Advances in Brief

Detection of Subclinical Cancers by Prostate-specific Antigen Screening in Asymptomatic Men from High-Risk Prostate Cancer Families

Mika P. Matikainen, Johanna Schleutker, Pertti Mörsky, Olli-P. Kallioniemi, and Teuvo L. J. Tammela

Laboratory of Cancer Genetics, Institute of Medical Technology, University of Tampere and Tampere University Hospital [M. P. M., J. S., O-P. K.], and Departments of Clinical Chemistry [P. M.] and Surgery Division of Urology [T. L. J. T.], Tampere University Hospital, FIN-33101 Tampere, Finland; and Cancer Genetics Branch, National Human Genome Research Institute, NIH, Bethesda, Maryland 20892-4470 [O-P. K.]

Abstract

Positive family history is a significant risk factor for prostate cancer. Improved knowledge of the epidemiology and molecular basis of hereditary prostate cancer has led to a need for counseling and clinical follow-up for men with a positive family history of prostate cancer. However, very little information is available on the efficacy of early screening procedures, such as serum prostate-specific antigen (PSA) measurements, in the management of genetically predisposed, high-risk individuals. In a nationwide study, we obtained family histories from 2099 Finnish prostate cancer patients and identified 302 families with two or more affected cases. Here, 209 asymptomatic 45–75-year-old males from these families were included in a study to determine the frequency of serum PSA positivity and the prevalence of subclinical prostate cancers. Serum PSA was elevated in 21 (10.0%) of these high-risk individuals. Seven prostate cancers (3.3%) and two high-grade prostatic intraepithelial neoplasia lesions were diagnosed, with three cancers occurring in men ages ≤59 years. Men from prostate cancer families with an average age of onset of <60 years had a significantly higher frequency of PSA positivity (28.6%, P = 0.01) as well as cancers (14.3%, P = 0.02) than those with a later age of onset. The results suggest that prostate cancer development in genetically predisposed individuals is preceded by a subclinical period when PSA detection is possible. Serum PSA screening may be particularly useful in men with a family history of early-onset prostate cancer.

Introduction

Prostate cancer is the most common malignancy in men in many industrialized countries. For example, in Finland, prostate cancer comprised 24.6% of all malignancies in men in 1995, with an age-adjusted incidence of 61.4 per 100,000 men. It was second only to lung cancer as a cause of cancer mortality (1). Positive family history is one of the strongest risk factors for prostate cancer (2). Approximately 5–10% of prostate cancer cases may be influenced by a germ-line predisposition (3, 4). Men with a positive family history have 2–10 times increased prostate cancer risks compared to those with no family history. The risk ratios are highest in families with multiple prostate cancer cases and in those in which the average age of cancer diagnosis is low (3–5).

The first gene conferring susceptibility to prostate cancer (HPC1) was recently mapped to chromosome region 1q24–q25 (6). Genetic linkage data suggest that it contributes to a fraction of early-onset prostate cancer families (7). HPC1 gene carriers may have a 60–90% lifetime risk of prostate cancer. Two other loci for prostate cancer predisposition, one at 1q42 (8) and another (HPCX) at Xq27–28 (9), were also reported recently. The relative impact of these three loci remains to be determined (10, 11). Furthermore, polymorphisms of several genes, such as androgen receptor, 5a-reductase, and vitamin D receptor may also influence the risk of prostate cancer (12–14). Further studies of such genetic risk indicators may eventually enable development of genetic testing for prostate cancer (6). However, awareness of inherited cancer risks is already increasing among urologists, patients, and their relatives. Consequently, a need for counseling and clinical follow-up for men with a strong family history of disease is emerging (15).

Serum PSA measurements and clinical examination are important strategies to screen for the presence of asymptomatic prostate cancer (16–18). PSA is highly sensitive in detecting subclinical prostate cancers, defined here as cancers causing no clinical symptoms, but its utility in reducing mortality is still under investigation. The efficacy of PSA screening in high-risk subgroups, such as those with a positive family history, has received very little attention (19, 20). Assuming that men with a strong family history have substantially increased risk of prostate cancer, these high-risk men may also have a high

1 The abbreviations used are: PSA, prostate-specific antigen; PIN, prostatic intraepithelial neoplasia.
prevalence of subclinical, PSA-detectable prostate cancer. This study was aimed at testing this hypothesis. In this study, 209 asymptomatic men from a nationwide material of 302 prostate cancer families in Finland were analyzed to determine the frequencies of elevated PSA values and of subclinical prostate cancer.

