beckman Coulter, San Diego, CA). All analyses were carried out at the Department of Clinical Chemistry, Helsinki University Central Hospital.

Screening Algorithm

All men with a PSA level ≥ 4.0 ng/mL were referred for diagnostic examinations involving digital rectal examination (DRE), transrectal ultrasound (TRUS) examination, and prostate sextant biopsies, supplemented by a directed biopsy if a focal finding was detected by either DRE or TRUS examination. DRE findings were regarded as suspicious if nodularity, induration, or asymmetry was found. In TRUS, a hypoechoic lesion was regarded as suggestive of prostate cancer.

Diagnostics

All diagnoses were made on the basis of histologic examination. Clinical staging was conducted according to the tumor, node, metastasis system.⁶ Histologic characteristics at biopsy were graded according to the Gleason score system.⁷ All cancers detected as a result of screening were regarded as screen-detected, regardless of the time interval from the initial PSA test.

Data Analyses

The ratio of detection rates (rate ratio [RR]) with 95% confidence interval (CI) was calculated for men with an affected family member(s) relative to those with no such family history. The 405 men with family history missing were excluded from all the analyses. The risk of prostate cancer was analyzed separately for screenees below and above 60 years of age, as well as by the age of an affected relative at diagnosis. The age of an affected relative was unavailable for 74 (0.4%) men who were excluded from this analyses. None of them were diagnosed with prostate cancer. Student's *t* test was used for the comparison of the mean ages at diagnosis by family history. For comparison of tumor characteristics, patients with unavailable Gleason score at biopsy (*n* = 5) or unavailable clinical stage (*n* = 3) were excluded. PSA concentrations by family history were compared by the Wilcoxon signed rank test. The specificity of the PSA test is given separately for men with and without family history, and corresponds to the proportion of men with PSA levels less than 4 ng/mL among all healthy screening participants with the corresponding family history. The approximation of program sensitivity for family history as a

supplemental screening criterion indicates the proportion of cancers detectable by selective screening policy in the screened target population with lacking information on interval cancers.⁸ In other words, it corresponds to the proportion of family history-positive cases with a PSA level ≥ 4 ng/mL among all screen-detected cancers with family history available. Program specificity for family history as a supplemental screening criterion indicates the proportion of men correctly identified as free of prostate cancer (ie, healthy screenees with a negative test combination of family history and PSA) among all healthy screening participants with family history known. Statistical analyses were performed on CIA Version 1.1 (Martin J. Gardner and British Medical Journal) and S-PLUS Version 4.0 (MathSoft Inc, Cambridge MA).

Ethics

The ethical committee of each participating hospital approved the trial protocol. Permission to obtain medical records was obtained from the Ministry of Social Affairs and Health and for cancer registry data from the National Research and Development Center for Welfare and Health.

RESULTS

Of the 20,716 participants, 98.0% (20,311 of 20,716) provided information regarding family history through a self-administered questionnaire before screening. A total of 964 of 20,311 (4.7%) gave a positive family history (ie, one or more affected first-degree relatives). Of these, 708 reported a father with a prostate cancer, and 266 had an affected brother (Table 1). Only 17 men had two or more affected first-degree relatives. Ninety (0.4%) men had a father or brother(s) affected at the age of 59 years or less. Approximately 300 had an affected uncle (either maternal or paternal), but few were aware of a prostate cancer diagnosed among their grandfathers. A family history of prostate cancer was associated with neither age nor screening center (data not shown).

Of the 964 men with a positive family history (ie, a father or brother[s] affected), 105 (10.9%) had a serum PSA concentration of ≥ 4.0 ng/mL and were referred for prostate biopsy (Table 1). Twenty-nine tumors were diagnosed corresponding to a detection rate of 3.0% (95% CI, 2.0% to 4.3%; 29 of 964) and a positive predictive value of 27.6% (95% CI, 19.1% to 36.2%; 29 of 105). The specificity of the PSA threshold of 4 ng/mL was 91.9% (95% CI, 89.9% to 93.5%; 859 of 935) among the men with a positive family history. Among the 19,347 men without a family history, 1,487 (7.7%) had a PSA level ≥ 4 ng/mL and 462 tumors were diagnosed. The detection rate was 2.4% (95% CI, 2.2% to 2.6%; 462 of 19,347) and the positive predictive value was 31.1% (95% CI, 28.7% to 33.4%; 462 of 1,487). The specificity of the PSA threshold of 4 ng/mL was 94.6% (95% CI, 94.2% to 94.9%; 17,860 of 18,885) among the men without family history. Eleven cancers were seen

Table 1. Detection Rates and RRs for Prostate Cancer by Family History (Finnish screening trial 1996 through 1999)

	Family History						RR*	95% CI
	Yes			No				
	No. of Men	No. of Prostate Cancers	Detection Rate (%)	No. of Men	No. of Prostate Cancers	Detection Rate (%)		
Affected first-degree relatives								
Any first-degree relative(s)	964	29	3.0	19,347	462	2.4	1.26	0.87-1.82
Father	708	20	2.8	19,603	471	2.4	1.18	0.76-1.83
Brother(s)	266	10	3.8	20,045	481	2.4	1.57	0.85-2.90
Any first-degree relative(s), age of screenee < 60 years	539	10	1.9	11,208	171	1.5	1.22	0.65-2.29
Affected second-degree relatives								
Any second-degree relative(s)	685	18	2.6	19,626	473	2.4	1.09	0.69-1.73
Maternal grandfather or uncle(s)	365	10	2.7	19,946	481	2.4	1.14	0.61-2.11
Paternal grandfather or uncle(s)	340	8	2.4	19,971	483	2.4	0.97	0.49-1.94
Any affected first- or second-degree relative(s)	1,558	47	3.0	18,753	444	2.4	1.27	0.95-1.71

*RRs were calculated with those reporting no corresponding family history as reference.

among the 405 men with missing family history of prostate cancer, corresponding to a detection rate of 2.7%.

