Prostate Cancer and PSA Screening in Asia: Incidence, Mortality and Future Perspectives of an Ongoing Asian Screening Study

KAZUTO ITO

Department of Urology, Gunma University Graduate School of Medicine
Prostate Cancer and PSA Screening in Asia
: Incidence, Mortality and Future Perspectives of an Ongoing Asian Screening Study

- Epidemiology of prostate cancer (PC) in Asia
- Head to head comparison in the risk of developing PC between Japan and Europe
- Impact of exposure rate of PSA screening on incidence of metastatic PC
- Screening effects on PC death: Asian view
- Ongoing Asian screening study: JPSPC
Prostate Cancer and PSA Screening in Asia
: Incidence, Mortality and Future Perspectives of an Ongoing Asian Screening Study

- Epidemiology of prostate cancer (PC) in Asia
- Head to head comparison in the risk of developing PC between Japan and Europe
- Impact of exposure rate of PSA screening on incidence of metastatic PC
- Screening effects on PC death: Asian view
- Ongoing Asian screening study: JPSPC
International Comparison of Age-Standardized Incidence Rates of Prostate Cancer in Selected Registries, Males, 2000-2004
Trends in the incidence of PC in Japan

International Comparison of Age-Standardized Mortality Rates of Prostate Cancer in Selected Registries, Males, 2000-2006

Source: WHO Mortality Database  
*Average of rates for six or fewer years in the time period 2000-2006

Asian countries
Trends in the mortality of PC in Japan

Prostate cancer

39% decrease

Number of death due to PC per year
Comparison with corresponding population in the US and Japan

Jemal, Cancer Statistics, 2009
Vital statistics in Japan, 2012

Total population (x10,000)
No. of death due to PC

USA: 27,360
Japan: 11,600
Which nation has more advantages in terms of decreasing PC mortality; Comparing very important four factors

Diet issue: Asian countries > Europe > USA

Treatment issue: USA = Europe = Developed Asian countries

Genetic issue: Asians > Caucasian > African Americans

PSA screening: Americans >> Japanese
Prostate Cancer and PSA Screening in Asia
: Incidence, Mortality and Future Perspectives of an Ongoing Asian Screening Study

• Epidemiology of prostate cancer (PC) in Asia
• Head to head comparison in the risk of developing PC between Japan and Europe
• Impact of exposure rate of PSA screening on incidence of metastatic PC
• Screening effects on PC death: Asian view
• Ongoing Asian screening study: JPSPC
Prostate Carcinoma Detection and Increased Prostate-Specific Antigen Levels after 4 Years in Dutch and Japanese Males Who Had No Evidence of Disease at Initial Screening

Cancer 103: 242-250, 2005

Kazuto Itô, M.D., Ph.D.¹
René Raaijmakers, M.D.²
Monique Roobol²
Mark Wildhagen²
Hidetoshi Yamanaka, M.D., Ph.D.¹
Fritz H. Schröder, M.D., Ph.D.²

¹ Department of Urology, Gunma University Graduate School of Medicine, Maebashi, Japan.
² Department of Urology, Erasmus Medical Center, Rotterdam, The Netherlands.

BACKGROUND. In the current study, the authors set out to investigate the possibility that increased prostate-specific antigen (PSA) levels in Dutch and Japanese men without suspicious findings at initial prostate cancer screening were indicative of the risk of newly developing clinical malignancy in the Netherlands and Japan.

METHODS. Between 1992 and 2000, 2650 men ages 55–74 years who had PSA levels < 4.0 ng/mL and no suspicious findings on digital rectal examination were entered into the current study from a population-based prostate cancer screening cohort in Gunma Prefecture, Japan. In addition, between 1994 and 1997, 3163 men with the same clinical background were entered into the current study from the Rotterdam (Netherlands) Section of the European Randomized Study of Screening for Prostate Cancer (ERSPC). Prostate carcinoma incidence and the cumulative probability of freedom from PSA increases to levels > 2.0, 3.0, and 4.0 ng/mL, respectively, after
Cumulative rates of PSA increase to above 2.0, 3.0 and 4.0 ng/ml during 4 years of observation stratified by baseline PSA levels in Dutch and Japanese men.

