

The Breast Cancer Working Group Presentation was Divided into Three Sections: The Epidemiology, Pathology and Treatment of Breast Cancer

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Epidemiology of breast cancer: The incidence and mortality of breast cancer are lower in Asia than in the West, particularly in post-menopausal women, but they are increasing. The age patterns of the incidence of breast cancer in Asia differ from in the West: in most Asian countries the peak incidence of breast cancer is at about age 45–50, whereas in western countries the incidence continues to increase even at older ages. Mortality is decreasing in western countries, whereas it is still increasing in Asian nations. There are many epidemiological factors involved in breast cancer, and important known risk factors include diet, obesity and diabetes. Asian studies found that high intake of isoflavones reduced the risk of breast cancer. Pathology of breast cancer: With regard to the pathology of breast cancer, for the molecular subtype, luminal A and luminal B are being used, while HER2 expression and rapid proliferation are also employed. Study results showed a somewhat higher prevalence of luminal A in Japanese compared with Americans. Ductal carcinoma *in situ* breast cancer is less frequent in Asian breast cancer patients than in Americans. The Working Group resolved to establish an international committee for pathological assessment of breast cancer in Asia. **Treatment of Breast Cancer:** Pharmacokinetics–pharmacodynamics studies are needed between ethnic backgrounds, investigating aromatase inhibitors and tamoxifen (endoxifen), as well as the effects of demographic factors such as diet, medical care, body mass index, etc. Correlations between adverse events and the clinical outcome also need to be studied.

Key words: breast cancer – epidemiology – hormone receptor – aromatase – HER2

EPIDEMIOLOGY

The incidence of breast cancer is increasing rapidly in most Asian countries. There is still a typical pattern for the incidence, which is age-specific and remarkably different from in western women. However, an important issue is how the incidence will change in the next 20 years. In most Asian countries, including Singapore, Japan, India, Korea, China and

Thailand, but not in the Philippines, the peak incidence of breast cancer is at about age 45–50 (Fig. 1). In Western countries, the pattern shows a continuous increase in the incidence, even at older ages. There are minor differences among Asian nations, with a bell-shaped pattern in Japan, China, Korea, etc., but a flatter pattern after the peak in the Philippines and Singapore. In Japan, comparison of the incidence of breast

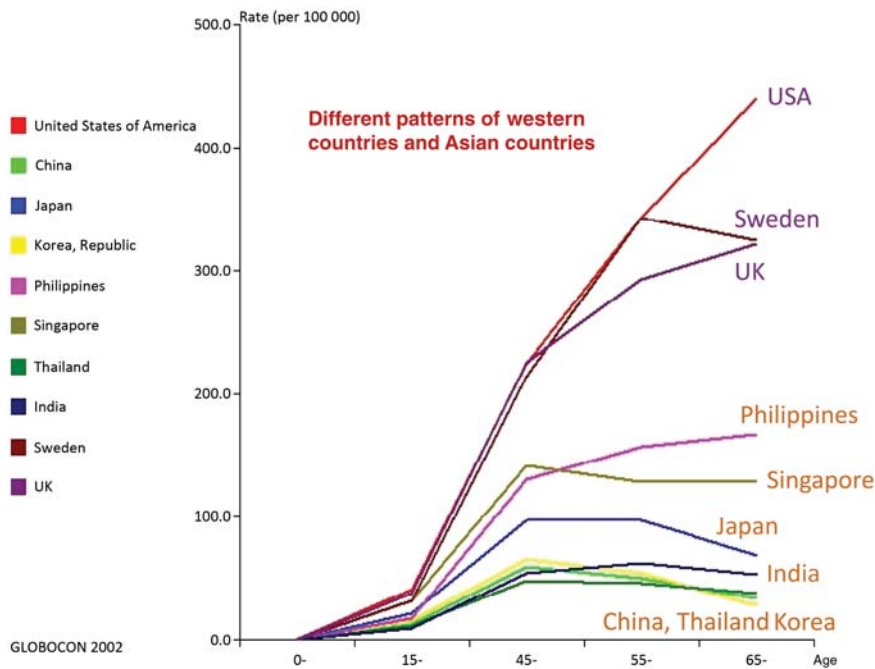


Figure 1. Age-specific incidence rate for breast cancer.

cancer over the last 25 years shows that the peak age remains the same, at ~50 years of age, but the number of cases has increased in each 10-year survey period. In Korea, as well, the same pattern as seen in Japan has prevailed, with the peak age for occurrence of breast cancer at about 50, and the number of patients has continued to increase with time between 1996 and 2006. Data for Malaysia investigated the three ethnic groups of Malay, Indian and Chinese. The results showed that the pattern was similar in the three groups, with decreasing incidence in post-menopausal women (1).