Men reporting a positive family history did not have a substantially increased risk of prostate cancer (RR, 1.3; 95% CI, 0.9 to 1.8). No materially increased prostate cancer risk was observed for men with an affected father, or affected brother, or other affected relative on either side of the family. The effect of a positive family history was also similar in the subgroup of men aged less than 60 years (Table 1). Of those 17 men with two or more first-degree relatives affected, only one was diagnosed with prostate cancer (RR, 2.5; 95% CI, 0.1 to 14.4).

Screenees with an affected first-degree relative with an early-onset prostate cancer were not more often diagnosed with a cancer at screening than those without such history. Of the 90 men with a father or brother(s) affected before the age of 60, only eight were screening-positive. Three of them were diagnosed with cancer, giving a detection rate of 3.3% (95% CI, 0.7% to 9.4%), an RR of 1.4 (95% CI, 0.5 to 4.3), and a positive predictive value of 38% (95% CI, 8.5% to 75.5%) (Table 2).

In the entire screened population, 502 cancers were detected, of which 29 cases were among the men with a positive family history. The program sensitivity for positive family history as a supplementary screening test was 5.9% (95% CI, 4.0% to 8.4%; 29 of 491) in the absence of information on interval cancers. In other words, restriction of screening to men with a positive family history would have missed 94.1% of all prostate cancers detectable by screening. The specificity for a family history was 99.6% (95% CI, 99.5% to 99.7%; 19,744 of 19,820), that is, limiting screening to men with positive family history would have correctly identified 99.6% of men without prostate cancer.

No significant differences were seen in the characteristics of the screen-detected cancers by family history. The mean age at diagnosis was 61 years among men both with and without a family history ($P = .62$). The PSA concentrations of tumors detected were also comparable, with median values of 6.2 ng/mL and 7.5 ng/mL, respectively ($P = .24$). Family history was not associated with Gleason score. The detection rate of clinically organ-confined cancers was 2.7%

Table 2. Risk of Prostate Cancer by the Age of an Affected Relative at Diagnosis (Finnish screening trial 1996 through 1999)

	No. of Men*	No. of Prostate Cancers	Detection Rate (%)	RR	95% CI
Affected first-degree relative(s) aged < 60 years at diagnosis	90	3	3.3	1.40	0.46-4.26
Affected first-degree relative(s) aged ≥ 60 years at diagnosis	800	26	3.3	1.36	0.92-2.01
No affected first-degree relative(s)	19,347	462	2.4	1	Reference

*A total of 74 men were excluded because their relatives' ages at diagnosis were not available. Of those excluded, three were screening-positive, but none of them were diagnosed with prostate cancer.

Table 3. Detection Rate of Prostate Cancer by Gleason Score at Biopsy and Clinical Stage Among Men With and Without a Family History (Finnish prostate cancer screening trial 1996 through 1999)

	Gleason Score*			Clinical Stage*		
	2-4	5-6	7-10	T1cNxM0	T2NxM0	T3-4NxM0/T1-4NxM1
Detection rate						
Family history positive, %	1.2	1.5	0.3	1.5	1.2	0.3
No. of cancers/no. of men	12/964	14/964	3/964	14/964	12/964	3/964
Family history negative, %	0.7	1.1	0.5	1.2	0.9	0.3
No. of cancers/no. of men	142/19,347	221/19,347	94/19,347	228/19,347	168/19,347	63/19,347
RR	1.7	1.3	0.6	1.2	1.4	1.0
95% CI	0.9-3.1	0.7-2.2	0.2-2.0	0.7-2.1	0.8-2.6	0.3-3.0

*Of the 491 patients with family history available, five cases with unavailable Gleason score and three cases with unavailable clinical stage were excluded from the table.

(95% CI, 1.8% to 3.9%; 26 of 964) among men with and 2.0% (95% CI, 1.9% to 2.3%; 396 of 19,347) among those without a family history (Table 3).

DISCUSSION

Family history did not identify a subgroup of men with a substantially increased risk of prostate cancer in the Finnish PSA-based screening trial. This was also true among the men with features commonly associated with an inherited susceptibility to prostate cancer (ie, relatively young age or a family history on the maternal side of the family).^{9,10} The findings were similar for men with an affected relative diagnosed before the age of 60 years. A screening program focusing solely on the basis of men with a positive family history would have missed nearly 95% of the screen-detected prostate cancers (ie, the program sensitivity was only 5.9% in the absence of information on interval cancers). Instead, practically all healthy men in the total target population would have been classified as free of prostate cancer (ie, the program specificity was 99.6% disregarding nonparticipants).

Controversy seems to prevail as to whether men with a family history have tumors presenting with features usually associated with a more aggressive type of disease.^{11,12} In our trial, family history was not associated with prognostic indicators such as Gleason score, clinical stage, PSA, or age at diagnosis, and hence suggested no greater importance of early detection of prostate cancer among men with a family history. However, we cannot exclude the possibility that these tumors would develop differently if they were detected years later on the basis of clinical symptoms.

