PROSTATE CANCER SCREENING – IS IT TIME TO CHANGE APPROACH?

Marek Vargovčák[1], Erik Dorko[2], Kvetoslava Rimárová[2], Viliam Knap[3]

[1]Urological Outpatient Clinic, Railway Hospital, Košice, Slovak Republic

[2]Department of Public Health and Hygiene, Faculty of Medicine, Pavol Jozef Šafárik University in Košice, Košice, Slovak Republic

[3]Department of Physiatry, Balneology, and Medical Rehabilitation, Faculty of Medicine, Pavol Jozef Šafárik University in Košice, Košice, Slovak Republic

SUMMARY

Objective: Prostate adenocarcinoma (CaP) is one of the most common malignancies in men in Slovakia and in the world. The disease accounts for more than 22% of all tumors in the male population. Screening studies show an increase in the diagnosis of CaP without improvement in overall or CaP-specific mortality. The main goal of the work is to evaluate the incidence of CaP in the group of patients examined and treated during the period from 2014 to 2019 at the urological outpatient clinic of the Railway Hospital (RH) in Košice, and to evaluate the risks and treatment options.

Methods: Men aged 40 to 75 years underwent a preventive examination in 2014–2019 at the urology outpatient clinic, RH Košice. The number of screened patients was 3,943. Epidemiological parameter, diagnosis-related examinations (prostate specific antigen – PSA examination, digital rectal examination, and ultrasonography examination) as well as the frequency of examinations were monitored during the specified period on the basis of documentation. The number of prostate biopsies, incidence of prostate cancer and relation to PSA values were also monitored, as well as the classification of prostate cancers according to the degree of risk. Initial treatment in individual patients was also evaluated.

Results: PSA values in patients who underwent biopsy ranged from 3.6 ng/mL to 2,000 ng/mL. We observed positive digital rectal examination in 52 patients. Of the number of patients examined, 231 (61.28%) were positive biopsies. There were negative biopsies with the finding of benign prostatic hyperplasia in 92 patients or chronic prostatitis in 54 patients, i.e., 146 (38.72%). According to the criteria for risk assessment based on the PSA value and the result of the histological examination, we diagnosed 109 low-risk patients, 57 medium-risk patients and 24 high-risk patients.

Conclusion: CaP is detected by prevention about 10 years before it develops clinically. The main aim of preventive examinations should be to detect, in particular, high-risk forms of early-stage prostate cancer and to improve the quality of life of men. Due to the results of extensive studies, it is necessary to continue the active search for prostate cancer. This reduces the risk of metastatic forms of CaP.

Key words: prostate cancer management, quality of life, conservative treatment, prostate cancer, prevention and health promotion

Address for correspondence: E. Dorko, Department of Public Health and Hygiene, Faculty of Medicine, P. J. Šafárik University in Košice, Šrobárova 2, 041 80, Košice, Slovak Republic. E-mail: erik.dorko@upjs.sk

https://doi.org/10.21101/cejph.a6807

INTRODUCTION

Prostate adenocarcinoma (CaP) is one of the most common malignancies in men in Slovakia and in the world (1). The disease accounts for more than 22% of all tumors in the male population. Active search in Slovakia takes place through outpatient urologists, where patients are sent by general practitioners. However, the actual incidence rate is much higher due to the latent disease. The spectrum of examinations at the urology outpatient clinic includes ultrasonography (USG) examination of the urinary tract and prostate, digital rectal examination (DRE) and examination of prostate specific antigen (PSA) (2). The Union and General Health Insurance Companies pay for the preventive examinations after the age of 40 of the man's life, Health Insurance Company "Dôvera" (Trust) after the age of 50. Recently, there has been a wide-ranging debate about whether this approach is the right one. In 2008, the United States Preventive Services Task Force issued a recommendation not to use PSA for screening in men over the age of 75. In October 2011, the recommendation was supplemented by not to seek active CaP in all asymptomatic men. In May 2012, adjusted to grade D recommendation for PSA screening in all asymptomatic men. The reason was that the negatives of screening outweigh the benefits. Screening studies have shown an increase in the diagnosis of CaP without an improvement in overall or CaP-specific mortality. The diagnosis can lead the patient to a treatment that he does not even need (3). However, treatment significantly affects the quality of life in men at risk of over-treatment. Treatment is often associated with a significant effect on quality of life (i.e., urine leakage, urological and gastroenterological symptoms, erectile dysfunction) (4).