A comparison was made of the age-specific breast cancer incidence rates in Sweden and Singapore at 5-year intervals from 1968 through 1993. The incidence in Sweden continued to increase even after menopause, whereas the incidence in Singapore peaked at ~50 years of age and then plateaued. Also, although Singapore maintained the same age-related pattern over the years, the number of cases increased a bit (2). In Singapore, they also looked at the age-specific incidence of breast cancer by birth cohort, and the results suggested that breast cancer may be associated with some event at a younger age (3). This may be important with regard to the incidence of breast cancer in Asia. There is a need to focus on what factors are important in order to change the incidence of breast cancer in the future.

The mortality of breast cancer is decreasing in many western countries such as the USA and UK, whereas it is still increasing in Japan.

In conclusion, the incidence and mortality of breast cancer are lower in Asia than in the West, particularly in post-menopausal women, but they are increasing. The age patterns of the incidence of breast cancer in Asia differ from those in the West.

There are many epidemiological factors involved in breast cancer, and important known risk factors include diet, obesity and diabetes. Passive smoking may be important in the development of breast cancer, and this issue requires more investigation (4). The body mass index (BMI), as well, is a very important factor in the incidence of breast cancer, and perhaps in mortality. In premenopausal Asian and Pacific women, the relative risk of breast cancer per 5 kg/m² was reported to be 1.16, whereas it was 1.31 in post-menopausal women, indicating that the BMI might be a risk factor in Asian women (5).

Soybeans, which contain isoflavones, have been studied both in the West and Asia. An important point is the daily dose of isoflavones that is ingested. The Western studies revealed a high dose of ~0.8 mg/day vs. a low dose of ~0.15 mg/day, whereas the Asian studies revealed doses over the range of 5–20 mg per day, or more than 20 times higher. A clear difference was not shown in the Western studies, but the Asian studies showed that high intake of isoflavones reduced the risk of breast cancer (6). Isoflavones thus inhibit the development of breast cancer (Table 1).

With regard to diabetes and breast cancer, a controversial issue, first reported by a German group, is whether insulin administration promotes the development of breast cancer. Various other groups issued follow-up reports, regarding both insulin and antidiabetic therapy (7). Metformin, a drug that is administered to control diabetes, was reported to result in a higher pathologic complete response rate to neoadjuvant chemotherapy compared with a non-metformin group and a non-diabetic group (8). It is known from pharmacologic studies that metformin modulates the metabolism of the M2 pathway, and that may

Table 1. Soy beans: isoflavone

| Description | No. of studies | Odds ratio | 95% confidence interval |
|---|----------------|------------|-------------------------|
| Western study | | | |
| Highest (~0.8 mg or more isoflavone per day) vs. lowest (~0.15 mg or less isoflavone per day) | | | |
| All | | 11 | 1.04 (0.97–1.11) |
| Cohort/nested case–control | | 4 | 1.08 (0.95–1.24) |
| Case–control studies | | 7 | 1.02 (0.95–1.11) |
| Asian study | | | |
| Highest (~20 mg or more isoflavone per day) vs. lowest (~5 mg or less isoflavone per day) | | | |
| All studies | 8 | | 0.71 (0.60–0.85) |
| All studies in | 7 | | 0.73 (0.61–0.89) |
| Asia | | | |
| Case–control studies | 7 | | 0.75 (0.62–0.89) |
| Premenopausal women | 6 | | 0.65 (0.50–0.85) |
| Post-menopausal women | 6 | | 0.63 (0.46–0.85) |
| Moderate (~10 mg isoflavone per day) vs. lowest (~5 mg isoflavone or less per day) | | | |
| All studies | 8 | | 0.88 (0.78–0.98) |

Adapted from Wu et al. (6).

result in improving the chance of a complete response to chemotherapy.