The present findings are inconsistent with those in previous studies showing an association between a positive family history and risk of prostate cancer in population-based PSA screening. In the Quebec screening trial, a significantly elevated risk of prostate cancer was observed among men with an affected first-degree relative (RR, 1.7;

95% CI, 1.2 to 2.4).¹³ The highest risk (RR, 2.6; 95% CI, 1.7 to 4.1) was noted among men with affected brother(s). In that trial, biopsies only on men with a positive family history would have detected 14% of all tumors. The most important limitation of the Quebec study was the low attendance rate (27%), which limits the applicability of the results and increases the possibility of selection bias. Moreover, the screening algorithm was somewhat different from ours, as all men with a PSA level ≥ 3.0 ng/mL or with an abnormal DRE were referred for TRUS examination, but biopsy specimens were taken only if a hypoechoic lesion was found. Eventually, biopsies were performed on approximately half of the 1,563 screen-positive men, resulting in the diagnosis of 264 tumors (detection rate of 4.1%). The results from the Rotterdam screening trial also suggested an approximately two-fold risk associated with a family history, but again the small data set, biopsy specimens from only 202 men, limited conclusions.¹⁴

Screening with PSA has also been studied separately in high-risk families.^{15,16} These studies suggested that the detection rate is relatively high among men with a family history, but provided no comparison with men without a family history or with the general population. Because the focus has thus been on small and highly selected subgroups of the population, recommendation of a more aggressive screening strategy among men with a family history, especially without evidence of mortality reduction, is hardly justified at the population level.

Figures indicating an increased risk associated with a positive family history are, however, invalid indicators of the feasibility of a selective screening program. Screening in high-risk families does not affect the validity of the screening test itself (eg, PSA) in terms of test specificity and sensitivity. Instead, the aim of selective screening is to improve the program specificity (ie, to reduce the costs and adverse effects of screening) without compromising the program sensitivity.⁴ In our trial, the program specificity of

99.6% determined on the basis of family history as a supplementary screening criterion would have eliminated nearly all the unnecessary examinations among the men free of prostate cancer. The program sensitivity of only 6% is, however, unlikely to provide substantial reduction in prostate cancer mortality at the population level.

Our trial is population-based and has a relatively high participation rate (68%), which enhances the representativeness of the material. Nearly all (98%) the screening participants provided information on family history, minimizing the possibility of selection bias. Because the information was obtained at the time of invitation (ie, before diagnostic examinations), the effect of possible diagnosis of prostate cancer on valid reporting (recall bias) was eliminated. Family history was self-reported, and could not be confirmed from medical records or the Finnish Cancer Registry. However, it has been shown that men are able to provide a family history of prostate cancer fairly accurately and reliably.¹⁷

Cross-sectional data, like ours, may be affected by two major shortcomings. First, the temporality between an exposure and an outcome remains unclear. Second, sampling of prevalent cases means selection is conditional on being diagnosed with the disease and surviving with it, which leads to inability to distinguish between risk factors for disease incidence and surviving with the disease. Our study is free from both limitations: first, exposure status (family history) was assessed before and irrespective of the screening result and diagnostic confirmation; second, the outcome measure in our article is the detection rate, which does not include prevalent, but incident cases.

PSA testing detects tumors at an early stage, which may weaken the effect of family history through overdiagnosis (ie, detection of tumors that previously remained undetected).¹⁸ Thus, the impact of a family history on detection by PSA screening may be lower than in earlier studies derived from clinically detected cases.^{1,19} The extent of possible overdiagnosis cannot be evaluated, because the natural history of screen-detected tumors is not sufficiently well known. No reliable method is yet available to identify indolent tumors. Nevertheless, this would explain the discrepancy between earlier findings and ours only if the

majority of the screen-detected cancers were the result of overdiagnosis, especially among the men without a family history.

Hereditary factors have been estimated to contribute to 5% to 10% or more recently up to 42% of incident cases of prostate cancer.^{20,21} In our material, the corresponding population-attributable risk was 1.2%. Identification of families with a strong hereditary component demonstrates the existence of genetic factors, but provides little information regarding their importance at the population level. In other words, a rare genetic variant may have high penetrance although accounting for only a minor proportion of the cancers in the population. This has in fact been shown for prostate cancer in Finland.²² Hence, identification of a high-risk group would not justify adoption of a selective screening policy (even if the effectiveness of screening was shown). Differences in genetic factors between populations have been reported: HPCX has been suggested to account for almost half of cases with a hereditary susceptibility in Finland, whereas in North America, HPC1 seems to be the most important locus. It would therefore seem unlikely that the lack of an association between family history and screen-detected prostate cancer could be because of the absence of predisposing genes in the Finnish population.

A great deal of the evidence for an association of family history with a risk of prostate cancer is derived from clinically detected cases from the era before widespread PSA testing, but the association has also been shown more recently.^{23,24} Contrary to these earlier findings, our screening program with PSA showed only a somewhat but not significantly increased risk of prostate cancer associated with a positive family history. A more important finding, however, is the poor program sensitivity of selective PSA screening on the basis of family history. Genetic factors are thus unlikely to provide a successful approach for selective prostate cancer screening. Instead of focusing on family history, the aim should be for wide coverage of the population. Currently, the cause of prostate cancer is not well enough known to enable identification of a high-risk group with a substantial population-attributable risk. In conclusion, our findings provide no support for selective screening among men with a positive family history.

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Featured Article

Second Round Results of the Finnish Population-Based Prostate Cancer Screening Trial

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Abstract

Purpose: Large randomized trials provide the only valid means of quantifying the benefits and drawbacks of prostate-specific antigen (PSA) screening, but the follow-up of ongoing studies is still too short to allow evaluation of mortality. We report here the intermediate indicators of screening efficacy from the second round of the Finnish trial.