Materials and Methods

We identified 302 prostate cancer families in Finland with two or more affected first- or second-degree relatives per family. A number of different methods for family ascertainment were used to obtain coverage of the entire country: (a) a nationwide cancer and parish registry based search was performed to uncover family history of 1547 prostate cancer patients diagnosed between 1988 and 1993 (including all 557 cases of prostate cancer diagnosed at the age of ≤60 years); (b) advertisements in newspapers, radio, and television resulted in 500 contacts with patients and their relatives; and (c) letters to practicing urologists resulted in 52 contacts with patients or family members. Diagnosis of cancer in the relatives was confirmed by information from hospital records or the Finnish Cancer Registry. Altogether, family history was obtained from 2099 men with prostate cancer. On the basis of the substantial overlap of families identified by the registry-based search and by other methods, the 302 families identified should represent a large fraction of all prostate cancer families in Finland. Of these families, 103 were selected for this study based on the criterion that at least one unaffected first-degree male relative relative ages > 44 years was available.

The study material consisted of 226 unaffected first-degree male relatives from the 103 families, of which 209 (107 brothers and 102 sons of probands) agreed to participate (92.5%) and gave written informed consent. One 10-ml blood specimen was obtained for DNA isolation, and another 10-ml specimen was obtained to prepare serum for PSA measurement. The mean age of the 209 unaffected men was 56.0 years (range, 45–75 years). The mean number of unaffected cases studied per family was 2.0 (range, 1–9). One hundred twenty men came from families with three to seven prostate cancers, and 89 came from families with two affected cases. The mean age of diagnosis of prostate cancer in these families was 69.7 years (range, 55–86 years).

Serum specimens were stored at −70°C until analyzed, for a maximum of 8 weeks. The AutoDELFIA PSA kit (Wallac, Turku, Finland) was used to determine total serum PSA concentrations. Age-specific reference values were used as a criterion for cutoff values of raised serum PSA levels. These reference values are used in the clinical routine at the Tampere University Hospital and are based on the results from the Gothenburg (21) and Rotterdam (22, 23) European Organization for Research and Treatment of Cancer screening studies with 5845 and 1726 unselected participants, respectively (95th percentile of the distribution). If serum PSA was elevated, the subject was referred to a local urology department for subsequent urological examination, which included a new PSA measurement, digital rectal examination, ultrasound, and one set of random biopsies.

Statistical analyses were performed using Fisher’s exact test, calculated with GraphPad Instat 228 software (GraphPad Software, San Diego, CA).

Results

Twenty-one of the 209 apparently healthy men (10.0%) from prostate cancer families had elevated serum PSA values compared to age-specific reference values (Fig. 1). The elevated values ranged from 2.6 to 28.3 mg/liter. Subsequent urological examination with first set of random biopsies revealed seven patients (3.3%) with prostate adenocarcinoma (Fig. 1 and Table 1) and two (1.0%) with PIN. One of the cancers was in the advanced stage, whereas the others were intracapsular (Table 1). The mean age of the PSA-detected cancer patients was 65.1 years (range 52–75), which is approximately seven years lower than the average age of diagnosis of prostate cancer patients in Finland. Three of the cases (43% of all screen-detected cases) were detected under the age of 60 years.

The frequency of PSA positivity (28.6%) and subclinical

---

4 M. P. Matikainen et al., Risk of prostate and other cancers in first-degree relatives of prostate cancer patients: a registry-based analysis in Finland, manuscript in preparation.
prostate cancer (14.3%) were significantly higher ($P = 0.010$ for PSA and $P = 0.024$ for cancer by Fisher’s exact test) in men from families with an average age of onset of $\leq 60$ years, as compared to those from families with a mean age of onset of $> 60$ years (Fig. 2). Furthermore, five of the seven new prostate cancers found in this screening study came from large families in which three or more men were previously known to be affected with prostate cancer (Fig. 3). Overall, six of the seven new cancer cases detected were in families that had either an average age of onset of $< 60$ years or three or more previous known affected cases.

Discussion

The overall frequency of subclinical cancers (3.3%) detected in asymptomatic men from prostate cancer families was similar to that reported (2.3–4.5%) in PSA screening studies of unselected populations (17, 18, 23–25). However, in men from early-onset prostate cancer families, cancer detection frequency was significantly higher, up to 14%. The high frequency of PSA-detectable cancer in men from early-onset prostate cancer families is in an excellent agreement with epidemiological data on familial cancer risks (3–5, 26–31). Men with a positive family history of prostate cancer are known to have 2–10 times higher risk of prostate cancer compared to those with no family history. This risk is influenced by the number of affected family members and particularly strongly by the average age of diagnosis of prostate cancer in the family. Taken together, our experimental results and the aforementioned epidemiological studies strongly support the concept that serum PSA screening is likely to be particularly useful in men with a family history of early-onset prostate cancer.

The number of prostate cancers detected in our study group was ~21 times higher than the expected annual number (0.3), as determined from age-adjusted incidence rates in the Finnish population (1). Such a high cancer detection frequency most likely reflects the fact that serum PSA screening is known to advance diagnosis of prostate cancer by 5–10 years as compared to clinical detection (32). In this study, only one set of random biopsies was performed for the patients with elevated PSA. It is known that with follow-up biopsies additional cancers are often detected (33). This suggests that the frequencies obtained in this study are likely to underestimate the true prevalence of subclinical prostate cancer. These results indicate suggest that prostate cancer development in genetically predisposed individuals is also preceded by a subclinical period when PSA detection may be possible. Detection of such subclinical cancers in these high-risk individuals may be useful because it may provide a chance for early treatment and cure.