With regard to the deteriorating quality of life, more than 50% of men with localized CaP prefer active monitoring, which is, however, also time-consuming and financially demanding. The annual cost of CaP treatment in the United States is $ 11 billion (5).

However, from the public health view the treatment of low-risk forms of CaP is always more effective with regard to the survival and quality of life of patients and 70% of prostate tumors are detected on the basis of a preventive examination. By detecting CaP

in the earlier stages, it is possible to achieve an overall survival in patients, comparable to the healthy population. In patients at any stage of CaP, it is possible to effectively improve the quality of life. The costs of treatment of patients with CaP in the initial stages are significantly lower than in advanced forms. After early treatment of CaP, patients are able to return to the work process and are not dependent on the social system of the state (5).

The main goal of the work is to evaluate the group of patients examined and treated during the years 2014 to 2019 at the urological outpatient clinic of the Railway Hospital (RH) Košice, to discuss the risks and ambiguities of screening, and to evaluate the probability that the tumor will be diagnosed.

MATERIALS AND METHODS

Men aged 40 to 75 underwent a preventive examination at the urological outpatient clinic, RH Košice, in 2014–2019. The number of screened patients was 3,943. During the specified period, the medical documentation of patients was thoroughly studied. Based on the documentation, demographic parameter (age), epidemiological and clinical parameters (comorbidities, positive family history), diagnosis-related examinations (PSA, DRE, USG, prostate biopsy) as well as frequency of examinations (on average once every 3 years) were obtained.

Patients with a positive family history (occurrence of prostate cancer in the father) underwent a preventive urological examination once a year. A positive family history was reported in the monitored group of 26 men. The obtained data were then stored in an electronic database and analysed. Worldwide, only a small subpopulation of men with CaP (~ 9%) has a real inherited disease. This is defined as three or more affected relatives or at least two relatives who developed early CaP (< 55 years). Hereditary CaP is associated with 6 to 7 years earlier onset of disease, but disease aggression and clinical course do not appear to differ in other ways. The probability of high-risk CaP at age 65 in men with an affected father and two brothers in the Swedish population study was 11.4% (compared to a population risk of 1.4%) (6).

Different approaches have been used to capture comorbidity, depending on the outcome measure, clinical setting and source of data. Comorbidity has been defined as the co-occurrence of 1 or more diseases or disorders in an individual (7). Comorbidity reflects the aggregate effect of all clinical conditions a patient might have, excluding the disease of primary interest.

The number of prostate biopsies, the incidence of prostate cancers and the relationship to PSA and Gleason score (GS) values (histopathological classification) as well as the distribution of prostate cancers according to the degree of risk were monitored.

A normal value is considered to be a PSA value up to 4 ng/mL, which, however, is also correlated with age. The normal finding on digital rectal examination is a smooth, elastic prostate without obvious rigid nodules. We consider a patient with PSA < 10 ng/mL, GS < 7, cT1-T2a to be low risk. Moderate-risk patients have a PSA of 10–20 ng/mL, GS 7, cT2b. High-risk patients are rated as PSA > 20 ng/mL, any GS, cT3-T4 or cN+. The criterion for prostate biopsy is an increase in PSA level or palpation in DRE. Biopsies were performed using a rectal ultrasound probe. We took 6 to 12 samples from both lobes of the prostate (8). We also evaluated the initial treatment in individual patients. Within the monitored group of patients, we evaluated the incidence of prostate cancer, risk factors and primary treatment modality in men who underwent preventive urological examination.