Experimental Design: The Finnish trial, with ~80,000 men in the target population, is the largest component in the European Randomized Study of Screening for Prostate Cancer. The first round was completed in 1996–1999. Each year 8,000 men 55–67 years of age were randomly assigned to the screening arm, and the rest formed the control arm. Men randomized to the screening arm in 1996 were reinvited 4 years later, in 2000, and PSA was determined.

Results: Of the eligible 6415 men, 4407 (69%) eventually participated in the second round of screening. Of the first-round participants, up to 84% (3833 of 4556) attended rescreening. A total of 461 screenees (10.5%) had PSA levels of ≥ 4 $\mu\text{g/liter}$. Altogether, 97 cancers were found, yielding an overall detection rate of 2.2% (97 of 4407). Seventy-nine cases were found among the 3833 second-time screenees (detection rate 2.1%) and 18 in those 574 men (3.1%) who had not participated previously. A PSA of ≥ 4 $\mu\text{g/liter}$, but

negative biopsy in the first screening round was associated with an up to 9-fold risk of cancer in rescreening relative to those with lower PSA levels at baseline. Ninety-one (94%) of all of the detected cancers were clinically localized.

Conclusions: As surrogate measures of an effective screening program, both compliance as well as the overall and advanced prostate cancer detection rates remained acceptable. Men defined as screen-positive but with a negative confirmation of cancer at prevalence screen formed a high-risk group at rescreening.

Introduction

Prostate cancer is the second leading cause of male cancer death in most industrialized countries (1). In the United States and also in some European populations prostate cancer mortality peaked in the late 1990s (2). The subsequent decrease has been assumed to be largely attributable to widespread prostate-specific antigen (PSA) testing. Nonetheless, temporal and geographical differences provide inconclusive evidence to establish the benefits of PSA screening. The best means to obtain valid evidence on PSA screening is through large, randomized screening trials. Such trials are currently under way in both the United States (Prostate, Lung, Colorectal and Ovary Cancer trial, Quebec trial) and Europe (the European Randomized Study of Screening for Prostate Cancer), but conclusive mortality analyses are not expected until 2008–2010 (3–5). The common feature in all of these trials is the use of serum PSA, with however variable cutoff criteria, as a principal test for screening (6). The trials also diverge in recruitment strategy (volunteer versus population-based programs) and frequency of screening (from annual screening up to an interval of 4 years). These differences may have a considerable influence on both program performance, including process indicators, and final outcome, *i.e.*, prostate cancer mortality. The Finnish trial represents a large, population-based study applying a conservative screening policy with a 4-year screening interval. So far, little is known regarding the program performance of PSA screening in a population of screened men at subsequent screens (5, 7–9). We here report intermediate screening efficacy indicators such as coverage of target population as well as the rate of prostate cancer detection and tumor characteristics at repeat screening in the second round of the Finnish trial, and compare these indicators with those of the first round.

Materials and Methods

Subjects. The Finnish prostate cancer screening trial, initiated in 1996 with a sample size of 80,000 men, forms the largest component in the European Randomized Study of Screening for Prostate Cancer. Study subjects residing in two metropolitan areas (Tampere and Helsinki) were identified from the Population Register of Finland, and those with a previous diagnosis of prostate cancer were excluded before randomization. Annually a random

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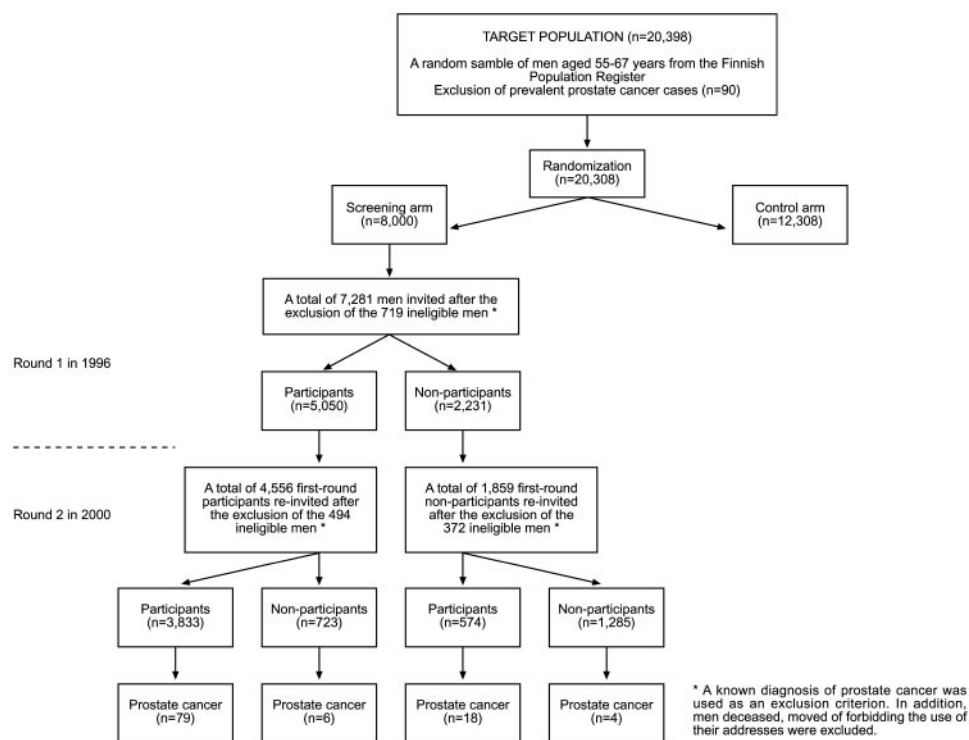


Fig. 1 Consort diagram of the Finnish prostate cancer screening trial for men recruited in 1996.

sample of 8000 men aged 55, 59, 63, or 67 years was allocated to the screening arm until 1999, and the remainder formed the control arm without intervention. A detailed description of the design has been published elsewhere (10). The present study covers the cohort of 8000 men randomly assigned to the screening arm in 1996 and invited for rescreening after an interval of 4 years, *i.e.*, in 2000 (Fig. 1). Men diagnosed with prostate cancer during the first round of screening, men deceased, moved outside the study area, or forbidding the use of their addresses were excluded. Eventually, a total of 6415 men were invited for rescreening at the ages of 59, 63, 67, or 71 years during the first year of the second screening round in 2000. The main outcome measure of the trial is mortality from prostate cancer.