The Working Group discussions regarding the epidemiology of breast cancer concluded that (i) the changes in the incidence and mortality of breast cancer in Asia may be due mainly to lifestyle changes; (ii) a prevention (lifestyle modification and screening) strategy should be planned and implemented based on evaluation of its impact and (iii) a database including a cancer registry should be established for identification and evaluation of new risk factors.

The Working Group members also completed a questionnaire regarding various issues relating to breast cancer in each of their Asian homelands. With regard to the anticipated age-specific incidence pattern in the next 20 years, more than half of the members thought that the pattern would be between the current Asian and Western patterns, perhaps similar to that seen in Singapore. About 90% of the members thought that diet is important, with ~45% thinking it very important. There was an opinion that the diet before 20 years of age might be most important. A solid majority of ~60% also thought that passive smoking is probably important to breast cancer development. The importance of exercise was also discussed, and it was concluded that

studies are needed to investigate the amount of exercise, timing and energy balance. Other factors that were debated included type II diabetes, which was thought to be important by all, and very important by 50% of the members. Diabetes will be an important issue in the future of breast cancer. Nearly 90% of the members thought that insulin treatment is probably important, but this thus remains a questionable issue. Metformin is a pharmacological issue and also remains controversial, and over 30% of the members felt a need for a clinical trial in the near future to elucidate this issue, whereas the remaining members believe there is a need for more information.

PATHOLOGY

With regard to the pathology of breast cancer in relation to the biological behavior and therapeutic regimen, the intrinsic subtype classification according to the molecular concept had been the topic that attracted attention the most. Luminal type, which indicates hormone receptor positive, is subdivided into luminal A and luminal B. HER2 (erbB-2) type is hormone receptors [both estrogen receptor (ER) and

progesterone] negative. Triple-negative tumors are all negative for ER, progesterone receptor (PR) and HER2, and many of them express basal-like features [i.e. CK5 and/or epidermal growth factor receptor (EGFR) positive]. All participants agreed to use CK5/6 and/or EGFR for this differential diagnosis. Other markers such as androgen receptor should be investigated in further depth.

The proportion of these intrinsic subtypes among breast cancer cases was assessed by some participants. Data from Malaysia showed that the proportions of ER and/or PR positive cases in Malaysians were quite similar to those among Black Americans, and lower than in White Americans. However, a report from Japan compared the prevalence of the breast cancer subtypes in Japanese, African Americans and non-African Americans (Table 2). These results as well as the subsequent discussion suggested that the proportion of various intrinsic subtypes may be different among the different races or countries. The prevalence of luminal A subtype may be higher, and the triple negative subtype may be lower in Asian women; especially the prevalence of triple-negative may be relatively low among Japanese patients with breast carcinoma, but this may require further investigations to clarify whether the same criteria of determining ER or PR positivity was employed in these cases or not as discussed below. The investigation of the Asian whole will be expected in the future.

Although it is considerable that there were some biological variations among different ethnic groups, there are still some problems according to the staining methodology and even technology. For example, even the cut-off line of ER positivity has not been the same among different countries in Asia, even though each participant noticed that the cut-off line of hormone receptor immunostainings had been changed at the St Gallen consensus conference in 2009. The 1% rule had been employed in Philippines on the basis of the guideline; in Malaysia, the line had changed from 10 to 1% recently. However, there are some controversies and each institute deals separately with this issue in Korea and in Japan (Table 2).

It is necessary to clarify clinicopathologic significance of basal-like breast carcinomas. There was no consensus of distinct basal cell markers, but all participants agreed to use CK5/6 and/or EGFR for this differential diagnosis. In Hong Kong, they are routinely stained in some centers, but in other countries they may still be considered a mere academic exercise. Unfortunately, no specified medications have been discovered for CK5/6 or EGFR positive carcinomas.

One of the new methods is to use Ki-67 (MIB-1) immunostains for ER-positive/HER2-negative (namely luminal A type) carcinomas to decide the indication for adjuvant chemotherapy. It is routinely stained for invasive breast carcinomas in Hong Kong, but it is not widely used in each case in other countries. Finally, the incidence of ductal carcinoma *in situ* (DCIS) in Asian women is still rare among Asian women.