The database was analysed by IBM SPSS 21.0 statistical software. Descriptive analysis was used to describe demographic features. Absolute and relative frequencies were also calculated. Chi-square test was used to compare the difference of prostate cancer occurrence between selected age groups. Odds ratio (OR) with 95% confidence interval (CI) were used to compare impact of age groups, alcohol consumption and smoking to prostate cancer development. The rejection level established for the null hypothesis was lower than or equal to 0.05 (5%).

RESULTS

The average age of the observed group of men was 58.3 years, while the median age was 59.5 years. Most of the men examined in our clinic were examined later than at 50 years of age. PSA values in patients who underwent biopsy ranged from 3.6 ng/mL to 2,000 ng/mL.

We observed positive DRE in 52 patients. Based on the indication criteria, we performed 377 prostate biopsies. Of the number of patients examined, 231 (61.28%) were positive biopsies. There were negative biopsies with the finding of benign prostatic hyperplasia in 92 patients or chronic prostatitis in 54 patients, i.e., 146 (38.72%) (Fig. 1).

Inheritance and race are an uncontrollable risk factors for CaP. We evaluated the presence of the so-called hereditary prostate cancer (occurrence in three or more relatives, or in at least two relatives with CaP with early onset < 55 years). We identified 19 (8.2%) patients of the total population meeting the criterion in question during the monitored period.

The controllable risk factors we observed were metabolic syndrome (hypertension, obesity), alcohol consumption and smoking. From the total sample of patients with a positive CaP finding up to 122 (52.8%) suffered from some form of metabolic syndrome; 84 (36.3%) patients with a positive CaP finding were considered regular consumers of alcoholic beverages; 112 (48.4%) patients were considered occasional consumers of alcoholic beverages. In the study group, 131 patients (56.7%) reported smoking. No single component of the metabolic syndrome was independently associated with CaP. However, the increasing number of components was associated with a higher degree of risk of CaP ($p < 0.001$).

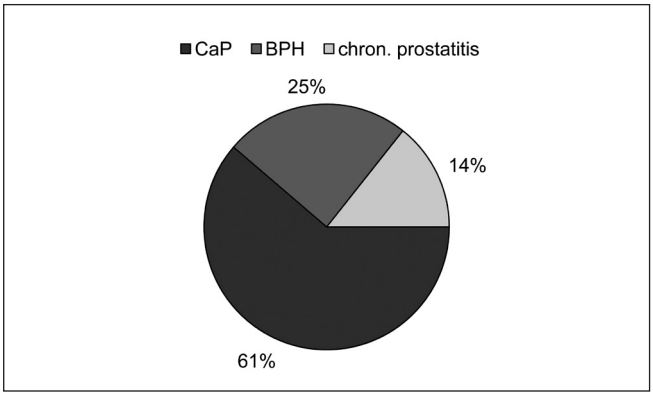

Fig. 1. *Results of prostate biopsies in 2014–2019.*

Comorbidity reflects the aggregate effect of all clinical conditions a patient might have, excluding the disease of primary interest. We have evaluated presence of diabetes mellitus, hypertension, ischaemic heart disease, urothelial carcinoma, and colorectal carcinoma. From the total of 231 patients with positive biopsy result, we identified 101 patients with hypertension, 82 patients with diabetes mellitus, 35 with ischaemic heart disease, 18 with urothelial carcinoma, and 7 with colorectal carcinoma.

We also evaluated the relationship between the absolute value of PSA and the presence of CaP. At PSA ≤ 4 ng/mL, we identified 2 positive findings. At PSA 4–10 ng/mL, 152 patients were positive, at PSA 10–20 ng/mL, 43 patients were CaP positive, and at PSA values above 20 ng/mL, 34 patients were positive (Fig. 2).