Laboratory Methods. A blood sample was drawn after written informed consent to determine the serum concentration of total PSA by both Hybritech Tandem-E and Wallac Delfia assays. Determination of the percentage of free PSA was performed with the Wallac ProStatus free/total PSA assay. All of the serum analyses were carried out at the Department of Clinical Chemistry, Helsinki University Central Hospital.

Screening Algorithm. The total concentration of serum PSA was used as screening criterion. All of the men with PSA ≥ 4 $\mu\text{g/liter}$ were referred for diagnostic examination including a digital rectal examination, transrectal ultrasound, and sextant biopsies of the prostate supplemented by a directed biopsy if a focal finding was seen in either digital rectal examination or transrectal ultrasound. The percentage of free PSA was used as a supplemental screening criterion at PSA levels between 3.0 and 3.9 $\mu\text{g/liter}$, and only those with percentage of free PSA $<16\%$ were referred for diagnostic work up.

Diagnostics. All of the prostate cancer cases were histologically confirmed. Tumor characteristics at biopsy were graded according to the Gleason score system (11). The WHO system was used in 3 cases due to insufficient biopsy material. Clinical staging was conducted according to the Tumor-Node-Metastasis classification using primarily digital rectal examination, transrectal ultrasound, and bone scan to evaluate possible extracapsular extension and distant metastases of prostate cancer (12). Bone scanning was not conducted in 42 cases with PSA levels <20 $\mu\text{g/liter}$, this indicating a low risk of bone metastases (13).

Data Analyses. Pearson's χ^2 test was used to calculate the statistical significance of the difference in compliance with rescreening according to baseline PSA with a cutoff of 4 $\mu\text{g/liter}$. The detection rates by total PSA, age at diagnosis, Gleason score, and clinical stage of detected tumors were given with 95% confidence intervals (CIs). The positive predictive value of PSA for the second round of screening was defined here as the proportion of cancers found in men tested as screen positives (*i.e.*, including also 31 men who did not undergo a biopsy). In addition, the positive predictive values were calculated for men rescreened (*i.e.*, attending the second time of screening) in relation to the baseline PSA levels. The positive predictive values were all given with 95% CIs. The risk of prostate cancer by PSA values in the first screening round was given in terms of the ratio of detection rates with 95% CIs using men with baseline PSA levels <3.0 $\mu\text{g/liter}$ as reference. Statistical analyses were performed on the CIA version 1.1 (Martin J. Gardner and British Medical Journal) and the S-PLUS version 4.0 (MathSoft Inc., Cambridge, MA).

Table 1 Numbers of men and detected prostate cancers by serum PSA^a concentration at the second round of the Finnish prostate cancer screening trial

	No. of men (%)	No. of men biopsied	No. of cancers	Positive predictive value, % (95% CI)	Detection rate, % (95% CI)
PSA, µg/liter					
0–2.9	3,632 (82)	—	—	—	—
3.0–3.9	314 (7)	71	13	18 ^b (10–29)	0.3 (0.1–0.5)
4.0–9.9	413 (9)	386	66	18 ^c (15–22)	1.5 (1.1–1.9)
≥10	48 (1)	45	18	38 ^c (24–53)	0.4 (0.2–0.6)
Total	4,407 (100)	502	97	NA ^d	2.2 (1.8–2.6)

^a PSA, prostate-specific antigen; CI, confidence interval.^b The positive predictive value of the percentage of free PSA ≤16% in 72 men at PSA levels of 3.0–3.9 µg/liter.^c The positive predictive value at the lower end of the PSA range.^d Not applicable.

Ethics. The ethical committee of each participating hospital approved the trial protocol. Permission to obtain medical records was obtained from the Ministry of Social Affairs and Health and for use of cancer registry data from the STAKES Research and Development Center for Welfare and Health.

Results

Overall, 69% (4407 of 6415) of eligible men participated in screening during the first year (*i.e.*, in 2000) of the second round of the Finnish trial. Of the eligible 4556 men, who participated in the first round (in 1996), 84% (3833) attended rescreening. Of the 1859 first-round nonattenders, 31% (574) participated in the subsequent screening round. Compliance was higher among men with a baseline PSA <4 µg/liter (85%; 3650 of 4272) as compared with those tested as positive on the basis of a PSA of 4 µg/liter (64%; 183 of 284) in the initial round ($P < 0.001$).

Of the 4407 second round participants, 461 (10.5%) were defined as screen positive based on a serum PSA concentration of ≥4 µg/liter and referred for prostate biopsies (Table 1). In addition, 314 (7.1%) screenees had a PSA between 3.0 and 3.9 µg/liter, and 72 of these were referred for biopsies based on a percentage of free PSA ≤16%. Forty-seven (1.1%) screenees had PSA levels of ≥10 µg/liter. A total of 31 men (5.8%; 31 of 533) either refused or did not undergo a prostate biopsy due to medical contraindications.