Two previous studies have investigated serum PSA levels in relation to positive family history. In the study by McWhorter et al. (19), 34 apparently healthy, 55–80-year-old, first-degree male relatives from 17 prostate cancer families were studied. Proportion of elevated PSA levels in the study by McWhorter et al. (19) was 17.6% (cutoff levels, 4.0 ng/ml), and cancer detection frequency was 8.8% (three cases). In addition, five additional cancers (14.7%) were detected by digital rectal examination, ultrasound, and biopsies. In the study by Narod et al. (20), 6390 unselected men ages 50–80 years were screened by PSA and rectal examination. Prostate cancer was detected in 10.2% of subjects who reported a brother and in 4.8% of those who had a father with prostate cancer. Only 3.9% of men with no first-degree relatives had subclinical prostate cancer. Our material differs from those of Narod et al. (20) and McWhorter et al. (19) in that several extended pedigrees were included, that the mean age of subjects (56.0 years; range, 45–75 years) was lower, and that cancer diagnoses were verified independently (in contrast to subjective family questionnaires). Especially when the age differences are taken into account, the 3.3% prevalence of subclin-
PSA Screening in High-Risk Prostate Cancer Families

Despite the substantial progress in dissecting the molecular basis of prostate cancer predisposition (6, 8, 9), it will take many years before specific genetic tests will be commonly available. Therefore, PSA screening is likely to have an important role in alleviating concerns of cancer in members of prostate cancer families who seek medical attention and genetic counseling. At the time being, long-term clinical follow-up procedures should probably be limited to men from those families in which the age of onset of prostate cancer is <60 years or three or more prostate cancers have been previously already diagnosed. Because half of the new cancer cases in our study were detected in 50–59-year-old men, PSA screening of high-risk groups should commence early, perhaps at the age of 45 years, as suggested by Walsh and Partin (34).

Finally, these results emphasize the importance of including PSA screening in genetic linkage studies of prostate cancer susceptibility. In all seven families in which new prostate cancer cases were diagnosed based on this PSA screening, logarithm of the odds ratio for linkage (lod) scores obtained for HPC1 (or for any other locus tested) were substantially influenced by the inclusion of these PSA-detected cases as affected cases in these pedigrees.

In conclusion, serum PSA screening may have utility in the management and follow-up of unaffected male individuals in prostate cancer families with an early age of cancer diagnosis. Because several cancers were diagnosed in 50–59-year-old men, PSA screening in high-risk groups should be started at an early age. Further research is required to establish how often PSA screening should be repeated and whether such a targeted and repeated screening affects the mortality or improves the quality of life of men with positive family history of prostate cancer.

Acknowledgments

All patients and families participating this study are cordially thanked for their cooperation. We thank Kaisa Vaherto for technical assistance and Dr. Pasi Koivisto for comments. The following colleagues and institutions are acknowledged for their cooperation: Dr. Mirja Ruutu from the Department of Urology, Helsinki University Hospital; Dr. Martti Ala-Opas from the Department of Urology, Kuopio University Hospital; Drs. Jukka Kallio, Christian Palmberg, Taina Isotalo, and Susanna Laakovirta from the Department of Urology, Tampere University Hospital; Dr. Matti Rauvala from the Department of Urology, Rovaniemi Central Hospital; Dr. Martti Talja from the Department of Urology, Päijät-Häme Central Hospital; Dr. Kari Jauhiainen from the Department of Urology, Mikkelni Central Hospital; Dr. Eero Kaasinen from the Department of Surgery, Hyvinkää District Hospital; Dr. Jukka Kärki from the Department of Surgery, Salo District Hospital; Dr. Asko Heikkinnen from the Department of Surgery, Valkeakoski District Hospital; and Dr. Erkki Rintala from the Department of Urology, Helsinki City Hospital.

References

Detection of Subclinical Cancers by Prostate-specific Antigen Screening in Asymptomatic Men from High-Risk Prostate Cancer Families


Updated version  Access the most recent version of this article at:  
[http://clincancerres.aacrjournals.org/content/5/6/1275](http://clincancerres.aacrjournals.org/content/5/6/1275)

Cited articles  This article cites 32 articles, 5 of which you can access for free at:  
[http://clincancerres.aacrjournals.org/content/5/6/1275.full#ref-list-1](http://clincancerres.aacrjournals.org/content/5/6/1275.full#ref-list-1)

Citing articles  This article has been cited by 4 HighWire-hosted articles. Access the articles at:  
[http://clincancerres.aacrjournals.org/content/5/6/1275.full#related-urls](http://clincancerres.aacrjournals.org/content/5/6/1275.full#related-urls)

E-mail alerts  Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions  To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions  To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.