

# Epidemiology and Natural History of Prostatic Diseases

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**Abstract:** The understanding of the epidemiology and natural history of a disease strongly contributes to appropriate diagnoses and the selection of optimal therapies. Epidemiological studies reveal that there are a large number of patients with benign diseases, such as benign prostatic hyperplasia (BPH) and prostatitis, and there are also many men who do not visit the hospital but who have lower urinary tract symptoms (ULTS). On the other hand, a substantial percentage of prostate cancer is detected in patients who seek medical care because of LUTS. Studies of the natural history of diseases demonstrate the importance of identifying factors that denote progressive BPH. Better identification of these factors will enable us to individualize treatment in a more effective way. The same is true for prostate cancer. To determine which treatment is best suited to each type of patient, we need to understand the natural history of prostate cancer, including observation. This approach will enable us to tailor individualized treatment.

**Key words:** Benign prostatic hyperplasia; Prostate cancer; Prostatitis; Epidemiology; Natural history

## Introduction

Including prostatic diseases, understanding the epidemiology and natural history of a disease strongly contributes to appropriate diagnoses and the selection of optimal therapies. For example, not all patients with benign prostatic hyperplasia (BPH) are good candidates

for surgery. We know from experience that some patients show no progression of lower urinary tract symptoms (ULTS) for over 10 years without surgery. The application of this experience to the entire population of patients with BPH will provide information that may greatly improve our ability to select treatment options.

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This article describes the epidemiology and natural history of BPH, prostate cancer, and prostatitis, as well as suggestions for clinical practice.

## Benign Prostatic Hyperplasia

Twenty years ago, the diagnosis of BPH in patients visiting urology clinics was relatively easy because they usually presented highly developed symptoms and signs of BPH, such as severe LUTS, definite enlargement of the prostate, and large amounts of residual urine. Recently, such patients are relatively rare. Most patients have slight or moderate LUTS, with no definite enlargement of the prostate and normal voiding conditions as assessed by uroflowmetry. The diagnosis of BPH, therefore, is not simple.

Because the number of patients with BPH is fairly large, we tend to misunderstand that patients visiting hospitals represent the entire patient population. However, a large number of patients with the disease reflects the presence of a larger number of men with slight LUTS. It is not appropriate to infer the whole picture of a disease from the number of patients visiting hospitals.

Several studies in the last decade have revealed the prevalence of LUTS or the number of men with these symptoms who do not visit hospitals in various parts of the world. In particular, data from population-based or community-based studies provide a relatively accurate measure of prevalence. These studies are considered to produce less biased results than data from health screenings.

According to a community-based study conducted by the authors in Hokkaido, the percentage of men with moderate or severe symptoms was 40% for those aged 50–59, 52% for those aged 60–69, and 63% for those aged 70–79.<sup>1)</sup> These percentages were slightly higher than those in the U.S. and similar to those in Korea.<sup>2)</sup> These interesting results offer insight into the ethnic differences in symptoms. On the

other hand, the percentage of men with a maximum flow rate ( $Q_{max}$ ) of 10 ml/sec or less, an indication of impaired voiding, was 6% for those aged 50–59, 19% for those aged 60–69, and 42% for those aged 70–79. The percentage of those with a prostate volume of 20 cc or more, an indication of prostatic enlargement, was 34% for those aged 50–59, 39% for those aged 60–69, and 38% for those aged 70–79.

If we tentatively define BPH by the presence of moderate or severe symptoms, a  $Q_{max}$  of 10 ml/sec or less, and a prostate volume of 20 cc or more, the percentage of men meeting these criteria is 6% for those aged 50–59, 6% for those aged 60–69, and 12% for those aged 70–79. At least one in 10 men aged 50 or higher, or 1.2 million men in Japan, are considered to have BPH.<sup>2)</sup> Because the above definition is fairly strict, we should assume that a larger number of men have BPH.