Altogether, 97 cancers were found, corresponding to an overall detection rate of 2.2% (95% CI, 1.8–2.6%; 97 of 4407; Table 1). Seventy-nine cases were seen in men attending both screening rounds, this corresponding to a detection rate of 2.1% (95% CI, 1.6–2.6%; 79 of 3833) among rescreened men (Table 2). The rate of prostate cancer detection was somewhat higher among the 574 men screened for the first time, with 18 diagnosed cases giving a detection rate of 3.1% (95% CI, 1.9–4.9%; 18 of 574). The rate of cancer detection increased with age from 1.0% (95% CI, 0.6–1.4%) among men aged 59 years to 1.5% (1.0–2.2%), 1.8% (1.1–2.7%), and 2.4% (1.6–3.4%) in the age groups of 63, 67, and 71 years, respectively (Fig. 2).

Of all of the detected cases, 13 were seen with PSA levels <4 µg/liter, 66 within the range of 4.0–9.9 µg/liter, and 18 at ≥10 µg/liter, corresponding to detection rates of 0.3% (95% CI, 0.1–0.5%; 13 of 4407), 1.5% (1.1–1.9%; 66 of 4407), and 0.4% (0.2–0.6%; 18 of 4407), respectively. The positive predictive value of the PSA threshold of 4 µg/liter was 18% (95% CI, 15–22%; 84 of 461) and 38% (24–53%; 18 of 48) for the 10 µg/liter threshold.

At PSA levels of 3.0–3.9 µg/liter, the percentage of free PSA with a cutoff of 16% gave a positive predictive value of 18% (95% CI, 10–29%; 13 of 72). In the 3833 second-time screenees, the positive predictive value was somewhat lower for both the PSA threshold of 4 µg/liter and 10 µg/liter yielding to the values of 17% (14–21%; 67 of 389) and 32% (17–51%; 10 of 31), respectively. The corresponding values for the first-time attenders were 24% (14–35%; 17 of 72) and 47% (23–72%; 8 of 17).

The initial PSA level at prevalence screening predicted a risk of prostate cancer in rescreening 4 years later. The risk was ~6-fold in men with the baseline PSA levels between 3.0 and 3.9 µg/liter compared with those at PSA levels <3 µg/liter (Table 3). The risk increased up to 9-fold in men testing screen positive on the basis of a PSA of 4.0–9.9 µg/liter in the first round of screening. Only 1 cancer was seen among those 13 men with a baseline PSA of ≥10 µg/liter. The positive predictive value for the PSA threshold of 4 µg/liter at baseline was 11% (6–15%; 20 of 183) and 8% (2–36%; 1 of 13) for the threshold of 10 µg/liter in the second-time participants of screening.

The detection rate of Gleason score 2–6 prostate cancer

Table 2 Numbers of men and detected PCs^a by clinical stage and Gleason score in the first (1996) and second round (2000) of screening in the Finnish trial

	Round 1	Round 2	
		Re-screen	Delayed 1st screen ^b
No. of men invited	7,281	4,556	1,859
No. of men screened (%)	5,050 (69)	3,833 (84)	574 (31)
No. of PCs	105	79	18
Stage (%)			
T ₁ N _x M ₀	42 (40)	43 (54)	10 (56)
T ₂ N _x M ₀	49 (47)	31 (39)	7 (39)
T _{3–4} N _x M _{0/1}	14 (13)	5 (6)	1 (6)
T _{1–4} N _x M ₁			
Gleason (%)			
2–6	85 (81)	57 (72)	15 (83)
7	10 (10)	15 (19)	2 (11)
8–10	7 (7)	3 (4)	1 (6)
Unknown	3 (3)	4 (5)	—
Detection rate, %	2.1	2.1	3.1

^a PC, prostate cancer.^b The first-round nonparticipants reinvited in 2000.

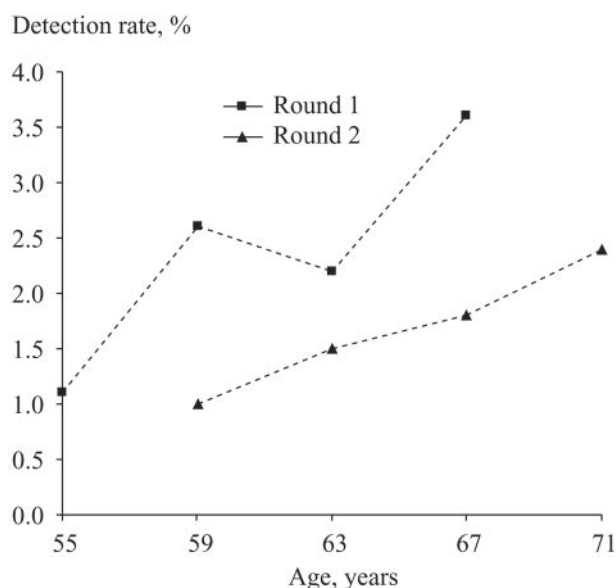


Fig. 2 The rate of cancer detection by age in the first and second round of the Finnish trial in 1996 (10) and 2000, respectively.

was 1.6% (95% CI, 1.3–2.0%; 72 of 4407), 0.4% (0.2–0.6%, 17 of 4407) for Gleason score 7, and 0.1% (0–0.2%; 4 of 4407) for Gleason score 8–10 tumors (Table 4). Of 97 screen-detected tumors, 91 cases or 94% were clinically localized, corresponding to a detection rate of 2.1% (95% CI, 1.7–2.5%; 91 of 4407) and 0.1% (0–0.2%; 6 of 4407) for nonlocalized disease. Of the 6 clinically advanced cases, 1 had not participated in the first round of screening, whereas the rest had tested negative. No cases were seen with distant metastases.