The distribution of prostate cancer in age groups varied. In the age group 50–59 years, 84 (36.36%) biopsies were positive. In the age group 60–69 years, 115 (49.78%) biopsies were positive, and in the age group 70–79 years were 32 (13.85%) positive biopsies.

According to the risk assessment criteria based on the PSA value and the result of the histological examination, we diagnosed 135 low-risk patients, 62 medium-risk patients and 34 high-risk patients (Fig. 3).

In the age group 50–59 years, there were 58 patients with low risk, 22 patients with moderate risk and 4 patients with high risk. In the age group 60–69, 61 patients with low risk, 38 patients with moderate risk and 16 patients with high risk were diagnosed. In the age group 70–79, there were 16 patients with low risk, 2 patients with moderate risk and 14 patients with high risk. Based on our observations, we can state that most of the diagnosed tumors are at low risk and that the risk of developing high-risk forms of CaP increases with age.

After prostate biopsy, patients subsequently received the recommended treatment. We also recommend active monitoring among the treatment options. We evaluate only primary therapy in this work. Possible follow-up therapy is beyond the scope of this work. The treatment modalities used in the examined group as initial treatment were as follows: active surveillance – 15 patients, surgery (radical prostatectomy) – 43 patients, radiotherapy – 59 patients, hormonal treatment – 78 patients, orchiectomy – 7 patients, chemotherapy – 20 patients, other treatment – 9 patients (Fig. 4).

In the age group 50–59 years there were 12 cases of active surveillance, 29 patients underwent radical prostatectomy, 20 patients underwent radiotherapy, 18 patients hormonal treatment, 4 patients chemotherapy, and 1 patient underwent other treatment. In the 60–69 age group, there were 3 cases of active surveillance, 13 patients underwent radical prostatectomy, 25 patients underwent radiotherapy, 54 patients hormonal treatment, 15 patients chemotherapy, and 5 patients underwent other treatment. In the age group 70–79 years, 1 patient underwent radical prostatectomy, 14 patients radiotherapy, 6 patients hormonal treatment, orchiectomy 7 patients, 1 patient chemotherapy, and 3 patients underwent other treatment.