A substantial number of men who do not seek medical care satisfy the definition of BPH. Why don't these men visit hospitals? The answer lies in the effects of LUTS on QOL and the degree of patient satisfaction. The authors examined the difference between the results of a community-based study (men not visiting hospitals) and the data from patients visiting hospitals. Among men showing a similar degree of LUTS, those with symptoms causing a stronger deterioration in their QOL or a decrease in satisfaction were more likely to seek medical care.<sup>3)</sup>

These results suggest that men visiting hospitals show not only higher degrees of symptoms but also stronger effects of symptoms affecting satisfaction regarding urination and QOL. From this observation, we can understand why we see patients with relatively slight symptoms mixed with those with severe symptoms. The key factor is patient QOL or satisfaction regarding urination. Deterioration in QOL or satisfaction prompts a man to consult a physician. This fact should be considered in the initiation of therapy and in the selection of treatment options.

As discussed above, studies on LUTS and the natural history of BPH provide important information in the selection of optimal therapy for individual cases. Past studies on natural history, in particular, natural history before treatment, show that symptoms, prostate volume, and Qmax in the general male population gradually progress with age or over time.<sup>4,5)</sup> The next question is what the predictors for progression of voiding condition are. In other words, how can we identify men who are going to receive treatment in the future?

A prospective study in the U.S. reports the association with age, LUTS, prostate volume, and Qmax.<sup>6)</sup> For example, men in the general population in the 70–79 age range were found to be at a risk of progression 7-fold more than those in the 40–49 age range. In addition, men showing marked symptoms during the initial examination had a high probability of receiving some form of treatment due to progression of symptoms.

Our 3-year study of the general population also shows that the degree of LUTS at the initial examination was proportional to the probability of men eventually having the surgery for BPH. These results suggest that the progression of LUTS in the general population is closely associated with the degree of symptoms and prostatic enlargement.<sup>5)</sup>

What is then associated with post-treatment natural history or clinical course? In a study using transurethral resection of the prostate (TURP) as the endpoint, it was shown to depend on the degree of symptoms at the time of the first examination.<sup>7)</sup> When patients with an indication for surgical treatment were followed according to the watchful waiting strategy, the probability of eventual surgery depended on the degree of symptoms at the time of the first examination.

A long-term study on sympathetic  $\alpha 1$  receptor blockers ( $\alpha 1$  blockers) indicates that the effectiveness of this treatment was lost in about 40% of cases in 4 years, and the loss of efficacy was strongly associated with prostate volume at

the time of the first examination.<sup>8)</sup> In fact, more than a 2-fold difference was seen in the occurrence of treatment changes between the patients with a prostate volume of less than 40 cc and those with 40 cc or more. If prostate volume affects clinical progress after treatment, it can be inferred that reduction of prostatic enlargement may be meaningful.

Results from the Medical Treatment of Prostatic Symptoms (MTOPS) are currently considered the most important source of information.<sup>9)</sup> It has been shown that a combination of  $\alpha 1$  blocker and a 5 alpha-reductase inhibitor is the most effective means of preventing the progression of the disease, which was defined as surgery after medical treatment, acute urinary retention, etc. If the progression of BPH is determined by a complex of the degree of symptoms, the degree of prostatic enlargement, and urination conditions, we may expect that  $\alpha 1$  blockers that improve symptoms and urination conditions and agents that reduce prostatic enlargement are both effective in controlling the progression of the disease.

We need careful verification of whether or not the above results apply to our patients particularly with respect to the degree of prostatic enlargement. In fact, ethnic differences have been reported to occur in prostate volume and its increase. The authors have also reported some of these differences.<sup>2)</sup> If we could generalize the findings from these studies, we would be able to partially predict what initial treatments are best for individual patients. At this point, we have just achieved several rationale for applying the knowledge of the natural history of BPH in the clinical setting.

## Prostate Cancer

Epidemiological studies of prostate cancer have shown recent remarkable increases in the number of patients and prevalence. Part of these increases must reflect the improvement in the detection of prostate cancer using prostate-specific antigen (PSA). However, the incidence

itself is considered to be increasing. At present, the age-adjusted prevalence per 100,000 population has increased to about 12, and this prevalence is 2- to 3-fold higher than 20 years ago. This increase in prevalence is anticipated to continue in the future. The prevalence of prostate cancer is predicted to increase at the highest rate among the types of cancer during the 25 years from 1990 to 2015. The death rate has also been increasing steadily since 1990. In 1997, the age-adjusted mortality from prostate cancer was about 5 per 100,000, and the annual number of deaths was greater than 7,000.

