No change in the prevalence of latent prostate cancer over the last 10 years: a forensic autopsy study in Japan

Masahito HITOSUGI¹, Kenichi MUKAISHO², Masahito KIDO³, Shuichi KAMIMURA⁴, Satoshi FURUKAWA¹, and Hiroyuki SUGIHARA²

¹ Department of Legal Medicine, Shiga University of Medical Science; ² Department of Pathology, Shiga University of Medical Science;

³ Department of Urology, Jikei University School of Medicine; and ⁴ Department of Urology, Utsunomiya Nishigaoka Hospital, Japan

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ABSTRACT

Although the morbidity rate of prostate cancer has increased with 2.3 times in these 10 years in Japan, little is known about the changes in the prevalence of latent prostate cancer. To understand changes in the prevalence of latent prostate cancer, a retrospective analysis was performed. Forensic autopsy findings from Tochigi Prefecture between September 2012 and February 2014 were collected. Two cross sections, from the base and apex of the prostate, were examined histopathologically. The prevalence of latent prostate cancer was compared with findings from forensic autopsies performed between August 2002 and July 2005 in the same region. The prevalence of latent prostate cancer in both groups was similar, showing an overall prevalence of 13.6% and 12.2% and a Gleason score >6 of 6.2% and 7.1%, respectively. When prevalence was compared by cause of death, the values were similar for both groups. The prevalence of latent prostate cancer in this Japanese population did not show any significant change over the past 10 years. The dramatic increase in morbidity rate for prostate cancer could be from the increase in prostate-specific antigen screening and subsequent referral to urologists.

Prostate specific antigen (PSA) screening for prostate cancer (PC) is undertaken globally in men aged older than 50 years. Screening has resulted in an increased observance of the incidence of PC and drastically changed the epidemiological characteristics of the disease (12). Because PC is usually a slow progressive disease with a long latent phase, many men with PC die from other causes before they manifest any symptoms of PC (1). In North America, although the lifetime risk for a diagnosis of PC is about 17.0%, the risk for death from PC is only 3.4% (5). The detection of PC may therefore have no clinical effect within the lifetime of some pa-

tients (6–8).

Determination of the prevalence and characteristics of latent PC may provide an understanding of its natural history. Along with changes in lifestyle, time-related trends must be considered. When considering the prevalence of PC, values are strongly influenced by the specimens available. Because prostate-specific antigen screening or cancer registration does not reflect the true incidence of latent PC, historically, latent PC was mainly assessed by pathological autopsy.

According to recent meta-analyses on autopsy studies, age-adjusted rates of latent PC have remained fairly constant over time (1, 12). Recently, some reports suggest that the incidence of PC has increased in Asian countries (11, 14). In Japan, according to The Center for Cancer Control and Information Services in Japan, the morbidity rate (per 100 000 population) of PC has increased in these ten years, from 47.1 in 2002 to 126.6 in 2011 (4). However, there

Address correspondence to: Masahito Hitosugi, MD, PhD Professor, Department of Legal Medicine, Shiga University of Medical Science, Tsukinowa, Seta, Otsu, Shiga 520-2192, Japan

Tel: +81-77-548-2200, Fax: +81-77-548-2201

E-mail: hitosugi@belle.shiga-med.ac.jp

have been little evidences whether the increase of morbidity was owing to the increase of the prevalence of latent PC or to increased participation in PSA screening and increased referral of patients to the urologists. To clarify the true trend in latent PC in Japan, a forensic autopsy study was performed.

Forensic autopsies are performed to determine causes of unnatural death, including sudden death from disease or external causes, such as accidents, suicide, and homicide. Because such people undertook their normal daily activities immediately before death and had not undergone long-term medical intervention, the natural history of PC can be more accurately evaluated using forensic autopsy specimens.

We previously examined the prevalence of latent PC using forensic autopsy specimens (13). As demographic characteristics play an important role in the incidence of latent PC, we examined changes in the prevalence of latent PC within the same region of Japan by comparison with recent data.

MATERIALS AND METHODS

Specimens. Prostate specimens were collected from forensic autopsies performed at Dokkyo Medical University, Tochigi Prefecture, northern Kanto, Japan between September 2012 and February 2014. Bodies severely affected by trauma or decomposition in which there was difficulty removing the entire prostate were excluded. Of the 271 people autopsied over the period, 177 were included in this analysis. General information including age, height, weight, body mass index (BMI), and past medical history was obtained. Each patient's past medical history was reviewed by interviews with their family and referring physicians, if possible. Because forensic autopsies routinely include pathological examinations of the entire body, prostates are usually examined both macroscopically and microscopically. Therefore, collection, processing, and examination of the prostate were not beyond routine forensic autopsy protocol.

At autopsy, the prostate gland was removed and cut into three pieces vertical to the urethra. Two cross sections, one from the base and one from the apex of the prostate, were embedded in paraffin and stained with hematoxylin and eosin using standardized protocols. The study was approved by the Ethics Committee of Shiga University of Medical Science (No. 16-22).

