Aim of the Working Group on the Asian Perspectives on Cancer Control: Asian Perspective on Prostate Cancer Prevention

Hideyuki Akaza*

Department of Strategic Investigation on Comprehensive Cancer Network Research Center for Advanced Science and Technology, The University of Tokyo, Tokyo, Japan

*For reprints and all correspondence: Hideyuki Akaza, Department of Strategic Investigation on Comprehensive Cancer Network Research Center for Advanced Science and Technology, The University of Tokyo, Tokyo, Japan. E-mail: akazah@med.rcast.u-tokyo.ac.jp

Although cancer is expected to become more serious in middle- and low-income countries, it has not attracted sufficient global attention, and those countries cannot afford and benefit from new technologies. The previous 19 APCC meetings, held in various Asian countries, provided a podium for presentation of technical papers, promoted cancer science and established good relationships. Future APCC goals should be to achieve visible improvements in cancer medicine and solve Asian scientific problems. During the 20th APCC in Tsukuba, Japan, it is focused on Asian consensus statements produced by Working Groups for each organ cancer showing different morbidity and mortality between the Asia-Pacific and Western regions. Each Working Group spent a year preparing for this conference by analyzing contributing factor(s) and writing a consensus statement of a strategy for improving morbidity and mortality.

Key words: cancer prevention — prostate cancer

INTRODUCTION

Research experience with prostate cancer, which shows a very different incidence and mortality between Western and Asian countries, represents a good example of one approach to finding a solution and reducing the morbidity and mortality of cancer. Population-based prevention is another approach, and Asians’ special diet, especially soybean-based foods, appears to play a very important role. This and similar investigations of other diet-cancer relationships have great potential for reducing cancer morbidity and mortality in the world.

A ‘PRODUCTIVE RELATIONSHIP’ BETWEEN EPIDEMIOLOGISTS AND CLINICIANS

Cancer is expected to become more serious in middle- and low-income countries; yet, it has not attracted sufficient global attention. New, effective techniques for diagnosis and treatment, including anti-cancer agents, are rapidly coming online around the world. However, only a small percentage of the populations of low-income countries can afford them and benefit from them. A ‘productive relationship’ between epidemiologists and clinicians that contributes to improving the results of clinical cancer medicine has not yet been established. The previous 19 APCC meetings were held in various Asian countries as APFOCC activities. The APCC is supported by UICC-Japan and also by UICCARO, in spirit. The APCC meetings have provided a podium for presentation of technical papers from various Asian countries, promoted cancer science mainly in the form of epidemiological studies and established good relationships and friendships among researchers.

The next goals for the APCC should be to achieve visible improvements in cancer medicine and to try to solve the scientific problems that arise in each Asian country.

PATIENTS AND METHODS

The steps to achieving these goals will be to summarize the problems, analyze the causes of the problems, seek...
resolutions, offer opinions for resolution of problems facing the world and continue the PDCA cycle of Plan, Do, Check again and Action.

For this APCC, we decided that we would focus on Asian consensus statements produced by the Working Groups for each organ cancer. That is, a working group was organized for each cancer whose morbidity and mortality differ between the Asia-Pacific and Western regions. Each working group was charged with analyzing the contributing factor(s) epidemiologically, scientifically and clinically. Then, each working group was to summarize, as a consensus statement, a strategy for improving the morbidity and mortality. For this 20th APCC, working groups were organized for lung cancer, hepatic cancer, gastric cancer, colon cancer, breast cancer, uterine cervical cancer, kidney cancer, bladder cancer and prostate cancer. In addition, we organized working groups for epidemiology and clinical trials in Asia.

The procedure for arriving at each working group consensus statement was as follows. The first step was preparation of Position Papers by discussion via E-mail, etc., before this APCC. The working group members had to work very hard before this Conference could be held. They summarized the epidemiological background (comparing Asia and the West), investigated the involved factors, discussed possible countermeasures and also the feasibility of clinical application, and summarized the future prospects. They then prepared the Working Group Consensus Statement in their Working Group meeting there, during the 20th conference. Each Working Group has presented its Working Group Consensus Statement in the plenary session, thereby establishing the APCC Consensus. A goal for next year is to publish the Working Group Consensus Statements. This work will be continuously advanced through periodic meetings.

**PROSTATE CANCER**

This President’s statement focuses on prostate cancer, which we all know shows a very different incidence (Fig. 1) and mortality between Western and Asian countries. Research experience with prostate cancer represents a good example of one approach to finding a solution and reducing the morbidity and mortality of cancer.