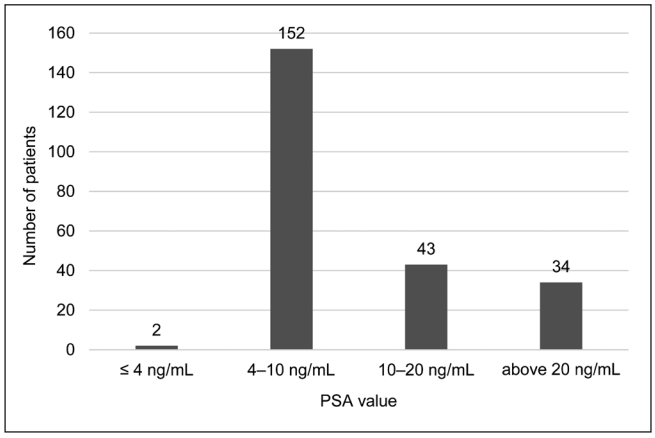

Fig. 2. *PSA value and presence of CaP.*

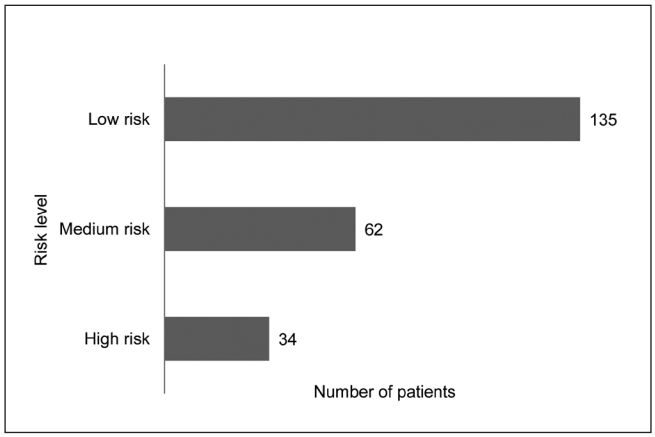

Fig. 3. *Distribution of patients according to prostate cancer risk.*

DISCUSSION

Prostate cancer is one of the most common malignancies in men in the Slovak Republic and other countries. The trend of a worldwide increase in the incidence of the disease of 3% per year is also attributed to the high and gradually increasing average age of the population, especially in developed countries. The incidence of prostate cancer in Slovakia is ascending from 14.6/100,000 in 1968 to 44.6/100,000 in 2007. However, mortality shows a slower upward trend from 7.2/100,000 in 1968 to 13.4/100,000 in 2007 (9).

There is an active search for CaP through the so-called preventive examinations in the Slovak Republic at urological clinics. However, the question remains whether this method can be called screening. The principles of screening are as follows: the disease

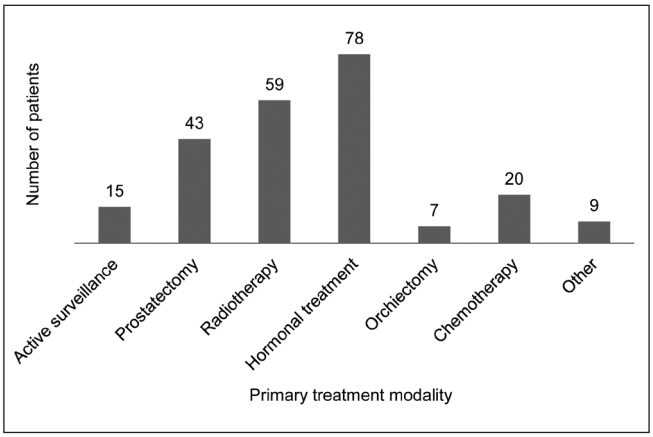

Fig. 4. *Primary treatment.*

must have a high incidence, biological behaviour and origin of the disease must be known, tests should have high sensitivity, specificity and positive predictive values, tests should be rapid, inexpensive, non-invasive, and acceptable to patients. There must be an acceptable and effective method of treatment for patients diagnosed with the disease. Screening should reduce disease-specific morbidity and prolong survival (10).

Unfortunately, it is currently not entirely clear that CaP screening meets these criteria. Today, the only oncomarker for CaP screening is PSA. PSA is not a perfect marker. It has low sensitivity (35–70%), specificity (60–90%) for prostate cancer. Biopsy capture at the best centres is 60–80% (11). The traditional PSA value of 4.0 ng/mL is no longer an absolute indication for biopsy. Other factors influencing PSA are infection/instrumental procedures, urinary retention, ejaculation, advanced age/benign hyperplasia (12).

The largest ongoing screening study is the European Randomized Study of Screening for Prostate Cancer (ERSPC) (13); randomized study in men aged 50 to 74 years in 7 European countries; 83,000 in the screened arm; 99,000 in the control arm, PSA monitoring on average every 4 years in the screening arm (14). The conclusion in the 19-year PSA monitoring and screening so far is that the disease reduces specific mortality by 21%, which is equivalent to 1 death per 781 screened men or 1 death per 27 CaP detected, PSA screening clearly reduces the number of men with metastatic CaP (15). However, the questions of the ERSPC study remain. Positive PSA value defined as 3.0 ng/mL in most centres, performed a so-called 6-core biopsy: uptake is up to 20% higher when using an extended biopsy (10–18 samples). Localized prostate cancer is more common in the screening group (16). The study confirms the clear benefit of preventing metastatic disease (17).

Meta-analyses of the data indicate the detection of prostate cancer worldwide using biopsy in men with a PSA 4–10 ng/mL in 56%. At PSA values above 10 ng/mL, the presence of cancer is almost 100% (18). Literature data indicate the percentage of positive biopsies, mainly depending on the biopsy technique. The percentage of positive findings ranges from 44% (19) to 90–93% using multiparametric magnetic resonance imaging (20).