Generally, mass screening for prostate cancer detects cancer in 1% of the men, who participate in the screening. This detection rate is clearly higher than that of mass screening for other cancers, such as gastric cancer, lung cancer, cervical cancer, and breast cancer. Because prostate cancer develops in men aged 50 or more, screening targeted at this age group is effective.

In addition, the detection of cancer in men visiting hospitals because of LUTS is also substantial. In our study, 25% of the approximately 300 men seeking medical care for LUTS had abnormal PSA levels, and 25% of the men with abnormal PSA levels had cancer.<sup>10)</sup> In the end, cancer was detected in 7% of men seeking medical care for LUTS. Seventy percent of the detected cancer was in the early stages, and this fact emphasizes the importance of detecting prostate cancer in men visiting hospitals because of LUTS. The need for PSA tests for prostate cancer screening in men without symptoms is somewhat controversial. In the case of men visiting hospitals with LUTS, PSA tests are an essential part of the examination to differentiate prostatic hyperplasia and prostate cancer.

The effectiveness of prostate cancer screening has been studied in the U.S. and Europe, and a similar evaluation has been conducted in Japan from last year. The conclusions of this study are awaited with interest.

Like all cancers, the natural history of pros-

tate cancer involves difficult problems. As a result of the progress in the detection of early-stage prostate cancer, it has been pointed out that there are some cases that do not need to be treated immediately. The so-called “watchful waiting” strategy is indicated for such cases.

A paper published last year provides a suggestion in this respect.<sup>11)</sup> This study compared radical prostatectomy and watchful waiting in patients of early-stage prostate cancer presenting similar clinical symptoms. The outcome of treatment was better for radical prostatectomy. These results indicate that radical prostatectomy should be the first-line therapy for early-stage cancer. However, this study also demonstrates the presence of cases that can be managed with watchful waiting. It is a challenge for future studies to clarify how we can select such cases and identify the characteristics of patients suitable for watchful waiting.<sup>12)</sup>

## Prostatitis

The epidemiological studies of prostatitis have been limited until recently. A group led by the National Institute of Health (NIH) in the U.S. developed a scoring system for chronic prostatitis-like symptoms, and an epidemiological study on prostatitis-like symptoms using this scoring system was commenced. The authors produced a Japanese translation of this scoring system, examined its validity, and reported its usefulness in Japan.<sup>13)</sup> The Japan Urological Association is now developing the final version of this symptom-scoring system.

A study in an area in Hokkaido using this symptom-scoring system detected chronic prostatitis-like symptoms in 5% of men in the 20–79 age range. A similar study in Canada reports a prevalence of 10%.<sup>14)</sup> Although the definition of the presence of symptoms differs slightly, a study in the U.S. reported a prevalence of 16%.<sup>15)</sup>

Thus, it is estimated that about 10% of men aged 20 or more in the general population have chronic prostatitis-like symptoms. Including

the study by the authors, several studies have pointed out a larger decline in QOL in patients with chronic prostatitis than those with prostatic hyperplasia. It is, therefore, important to diagnose and treat men with these symptoms.

Little has been clarified with respect to the post-treatment natural history of prostatitis, in particular chronic prostatitis and chronic pelvic pain syndrome, except that we know there are remissions and exacerbations. The reason for this situation is diversity in the causes of this disease and the resulting lack of our ability to provide appropriate treatment. Another reason seems to have been the lack of an established treatment-evaluation system, in particular a symptom-evaluation system. As mentioned above, a symptom-scoring system has been developed, and randomized clinical trials using this system have commenced. We expect to gain a clearer understanding of the clinical course of the disease after treatment in the future.<sup>16)</sup>

## Conclusion

The clarification of the epidemiology and natural history of prostatic diseases is essential for the overall understanding of these diseases. Achievements in these fields surely affect the diagnosis and treatment of these diseases. In particular, the introduction of new therapies needs adequate evaluation of the post-treatment natural history or clinical course. A standard therapy may not be established without such evaluation. In addition, the selection of treatment options suitable for individual patients is also important to provide tailored treatment. Studies of the natural history of diseases are essential prerequisites for achieving these goals.

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