Five-$\alpha$-reductase is an enzyme that converts testosterone to dihydrotestosterone (DHT). DHT is the most potent androgen in promoting prostate cancer. Five-$\alpha$-reductase inhibitors are the only drugs that have been successful in large-scale, randomized, double-blind, placebo-controlled trials on the chemoprevention of prostate cancer. Five-$\alpha$-reductase plays a very important role in the action of androgens on prostate cells. Prostate cancer cells have receptors for 5-$\alpha$-reductase, which are known as type 1 and type 2 receptors. Especially, type 1 receptors are found in prostate cancer tissues.

To date, two very big, prospective prostate cancer prevention trials have been carried out. One of them was the PCPT trial (1), which was started in 1993 and finalized several years ago. This double-blind, placebo-controlled trial enrolled 18,000 low-risk subjects, who were followed up for 7 years and then underwent prostate biopsy. Compared with the placebo, finasteride, which is a 5-$\alpha$-reductase inhibitor, clearly showed a decrease in the probability of prostate cancer.

The second clinical study was the REDUCE trial (2), a very large global study. This trial was just finished earlier in 2009, and it included countries from almost all over the world, including Japan. The active drug in this study was dutasteride, which is an inhibitor of type 1 and type 2 5-$\alpha$-reductase receptors. The design of this study was unique, in that it enrolled men at increased risk of prostate cancer.
cancer. They were 50–75 years of age, had a prostate-specific antigen (PSA) value in the so-called gray zone of 2.5–10 ng/ml and had undergone a single, negative biopsy within 6 months before enrollment. The observation period was 4 years, and the subjects underwent a 10-core biopsy twice, at 2 and 4 years. There were two arms, each containing 4000 subjects, for a total of 8000. The baseline demographic data show that the men were at high risk, with a mean total PSA value of almost 6 ng/ml. The results showed a prostate cancer reduction rate of 23.5% in the dutasteride group, or almost 25% reduction, in this well-controlled study. The study group is now performing more-detailed analyses of the data, and the results should be available soon.

Thus, those two clinical studies demonstrated successful chemoprevention of prostate cancer by using 5-alpha-reductase inhibitors. However, if such drugs are to be used clinically, there are still various questions and problems remaining, such as who should receive them? When should treatment be started and when stopped? How can the cost be managed?

An alternative approach to prevention of prostate cancer is population-based prevention. It is very important to improve the lifestyle, such as the diet. The prostate cancer incidence is highest in the USA and very much lower in Asia. Why? This is an important point to investigate and discuss so that the incidence of prostate cancer can be decreased all over the world.

Data from Hawaii are very interesting. The incidence of stomach cancer is high in Japanese living in Japan, but it decreases with each generation of Japanese immigrants to Hawaii. The opposite trends are seen with each of breast, prostate and colon cancer; they are each low in incidence in Japanese living in Japan, but increased in Japanese immigrants to Hawaii. These data indicate that some changes in the incidences of certain cancers are not related to genetic factors and are more related to lifestyle factors, probably mostly diet.

The data on the age-adjusted prostate cancer mortality rates are very interesting. Although the incidence in Japan is still lower, it is increasing more rapidly than in Western countries. Why are Japanese men showing this rapid increase in prostate cancer mortality? This is also an important point to consider. And why not transfer the reasons for the very low incidence of prostate cancer in Japan to high-incidence countries to reduce their incidence? Asians’ special diet appears to play a very important role, especially soybean-based foods. Various Asian countries, not only Japan, but also China, Korea and Indonesia, consume a variety of soy-based foods. Hong Kong, Japan, Korea, Singapore and Thailand have very low prostate cancer mortality rates compared with Australia, Austria, Canada, France, Italy and the USA. The difference in the prostate cancer mortality rates is very large. Conversely, those Asian countries consume a lot of soy energy, whereas the Western countries with high prostate cancer mortality do not eat soy foods at all. These differences are striking (Fig. 2).

Moreover, various cohort and case-controlled epidemiological studies on soy consumption and prostate cancer have been conducted. The data clearly show that the cohort consuming a higher amount of soy foods, including soymilk, soy products, tofu or genistein, which is an isoflavone and a key ingredient of soy foods, had lower odds ratios for prostate cancer (Fig. 3). Soy isoflavones include genistein, daidzein and equol, although the latter does not naturally exist in soy. Equol is a metabolite of daidzein, due to the action of some kind of intestinal bacteria. A daidzein-equol-metabolizing bacterial strain was isolated from the human normal intestinal flora. It was named NATTS (Fig. 3).