Prostate examination. PC was identified by experienced pathologists (KM, HS). For each specimen, if

evaluation was difficult owing to postmortem changes to epithelial cells, it was excluded from further analysis. PC was examined and a Gleason score assigned according to previously established morphologic criteria (2, 3). Gleason score is a grading system for PC based on the glandular pattern. Architectural patterns are identified and assigned a grade from 1 (most differentiated) to 5 (undifferentiated). Because the most common and second most common grades were combined in this study, the Gleason scores ranged from 2 (1+1) to 10 (5+5). The location of each PC was mapped on a schema of the prostate.

Comparison of the data to previous results. We previously examined the prevalence of latent PC at forensic autopsy at the same facility between August 2002 and July 2005 (13). Because the main person performing the autopsies (MH) and the methods of examination were the same, we were able to evaluate changes in prevalence over a 10-year period by comparing the latter results with earlier results. The overall prevalence of latent PC and the prevalence of PC with a Gleason score >6 were compared by manner of death.

Statistical analysis. The *chi*-squared test was used to compare the prevalence of PC between the two groups. To compare mean age, an F-test was first performed to examine the homogeneity of variance. An unpaired *t*-test was used for equal variance and a Welch's *t*-test was used for unequal variances. A *P*-value <0.05 was considered statistically significant.

RESULTS

Overview

Among the 177 cases, 15 were excluded because of postmortem changes. For the remaining 162 cases, average postmortem duration was 2.3 ± 1.8 days. Age at death ranged from 12 to 94 years, with a mean age of 56.2 ± 17.8 years (Fig. 1). Mean BMI was 21.6 ± 4.9 . Of the 162 cases, 75 (46.3%) died suddenly from disease and 87 (53.7%) from external causes. No cases died of PC. Four patients had been thought to have had PC; however, a biopsy had not been performed, none of these people had a history of prostate surgery, and none had a confirmed diagnosis of PC.

Prevalence of PC

PC was identified in 22 (13.6%) of the 162 autopsied people, who ranged in age between 27 and 88

Fig. 1 Comparison of age distribution of all individuals and those with prostate cancer (PC) between two study periods.

Fig. 2 Representative PC cases with Gleason scores of 9 (A) and 6 (B). Hematoxylin and eosin stain ($\times 200$).

years, with a mean age of 67.9 ± 15.4 years (Fig. 1). The overall prevalence of PC among people >49 years of age was 16.7%. When analyzed by age group, PC was most prevalent among people who had died in their 80s (25.0%), followed by those in their 70s (21.2%), 60s (17.1%), and 50s (10.9%) (Fig. 1). The prevalence of PC was similar in people who died from disease or from external causes (13.3% vs. 13.8%; $P = 0.71$). Representative PC cases including an 83-year-old man with Gleason score 9 and a 76-year-old man with Gleason score 6 are shown in Fig. 2A and 2B, respectively. Both these cases died of thoracic injuries.

Of the 22 PC identified, 10 (45.5%) had a Gleason score >6 . For these clinically significant PC, prevalence was 6.2% (Fig. 3). When comparing the

prevalence of PC with a Gleason score >6 by cause of death, prevalence was 5.3% for those who died from disease and 6.9% for those who died from external causes (Table 1). When the same analysis was restricted to only those aged >49 years, prevalence increased to 5.7% and 9.1%, respectively. Among the four patients thought to have PC, two were diagnosed with PC postmortem, both with Gleason scores of 9.

Comparison of latest data to previous results

Both groups (current and previous data) had normal age distributions and similar mean ages (56 and 54 years, respectively, Fig. 1) (13). The prevalence of latent PC by overall age group was similar at 13.6% for current data and 12.2% for previous data (statis-

Fig. 3 Comparison of the prevalence of latent prostate cancers, overall and Gleason score (GS) > 6, between two study periods.

tically not significant, $P = 0.71$, Fig. 3). For PC with a Gleason score >6, prevalence was also similar at 6.2% for current data and 7.1% for previous data (statistically not significant, $P = 0.72$, Fig. 3). The prevalence of clinically significant latent PC was compared by cause of death and found to be similar for both periods (Table 1).

DISCUSSION

The present results suggest that the prevalence of latent PC did not change significantly over the 10-year study period. From current and previous data, PC was examined from forensic autopsy cases in the same region, and mean age and age distribution were found to be similar. Therefore, the comparison undertaken should return results with a high accuracy. Although the morbidity of PC has increased with 2.3 times for these ten years in Japan, it is suggested to be because of the increase in prostate-specific antigen screening and the increased referral of patients with high prostate-specific antigen levels to urologists in Japan. As prostate-specific antigen screening is performed in approximately 40% of men older than 50 years, and as it is likely to increase in the future, it is expected that this discrepancy would become more apparent (17).