Another study is the PLCO "American Study": 38,000 men randomized to annual screening. Compliance for PSA and DRE was 85% and 86%, once a year PSA sampling and once a year DRE examination, the follow-up period in the study was 7–10 years. PLCO results: 116 vs. 95 new CaPs per 10,000 patients in screening vs. control group; 2 vs. 1.7 deaths per 10,000 patients in screening vs. control group (21). PLCO study questions: a follow-up of 7 to 10 years is not long enough to compare mortality, using an absolute PSA of 4.0 ng/mL as a "positive" PSA may lead to underdiagnosis (3, 22).

Bell et al. prepared a systematic review of biopsy results in 2015 depending on age. The estimated mean prevalence of cancer at age < 30 years was 5%, which increased non-linearly to 59% at age > 79 years. There were significant differences in cancer prevalence between populations; for example, at the age of < 30 years it was 2.5–17%. At the age of 40–50 years it was 15–37%, and at the age of > 79 years 30.59–84% (23). A meta-analysis of Zhao et al. found that regular consumers (> 14 drinks/week) had a 1.46 higher risk (HR 1.46; 95% CI: 1.12–1.91) of prostate cancer compared to occasional alcohol users (≤ 3 drinks). Abstainers had a 1.90 higher risk (HR 1.90; 95% CI: 1.04–3.47) of prostate cancer-specific mortality compared to occasional consumers but no other significant association with mortality was found. Analyses suggest that alcohol consumption may be associated with a prostate cancer risk independent of early environmental and genetic factors (24). Summary data from 24 cohort studies involving more than 26,000 participants with prostate cancer showed a modest increase of 9% to 30% in the incidence and fatal prostate cancer associated with smoking. Former smokers had the least increased risk of prostate cancer. Their risk of incidental tumors was 9% higher than that of non-smokers (25).

From a public health perspective, the importance of prevention can be assessed as follows: treatment of low-risk forms of CaP is more effective and increases the quality of life of patients. Up to 70% of all CaPs are detected in a preventive examination. By prevention, CaP is detected on average 10 years before it manifests clinically. By screening, we detect CaP in earlier stages, thus achieving a patient survival comparable to a healthy population. At any stage of CaP, we can increase the quality of life with an adequate approach. By sending a patient for a preventive examination, we emphasize the importance of individual health care. The cost of treating early stages of CaP is significantly lower than in advanced stages, and patients tend to return to work. Complications and side effects of treatment are significantly higher in more advanced forms of the disease.

CONCLUSION

The study approved the importance of screening for CaP in population. Most of the CaP patients in our study were diagnosed in early stages with low-risk tumors. Our study provides good evidence that by detecting CaP in the earlier stages, it is possible to achieve an overall survival in patients, comparable to the healthy population. On the other hand, we confirmed that in patients at any stage of CaP, it is possible to effectively improve the quality of life. However, it is necessary to find a reasonable balance between benefits and unnecessary overtreatment. We suggest to focus on better understanding of PSA test and start applying new biomarkers in diagnostics, which will contribute to a better indication of patients for biopsies in the future.

Due to the results of extensive studies, it is necessary to continue the active search for prostate cancer. This reduces the risk of metastatic forms of CaP. However, an active approach must in no case harm the patient in terms of a significant reduction in quality of life.

Acknowledgements

This work was supported by grants: KEGA 007/UPJŠ-4/2018, KEGA 008UPJŠ-4/2020, KEGA 010UPJŠ-4/2021 of the Ministry of Education, Science, Research and Sport of the Slovak Republic and project grants VVGS IPEL 2020/1485 and VVGS IPEL 2020/1662. We thank also the Directory Board of University Hospital in Košice for assistance with organization of samples collection at the hospital wards.

Conflict of Interests

None declared

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Received February 20, 2021
Accepted in revised form January 3, 2022