Discussion

Compliance with screening remained at an acceptable level (69%) in the second round of the Finnish population-based trial. Of the first-round participants, up to 84% attended rescreening. The overall rates of prostate cancer detection were practically the same in the first and second round of screening, but the reduction in age-specific detection rates was obvious at the

second round (Fig. 2; Ref. 10). A substantial decrease was seen particularly in the rate of advanced cases, from 0.3% to 0.1%. Because tumor characteristics represent an intermediate indicator of screening efficacy, the few advanced cancers at rescreening constitutes encouraging, yet inconclusive, evidence for eventual mortality reduction attributable to PSA screening. In particular, early cases represent those with a potential to benefit from screening through early diagnosis and treatment, but are confounded by overdiagnosis. Advanced cases indicate failure of screening to reach these aims, and, hence, a reduction in them is a better surrogate for mortality as a definitive end point.

Tumor stage as a surrogate measure of screening efficacy is, however, closely associated with length bias, indicating a higher likelihood of detecting slow growing as against aggressive tumors in multiple screens. Slow-growing tumors are strongly overrepresented at the first (prevalence) screen, and, hence, these initially detected cases comprise the most biased sample of screen-detected cancers. Most prevalent, slow-growing tumors (length bias) are likely to be eliminated with the introduction of screening followed by a steady state in incident cases in successive screening cycles. Tumor characteristics at later (incidence) screens are, thus, more informative in assessing the efficacy of screening than those derived from prevalence screens (14). The efficacy of screening should after all be evaluated in terms of an outcome in screen-detected cases relative to what would have occurred if there had been no screening (which is not directly observable), and is estimable only after several years of follow-up in terms of mortality reduction in those screened compared with those in the control arm.

The American Cancer Society and American Urological Association have recommended annual PSA screening for men aged 50 years or older despite the lack of evidence for either optimal screening interval or eventual mortality reduction (15, 16). Several trials, including ours, use substantially longer screening intervals (6). Short intervals increase drawbacks, such as overdiagnosis and costs of screening without necessarily improving efficacy in terms of advanced cancers prevented, whereas too long an interval is likely to miss potentially lethal tumors at curable stages. Both observational and simulation studies have recently suggested the alternative of biannual instead of annual screening with a minimal risk of nonlocalized cancer (17, 18). Nonrandomized studies and modeling are, however, prone to several biases. The recent findings from the

Table 3 Numbers of men and detected PCs^a in the second round in relation with total PSA found at prevalence screen, the Finnish prostate cancer screening trial

1st screen PSA (μg/liter)	2nd screen				
	No. of men	No. of men with PSA ≥3	No. of PC	RR ^b	95% CI
<3	3,459	368	45	1	Reference
3.0–3.9	191	145	14	5.6	3.2–10.1
4.0–9.9	170	144	19	8.6	5.1–14.4
>10	13	11	1	5.9	0.2–47.8
Unscreened	574	105	18	2.4	1.4–4.1

^a PC, prostate cancer; PSA, prostate-specific antigen; CI, confidence interval.

^b The ratio of detection rates.

Table 4 Clinical stage and Gleason score of prostate cancer by serum PSA^a concentration among the 4407 men screened at the second round of the Finnish prostate cancer screening trial

	PSA, µg/liter						Total	
	3.0–3.9		4.0–9.9		≥10			
	No. of PC	(DR, %)	No. of PC	(DR, %)	No. of PC	(DR, %)	No. of PC	(DR, %)
Stage								
T ₁ N _x M ₀	7	(0.2)	36	(0.8)	10	(0.2)	53	(1.2)
T ₂ N _x M ₀	6	(0.1)	26	(0.6)	6	(0.1)	38	(0.9)
T _{3–4} N _x M _{0/1}	—		4	(0.1)	2	(0.0)	6	(0.1)
T _{1–4} N _x M ₁								
Gleason score								
2–6	10	(0.2)	49	(1.1)	13	(0.3)	72	(1.6)
7	1	(0.0)	15	(0.3)	1	(0.0)	17	(0.4)
8–10	—		—		4	(0.1)	4	(0.1)
Unknown	2 ^b	(0.0)	2 ^b	(0.0)	—		4	(0.1)
Total	13	(0.3)	66	(1.5)	18	(0.4)	97	(2.2)

^a PSA, prostate-specific antigen; PC, prostate cancer; DR, detection rate.

^b Gleason score was unavailable for a total of 4 patients due to small sample size at biopsy. Three of these tumors were graded as well differentiated according to the WHO system. In one case grading was not possible.

Swedish section of the European Randomized Study of Screening for Prostate Cancer are also in favor of longer screening intervals (9). Only a few of both interval and advanced cancers were seen during the follow-up of biannual PSA screening in Sweden. In our randomized trial, 5 of 6 clinically advanced cases were negative in the initial screening. Nevertheless, a clear reduction was seen in the rate of advanced cancer in the second round of screening, but lack of data on interval cancers limits the applicability of our findings.