Table 2. Pathology

| | Japan | Philippines | Malaysia | Singapore | Hong Kong | Korea |
|------------------------------|----------------------|-----------------------|---------------------------------------|-----------|--|---------------------------------|
| ER cut-off | 1% or 10% | 1% by guideline | 10% previously, 1% since 2009 | | Clinically 1%, 10% for research | Clinically 1%, 10% for research |
| Basal marker | Research purpose | | CK5/6 and EGFR, not in daily practice | | Need good evidence, Routine in some centers | Research purpose |
| Ki67 | Depends on institute | Not in daily practice | Not in daily practice | | Routinely | Routinely |
| Micro-metastasis | | | | | No unique Asian data available | |
| Other issues to be discussed | | | | | Androgen receptor, molecular markers of DCIS | |

EGFR, epidermal growth factor receptor; DCIS, ductal carcinoma *in situ*.

In conclusion, three major issues have been discussed, comprising of the biology, the methodology and the quality of assessment. The Working Group, on the basis of the discussions, decided to establish an international committee for pathological assessment, with registration of the assay methodology for ER, HER2, basal-like markers, etc., performance of quality assurance, preferably externally and collaboration on epidemiological studies.

Yet another issue is mass screening mammography. In Hong Kong, this diagnostic technique was not very popular, and one Working Group member, Dr Chow, conducted a questionnaire survey of the knowledge, perceptions and attitudes of women to determine why. The major reasons cited were a lack of time and the cost. Insufficient knowledge regarding the procedure was another prime reason, with many women being unsure of the benefit. Thus, more comprehensive thinking is needed with regard to mammography, especially concerning the cost, i.e. who will pay, and how to promote this diagnostic procedure. Problems associated with breast screening in Asia include the younger incidence of breast cancer in Asia compared with the West, dense breasts in the younger generation, and a lack of evidence for mammographic screening in the younger generation or a screening program for Asian females. Moreover, a good education program is needed.

TREATMENT

The metabolic pathway of tamoxifen leads to endoxifen, which is more than 100 times more potent than the parent molecule (tamoxifen). The important enzyme in this metabolism is CYP2D6, which carries out the conversion from the relatively inactive molecule (tamoxifen) to the more active molecule (endoxifen) (9). Ethnic differences are seen in the distribution of the alleles of *CYP2D6*, and the inactive *4 allele is relatively common in Caucasians but rare in Asians. The *10 allele, with reduced activity, is more common in Asians, and rare in Caucasians (10). The inhibitor of CYP2D6, paroxetine, suppresses the endoxifen level almost to that with the *4 homozygote (9). It is necessary to take into account the genotype and external factors, and their combinations can make it possible to predict the clinical outcome of breast cancer (Fig. 2).

A questionnaire survey was conducted of the Working Group members from Korea, Hong Kong, Singapore, Malaysia, the Philippines and Japan, who were mostly breast surgeons. Case scenarios were presented regarding pharmacogenetics. The scenario, for hypothetical Country X, consisted of the use of a cytotoxic drug, A, that is inactivated by enzyme B, which can be detected in the population by *single-nucleotide polymorphisms* (SNPs). The population ratio of normal- to poor-metabolizers in Country X was 7–3. The scenario postulated that 100 mg was the recommended dose of drug A for normal metabolizers, whereas 50 mg would be ineffective. For poor metabolizers, the

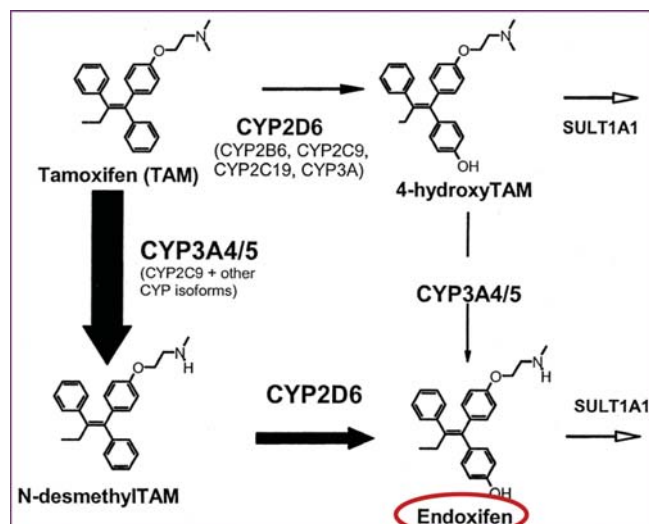


Figure 2. Tamoxifen and its active metabolites. Adapted from Jin et al. (9).