<table>
<thead>
<tr>
<th>Baseline PSA</th>
<th>Race</th>
<th>Risk of increased PSA above</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>2.0 ng/ml</td>
</tr>
<tr>
<td>0.0-0.9 ng/ml</td>
<td>Dutch</td>
<td>2.4%</td>
</tr>
<tr>
<td></td>
<td>Japanese</td>
<td>2.7%</td>
</tr>
<tr>
<td>1.0-1.9 ng/ml</td>
<td>Dutch</td>
<td>32.8%</td>
</tr>
<tr>
<td></td>
<td>Japanese</td>
<td>27.6%</td>
</tr>
<tr>
<td>2.0-2.9 ng/ml</td>
<td>Dutch</td>
<td>51.9%</td>
</tr>
<tr>
<td></td>
<td>Japanese</td>
<td>45.7%</td>
</tr>
<tr>
<td>3.0-3.9 ng/ml</td>
<td>Dutch</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Japanese</td>
<td></td>
</tr>
</tbody>
</table>
CONCLUSIONS. The risk of developing prostate carcinoma within a given 4-year period is greater for Dutch males ages 55–69 years compared with their Japanese counterparts, because the former have higher PSA levels. Nonetheless, there appears to be no significant difference in prostate carcinoma risk between Dutch and Japanese males whose baseline PSA levels fall within the same range.

<table>
<thead>
<tr>
<th>Factor</th>
<th>Subdivided groups being compared</th>
<th>Regression coefficient</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>55–59 vs. 60–64 vs. 65–69 vs. 70–74</td>
<td>-0.001</td>
<td>0.986</td>
</tr>
<tr>
<td>Baseline PSA level (ng/mL)</td>
<td>0.0–0.9 vs. 1.0–1.9 vs. 2.0–2.9 vs. 3.0–3.9</td>
<td>1.595</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Region</td>
<td>Gunma vs. Rotterdam</td>
<td>-0.08</td>
<td>0.451</td>
</tr>
</tbody>
</table>

PSA: prostate-specific antigen.
Which is an ideal screening interval?
Which is an ideal screening interval?

- **Cancer onset**
- **Progression**
- **Clinically manifested cancer**
- **Screen-detectable cancer**

**ERSPC PROTOCOL**

**Every 4 years screening**
Which is an ideal screening interval?

<table>
<thead>
<tr>
<th>Baseline PSA</th>
<th>screening interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0-1.0 ng/ml</td>
<td>every 3 years</td>
</tr>
<tr>
<td>1.1 ng/ml-</td>
<td>yearly</td>
</tr>
</tbody>
</table>

Clinically manifested cancer

Screen-detectable cancer

JUA recommendation

Baseline PSA-adjusted screening interval

Cancer onset

Progression
Prostate Cancer and PSA Screening in Asia
Incidence, Mortality and Future Perspectives of an Ongoing Asian Screening Study

• Epidemiology of prostate cancer (PC) in Asia
• Head to head comparison in the risk of developing PC between Japan and Europe
• Impact of exposure rate of PSA screening on incidence of metastatic PC
• Screening effects on PC death: Asian view
• Ongoing Asian screening study: JPSPC
Impact of exposure rate of prostate specific antigen (PSA) screening on incidence of metastatic prostate cancer in Japan

Kazuto Ito, Takumi Yamamoto, Mai Miyakubo, Masaru Ohi, Hiroyuki Takechi, Kazuhiro Suzuki

Department of Urology, Gunma University Graduate School of Medicine, Japan

The annual meeting of the AUA in 2009

PATIENTS AND METHODS

Among 70 municipalities in Gunma Prefecture, 50 (71%) were enrolled in the present study.

The exposure rate of PSA screening between 1992 and 2004 was investigated in each municipality.

The clinical stage of prostate cancer registered in the cancer registry between 1992 and 2005 were also investigated in each municipality.

Then, 50 municipalities were divided into 3 groups according to the exposure rates of PSA screening; 1 to 20%, 21 to 30% and higher than 30%.

The relationship between the exposure rate of PSA screening and the changes in the age-adjusted incidence rate of metastatic PC was investigated.
Changes in the number of patients diagnosed with prostate cancer and the percentage of locally advanced/malignant prostate cancer

- No. of newly detected prostate cancer
- Percentage of locally advanced/metastatic PC
- Percentage of metastatic PC

Distribution of locally advanced and/or metastatic PC in Cancer registry (%)

- No. of PC detected in each calendar year
- Percentage of locally advanced/metastatic PC
- Percentage of metastatic PC
Changes in the age-adjusted incidence rate of metastatic prostate cancer, stratified by the exposure rate of population-based PSA screening

Exposure rate of PSA screening: 1-20%

Incidence rate of metastatic prostate cancer (per 100,000; world standardized population)

Calendar year
Changes in the age-adjusted incidence rate of metastatic prostate cancer, stratified by the exposure rate of population-based PSA screening