The findings of the Rotterdam section of the European Randomized Study of Screening for Prostate Cancer are consistent with those in the Finnish trial showing only a modest reduction in the overall rate of prostate cancer detection in multiple screens with a 4-year interval even after correction for age (7). It is generally assumed that cancer detection rates will drop in subsequent screens as compared with the initial prevalence screen. Failure to achieve this may indicate too long a screening interval. The second round findings in both the present and the Dutch trial were, however, indicative of a favorable effect on tumor stage in repeat screening (7). The comparable cancer detection rates at prevalence and incidence screens may also be attributable to overdiagnosis, but this cannot be evaluated without information on interval cancers and incidence rates in the control population. The recent report from the Dutch trial, however, shows the rate of interval cancers to be modest (19). In our trial, the cumulative incidence of 4.6% in the two screens is thus far substantially lower than the lifetime risk of 7% in men aged 55–74 years in Finland, with relatively low rate of opportunistic screening (data from the Finnish Cancer Registry).

The Finnish trial is population-based, and, hence, our findings are readily applicable to a PSA-based screening program as a national health policy. The effectiveness of such programs is dependent upon the coverage of the target population. In our trial, the overall attendance rate in the second round of screening remained the same as in the first (*i.e.*, at 69%), and it was close to rates obtained in multiple screens based on recruitment of volunteers (7, 8). However, 16% of the first-round screeners dropped out at rescreening, which is consistent with volunteer-based trials show-

ing incomplete attendance after initial screening. Plausible explanations for this are both the possibility that men with a negative initial screen are opting out, as well as the increasing use of PSA testing (opportunistic screening) outside the trial. This issue may compromise the effectiveness of any organized screening, and it also complicates evaluation of the ongoing trials.

The overall detection rate of Gleason score 7–10 cancers was comparable (~0.5%) in the first and second screening rounds of the Finnish trial, although a shift toward cases with a Gleason score of 7 was observed at rescreening (20). On the other hand, the rate of Gleason score 2–6 tumors decreased slightly. Tumor grade is highly relevant for screening, as survival of patients with a well-differentiated tumor have proved similar to age-matched controls, whereas those with a more aggressive disease have substantially reduced life expectancy without potentially curative intervention (21). Hence, our screening strategy revealed a smaller number of potentially insignificant tumors at rescreening but maintained the diagnosis of aggressive ones (more likely to benefit from screening). This is in contrast with the results of the Dutch trial, where no change was seen in well-differentiated tumors, but a clear reduction in more aggressive cancers with a Gleason score of 7 or higher (7). A plausible explanation for this is the lower PSA cutoff of 3 µg/liter used as biopsy criterion in Holland. In that study more than a third of all of the cases were in fact found at PSA levels < 4 µg/liter. However, a shift in learning curve associated with the adoption of Gleason score system in the initial phase of the Finnish trial may attenuate the comparability of tumor grades.

The positive predictive value of PSA was lower in the second round of the Finnish trial compared with that at the initial screen (in the previously unscreened population). This corresponds to an increase in biopsy to cancer ratio from 3.9 to 5.5 per detected cancer for the PSA cutoff of 4 µg/liter (10). A similar change has been observed in two other trials (5, 7). The reduction in positive predictive value is presumably attributable to the elimination of large, slowly growing prostate cancers from the prevalence pool at the first screen, whereas the prevalence of benign prostatic hyperplasia causing elevated PSA

levels will increase with age. In other words, positive predictive value is determined not only by the test itself, but also by the prevalence of the target condition in the source population. This is an important finding affecting interpretation of PSA measurements in both screening and clinical settings.

Few reports have assessed the association between baseline PSA levels and later risk of prostate cancer in screening (7, 9, 22). In our trial, the first-round PSA level predicted the risk of prostate cancer at repeat screening 4 years later. The risk was particularly high in men with a PSA of ≥ 4 $\mu\text{g/liter}$, but without cancer diagnoses at baseline. Studies with shorter screening intervals have also suggested an elevated risk of cancer at follow-up screens in men with initially increased PSA levels already within a year from entry in screening (9, 23). Both these and our findings are contrary to the Dutch study, indicating that baseline PSA levels do not predict a risk of prostate cancer at later screens (7). Concern must prevail that a negative biopsy may give false assurance of a low future risk of cancer in screen-positive men, which may affect compliance with repeated screening. In the present study, such men formed a high-risk group at rescreening, indicating precisely the opposite. In fact, more than a fifth of cancers found in the second round of screening were seen in this group. In the Swedish trial based on biannual screening, more than half of the cancers detected at the second round were seen in men with elevated baseline PSA levels. This is conceivably a result of missing smaller tumors at biopsy in the first round. However, most screen-positive men were referred for rebiopsies in the initial phase of our study to maximize sensitivity at biopsy. It is, hence, unlikely that the increased risk in men screen-positive in the first round is solely due to limited sensitivity of prostate biopsy. The fact that only 1 cancer seen in men with a baseline PSA >10 $\mu\text{g/liter}$ limits conclusions, but is also consistent with a lower risk of missing large tumors at biopsy as well as with increased clinical surveillance after a markedly elevated PSA at screening. Nevertheless, an abnormal finding (PSA) at prevalence screen represented a significant risk factor for prostate cancer in repeat screening in the Finnish trial. It remains to be shown whether this finding can be confirmed at subsequent screens, and whether this information is applicable to the current screening practices (such as the follow-up of screen-positive men with negative biopsies as well as the frequency of screening).

In conclusion, the second round of screening in the Finnish population-based trial showed an acceptable level of compliance after a 4-year interval as well as a lower detection rate especially of advanced cancers compared with the initial (prevalence) screen. These are necessary conditions for an effective screening program, but comprise nonetheless inconclusive evidence for eventual mortality reduction attributable to PSA screening. Moreover, recognition of high-risk groups on the basis of the screening history may facilitate improvement of the performance of screening programs in future.

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