<table>
<thead>
<tr>
<th>Country</th>
<th>PC mortality</th>
<th>Total energy</th>
<th>Fish energy</th>
<th>Soy energy</th>
<th>Animal energy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australia</td>
<td>29.59</td>
<td>3055</td>
<td>22</td>
<td>0</td>
<td>1019</td>
</tr>
<tr>
<td>Austria</td>
<td>31.23</td>
<td>3575</td>
<td>15</td>
<td>0</td>
<td>1233</td>
</tr>
<tr>
<td>Canada</td>
<td>29.20</td>
<td>3340</td>
<td>29</td>
<td>0</td>
<td>1297</td>
</tr>
<tr>
<td>France</td>
<td>31.43</td>
<td>3294</td>
<td>34</td>
<td>0</td>
<td>1343</td>
</tr>
<tr>
<td>Italy</td>
<td>22.57</td>
<td>3668</td>
<td>25</td>
<td>0</td>
<td>913</td>
</tr>
<tr>
<td>US</td>
<td>32.19</td>
<td>3364</td>
<td>23</td>
<td>1</td>
<td>1316</td>
</tr>
<tr>
<td>Hong Kong</td>
<td>5.44</td>
<td>2771</td>
<td>89</td>
<td>36</td>
<td>834</td>
</tr>
<tr>
<td>Japan</td>
<td>5.87</td>
<td>2852</td>
<td>195</td>
<td>93</td>
<td>590</td>
</tr>
<tr>
<td>Korea</td>
<td>0.90</td>
<td>3056</td>
<td>67</td>
<td>94</td>
<td>269</td>
</tr>
<tr>
<td>Singapore</td>
<td>7.47</td>
<td>3165</td>
<td>63</td>
<td>29</td>
<td>689</td>
</tr>
<tr>
<td>Thailand</td>
<td>0.53</td>
<td>2330</td>
<td>37</td>
<td>18</td>
<td>152</td>
</tr>
</tbody>
</table>

Figure 2. Prostate cancer and amount of soy food consumption. PC, prostate cancer.
Equol has specific binding ability with DHT and acts as a novel anti-androgen.

The two successful, large-scale, randomized trials described earlier both studied 5-α-reductase inhibitors. It can be surmised that equol should show the same effects as the 5-α-reductase inhibitors because it has binding ability with DHT and reduces its activity, as a result of which equol may show natural DHT inhibitory activity. Accordingly, isoflavone was administered at 60 mg/day to normal adults, and the change in their serum 5-α-DHT was monitored. The serum 5-α-DHT level was decreased by that 60 mg/day dose of isoflavone, which is not a really large amount and can usually be obtained by eating tofu or other soy foods (4).

In addition, our study demonstrated that equol producer who has a capability to metabolite daidzein into equol has a lower incidence of prostate cancer (5) (Fig. 4).

Next, a clinical study was conducted to investigate the influence of isoflavone intake and equol production on the risk of prostate cancer. This was like a Phase II clinical trial, and it was designed as a double-blind, placebo-controlled study. The study population was similar to that in the REDUCE study: a PSA gray zone and biopsy-negative, and age 50–75 years. The observation period was only 1 year, after which prostate biopsy was performed to determine the incidence of prostate cancer. The tentative results for subjects 65 years of age and above show a statistically significant reduction in prostate
cancer in the isoflavone group compared with the placebo, although the number of subjects was not large.

In conclusion, first, epidemiological studies are very important and need to be performed. Then comes elucidation of the risk factors, followed by basic studies of cancer prevention and feasibility studies, Phase II studies, such as that for isoflavone/equol. Education of the public, publishing of findings and, if possible, generation of evidence by Phase III studies would be needed. Also, if we could find a chemopreventive material such as equol, industrialization should be carried out in cooperation with a pharmaceutical or other company and may contribute to decreasing the incidence and mortality of cancer in the world (Fig. 5).

Funding
The study is partly supported by Grant-in-Aid for Scientific Research on Priority Areas, Cancer, from the Ministry of Education, Science, Sports, and Culture, Japan.

Conflict of interest statement
None declared.

References