Exposure rate of PSA screening: 1-20%

Exposure rate of PSA screening: 21-30%

Incidence rate of metastatic prostate cancer (per 100,000; world standardized population)

Calendar year
Changes in the age-adjusted incidence rate of metastatic prostate cancer, stratified by the exposure rate of population-based PSA screening.
Prostate Cancer and PSA Screening in Asia
: Incidence, Mortality and Future Perspectives of an Ongoing Asian Screening Study

• Epidemiology of prostate cancer (PC) in Asia
• Head to head comparison in the risk of developing PC between Japan and Europe
• Impact of exposure rate of PSA screening on incidence of metastatic PC
• Screening effects on PC death: Asian view
• Ongoing Asian screening study: JPSPC
Editorial

Controversy over prostate-specific antigen screening has shifted from mortality to overtreatment issues

Kazuto Ito MD PhD
Department of Urology, Gunma University Graduate School of Medicine, Maebashi, Gunma, Japan
kzito@med.gunma-u.ac.jp
Japanese Urological Association guidelines on prostate-specific antigen-based screening for prostate cancer and the ongoing cluster cohort study in Japan

Kazuto Ito,1 Yoshiyuki Kakehi,2 Seiji Naito,3† Akihiko Okuyama4‡ and Japanese Urological Association5*

1Department of Urology, Gunma University Graduate School of Medicine, Gunma, 2Department of Urology, Kagawa University Graduate School of Medicine, Kagawa, 3Department of Urology, Kyushu University Graduate School of Medical Science, Fukuoka, 4Department of Urology, Osaka University Graduate School of Medicine, Osaka, and 5Japanese Urological Association, Tokyo, Japan

The exposure rate of screening for prostate cancer using prostate-specific antigen (PSA) in Japan is still very low compared with that in the USA or Western Europe. The mortality rate of prostate cancer will increase in the future and in 2020 it will be 2.8 times higher than in 2000. Therefore, there is an urgent need to determine the best available countermeasures to decrease the rate of prostate cancer death. PSA screening, which can reduce the risk of death as a result of prostate cancer, should be offered to all men at risk of developing prostate cancer with fact sheets showing updated benefits and drawbacks of screening for prostate cancer.

Updated Japanese Urological Association Guidelines on prostate-specific antigen-based screening for prostate cancer in 2010

The Committee for Establishment of the Guidelines on Screening for Prostate Cancer* and Japanese Urological Association

Abstract: The exposure rate of screening for prostate cancer using prostate-specific antigen (PSA) in Japan is still very low compared with that in the USA or western Europe. The mortality rate of prostate cancer will increase in the future and in 2020 it will be 2.8-fold higher than in 2000. Therefore, there is an urgent need to determine the best available countermeasures to decrease the rate of prostate cancer death. PSA screening, which can reduce the risk of death as a result of prostate cancer, should be offered to all men at risk of developing prostate cancer with fact sheets showing updated benefits and drawbacks of screening for prostate cancer.

Key words: prostate cancer, PSA, screening, guidelines.
The Japanese Urological Association (JUA) recommends prostate-specific antigen (PSA) screening, which can reduce the risk of death as a result of prostate cancer, for men at risk of prostate cancer.

The recommendation is based on fact sheets showing the benefits and drawbacks of screening for prostate cancer.

The JUA provides the best available screening system for men who want to be screened.
Mortality results from the Göteborg randomised population-based prostate-cancer screening trial

Jonas Hugosson, Sigrid Carlsson, Gunnar Aus, Svante Bergström, Ali Khataee, Pär Lodding, Carl-Gustaf Pihl, Johan Stranne, Erik Holmberg, Hans Lilja

Summary
Prostate cancer is one of the leading causes of death from malignant disease among men in the developed world. One strategy to decrease the risk of death from this disease is screening with prostate-specific antigen (PSA); however, the extent of benefit and harm with such screening is under continuous debate.

Methods
In December, 1994, 20000 men born between 1930 and 1944, randomly sampled from the population register, were randomised by computer in a 1:1 ratio to either a screening group invited for PSA testing every 2 years (n=10000) or to a control group not invited (n=10000). Men in the screening group were invited up to the upper age limit (median 69, range 67–71 years) and only men with raised PSA concentrations were offered additional tests such as digital rectal examination and prostate biopsies. The primary endpoint was prostate-cancer specific mortality, analysed according to the intention-to-screen principle. The study is ongoing, with men who have not reached the upper age limit invited for PSA testing. This is the first planned report on cumulative prostate-cancer incidence and mortality calculated up to Dec 31, 2008. This study is registered as an International Standard Randomised Controlled Trial ISRCTN54449243.
RE: Mortality Results From the Göteborg Randomised Population-Based Prostate-Cancer Screening Trial

Lancet Oncol 2010;11:725–32

Expert’s summary:
After 14 yr of median follow-up, the Göteborg randomized population-based study of screening for prostate cancer (PCa) demonstrated a significant mortality reduction of 44% in the screening group compared with the control group in the intention-to-screen analysis. This translated into a relative risk reduction of 56% for those men who were in fact screened after adjustment for noncompliance (25% in the screening group).