Results of this study align with results from meta-analyses of autopsy studies worldwide, which found no strong trends for changes in the prevalence of PC (2, 12). However, in Asia, unique observations were found. Yatani *et al.* compared the prevalence of latent PC from Japanese pathological autopsy cases between the periods 1965–1977 and 1982–1986, and found that the prevalence of PC increased from 22.5% to 34.6% between the two periods and that the number of pathologically aggressive tumor phe-

Table 1 Comparison of the prevalence of clinically significant latent prostate cancers (Gleason score > 6) in each cause of death between two study periods

	Present (2011–2014)	Previous (2002–2005)	<i>P</i> -value
Death due to			
disease	5.3%	5.1%	0.96
external causes	6.9%	7.0%	0.98

notypes also increased (21). A recent study suggested that the prevalence of latent PC is more frequent in pathological autopsy cases between 2008 and 2013 than in those between 1983 and 1987 (43.3% and 20.8%, respectively) (14). Diet and metabolic parameters are factors that have been previously discussed as influencing the prevalence of PC (9, 10, 18). In Japan, the Westernization of dietary habits has progressed remarkably over the last few decades (16). Therefore, as some reports suggest, the recent prevalence may be higher than in the 1960s to 1980s (14, 20). The difference between the previous and present results may be at least partly attributable to differences in the survey periods.

When considering recent trends in nourishment intake in Japan, values are almost constant or only slightly down on those seen between 2002 and 2011; with the average daily intake of carbohydrates going from 297.3 g to 281.6 g, protein going from 78.6 g to 73.2 g, lipids going from 58.7 g to 58.3 g, and sodium chloride going from 12.2 g to 10.9 g (16). Therefore, the similar prevalence of latent PC over the 10-year study period is well accordance with the constant or only slightly decreased nutritional trends in Japan over the same time. It is possible that some background characteristics of pathological autopsy subjects may have changed, *e.g.*, mean age, cause of death, and number of patients with cancer, and other studies using pathological autopsies to examine recent 10-year-trends are required to confirm the present results.

From current data and previous data, mean ages of the autopsied victims were 56 and 54 years, respectively, and overall prevalence of PC was 13.6% and 12.7%, respectively. In a study in which men had a median age of 63.2 years, PC was detected by biopsy in 24% (19). A comprehensive summary of 19 published studies found that PC was diagnosed at autopsy in Asia in 1.8% for 20–29 years; 0.9% for 30–39 years; 2.8% for 40–49 years; 7.9% for 50–59 years; 14.5% for 60–69 years; 21.3% for 70–79 years; and 28.9% for 80–89 years (12). Other autopsy studies have reported that the prevalence of

PC increases with each decade of age, and this increase is similar for all studies (1, 15). These results align with our current and previous data.

Clinically significant PC has been defined as a tumor with a Gleason score >6 . PC that does not meet this criterion are regarded as clinically insignificant and unlikely to adversely affect the health of the patient. In the current study, the prevalence of PC with a Gleason score >6 was 6.2%, which was similar to data from 10 years ago. This value increased to 7.5% if patients were aged 50 years or older. PC with a Gleason score >6 was 43.5% in all latent PC, which is in accordance with a recent pathological autopsy study that found that 24 of 55 (43.5%) latent PC patients had a Gleason score of 7 or higher (14).

Some points need to be kept in mind when comparing the prevalence of PC between our study and other studies. For example, the studies included in the meta-analyses performed full slicing of the prostate gland into thin sections (1, 12, 15). In the current study, the prostate was only cross sectioned into two pieces, which may result in our data underestimating the prevalence. Also, most studies in the meta-analyses did not include clinically diagnosed PC cases, and may mean that the data underestimate the true cumulative incidence of total PC (1). At the time of the pathological autopsy, many had been on medical interventions such as carcinostatics, were elderly at the time of death, or had cancers other than PC, all factors which might increase the prevalence of PC. We found that the prevalence of PC was similar in both men who died suddenly from disease and from external causes, indicating that the use of forensic autopsy specimens, including those of people who died suddenly from disease or from external causes, can be used to determine the prevalence of latent PC. It is suggested that, when comparing the prevalence of latent PC, using forensic autopsy data is suitable.

In this study, the postmortem duration was 2.3 days, longer than other pathological autopsy studies. Most forensic autopsies were performed on people who were found dead and, in some cases, people were found in places with a low temperature. Despite the long postmortem duration, we were able to evaluate microscopic changes of the prostate for some of those people who were found in cold temperatures. Cases were not chosen based on any limitations on postmortem duration. Pathologists determined, in a blind manner, whether microscopic observation was possible. Therefore, it is suggested that our method did not bias the results. It is considered that the most crucial possible limitation of the current study was

the sectioning of each prostate specimen into cross sections. Section thickness during prostate processing may have influenced the prevalence of PC. Furthermore, other pathologic information, *i.e.*, tumor volume and location, is lacking. However, as the objective of the study was to compare the prevalence of latent PC, and as this method was used for both current and previous comparison data, it is suggested that this method does not influence the results.

The prevalence of latent PC did not change significantly over the 10-year study period in this population of Japanese people. The dramatic increase in morbidity rate for PC is considered to be because of the increase in prostate-specific antigen screening and subsequent referral to urologists. As forensic autopsy specimens are suitable to determine latent PC, trends and racial and regional differences in latent PC should be examined in the future.

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CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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