Kazuto Ito
Gunma University Graduate School of Medicine,
Department of Urology, Maebashi, Gunma, Japan
E-mail address: kzito@med.gunma-u.ac.jp
Prostate-specific antigen testing in Tyrol, Austria: prostate cancer mortality reduction was supported by an update with mortality data up to 2008

Willi Oberaigner · Uwe Siebert · Wolfgang Horninger · Helmut Klocker · Jasmin Bektic · Georg Schäfer · Ferdinand Frauscher · Harald Schennach · Georg Bartsch

64% decrease in the mortality due to PC

Fig. 1 Prostate cancer mortality: age-standardized rate in Tyrol and in Austria excluding Tyrol for years of death 1970–2008 (vertical line is end of previous publication)
CONCLUSIONS

Analyses after 2 additional years of follow-up consolidated our previous finding that PSA-based screening significantly reduced mortality from prostate cancer but did not affect all-cause mortality. (Current Controlled Trials number, ISRCTN49127736.)
RE; Prostate-Cancer Mortality at 11 Years of Follow-up.
(N Engl J Med 366; 11)

#1 The initial exposure of PSA screening in men aged 55-69 years may relate with high likelihood of delay to detect potentially lethal prostate cancer (PC) because 74% PC death were in cancers diagnosed at the first screening round.

#2 A significant (38%) decrease in PC death at 11 and 12 years was found indicating that long-term PSA screening exposure in the community may substantially decrease life-time risk of PC death.

#3 Although, all-cause mortality was identical between two arms, any screening or definitive treatment intervention would not significantly affect it. PC death could be the defined endpoint. Progress in effective primary prevention and substantial number of medical interventions, intelligent use of PSA could be at least one of them, can significantly prolong life-expectancy.
Prostate Cancer and PSA Screening in Asia

: Incidence, Mortality and Future Perspectives of an Ongoing Asian Screening Study

- Epidemiology of prostate cancer (PC) in Asia
- Head to head comparison in the risk of developing PC between Japan and Europe
- Impact of exposure rate of PSA screening on incidence of metastatic PC
- Screening effects on PC death: Asian view
- Ongoing Asian screening study: JPSPC
Japanese Prospective Cohort Study of Screening for Prostate Cancer (JPSPC): The Study Concept and the First Analyses on Compliance and Contamination for the PSA test.

Kazuto ITO, M.D., Ph.D.
Associate Professor, Department of Urology
Gunma University Graduate School of Medicine
Study concept of JPSPC

● JPSPS is prospective cluster cohort study, which compare the changes in the age-adjusted mortality rate of prostate cancer between screening cohort and the control cohort.

● The total population of men aged 50 to 79 years old in the screening cohort is almost 100,000.

● The exposure rate of PSA screening in the screening cohorts during 5 years would be over 60% in all inhabitant aged between 50 and 79 years.

● The municipalities in the control cohort were selected from the same province and from municipalities including the same number of men aged 50 to 79 years old.
Changes in the cumulative number of men screened in the Screening Cohort (Iseasaki city): tentative

The number of men aged 50 to 79 years in Iseasaki city

Exposure Rate: 53.7%
Changes in the cumulative number of men screened in the Control Cohort (Kiryu city)

- The number of men aged 50 to 79 years in Kiryu city:
  - Exposure Rate: 13.1%
JPSPC (screening cohort)

Male inhabitants aged 50-79

Men participated in the screening program

Men with abnormal PSA and proceeded to Urologic clinics

Men biopsied

Patients diagnosed with PC

Men dead due to PC
Conclusion and Future perspectives on JPSPC

JPSPC has been successfully done in terms of compliance and contamination for the PSA test in the screening and control cohort, respectively.

The first analysis on the changes in the mortality rate of prostate cancer will be carried out at around 2013.

ICER (incremental cost-effectiveness ratio) is also investigated using JPSPC datasets.
Prostate Cancer and PSA Screening in Asia: Incidence, Mortality and Future Perspectives of an Ongoing Asian Screening Study

KAZUTO ITO

Department of Urology, Gunma University Graduate School of Medicine