recommended dose was 50 mg, while 100 mg would be too toxic. The surveyed members were asked, ‘In this situation, what would you recommend as the drug A dose?’ Most of the members recommended PGx-based dosing, and otherwise recommended pharmacokinetics (PK)-based dosing followed by 100 mg in all patients. For hypothetical Country Y, the scenario postulated the reverse population ratio for normal- to poor-metabolizers, i.e. 3–7. Again, the scenario postulated that 100 mg was the recommended dose of the drug for normal metabolizers, while 50 mg was ineffective. For poor metabolizers, the recommended dose was postulated to be 50 mg, while 100 mg would be too toxic. The most common response of the surveyed members again was that the dose should be PGx based, followed by PK-based and then 50 mg with intra-patient dose escalation. As the third scenario, in hypothetical Country Z, the assumptions were similar to those in Country X with regard to the population ratio of normal- to poor-metabolizers (7:3) as well as the recommended dose (50 mg) and toxicity (100 mg) of drug A. However, for Country Z, it was postulated that a herb that is commonly prescribed actually inhibits drug metabolism by enzyme B. To the question ‘What dose of drug A would you recommend?’ the members’ recommendation was ‘No allowance for tea intake’. Also, it was felt that the package insert should probably mention about this herb–drug interaction. PK-based dosing was the second most common answer.

Southeast and East Asian countries share similar ethnic backgrounds but have different external factors, including the diet, medical practice, culture, etc. In this reality, ‘What is needed to decide the recommended dose?’ One-third of the surveyed Study Group members thought that the same recommended dose should be used across Asia, which would mean performing limited number of Phase I clinical trial within Asia. Another third thought that each country should conduct a separate Phase I clinical trial, and another third

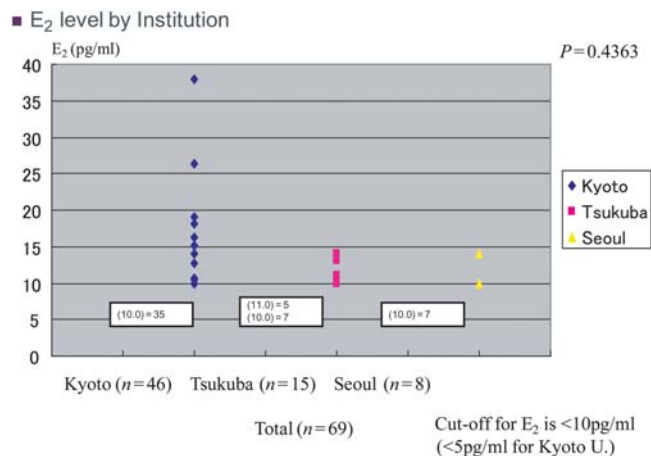


Figure 3. Inter-ethnic variation in the pharmacodynamic parameters of aromatase inhibitors.

thought the recommended dose should be decided by a PK- [or pharmacodynamics- (PD)] based approach.

Aromatase is a major source of estradiol (E₂) in post-menopausal women. Compared with without treatment, aromatase inhibitor (letrozole or anastrozole) administration suppressed the plasma E₂ level to a non-detectable level (11). In one patient, despite anastrozole being taken only every 3 or 4 days due to hot flashes, the plasma E₂ level was sufficiently suppressed, whereas in another patient who took letrozole daily the plasma E₂ level was not suppressed at all. On the basis of those observations, a study was conducted regarding ethnic variation in the pharmacodynamic parameters of aromatase inhibitors in post-menopausal patients in Kyoto, Tsukuba and Seoul. Even within the two Japanese populations, a regional difference was found for the E₂ level, which was not suppressed in many Kyoto patients, although statistically not significant due to the small sample size (Fig. 3). The reason for this is unclear. There seemed to be also differences in terms of the toxicity (hot flashes, sweating, and joint pain) relative to the E₂ level (20th Asia Pacific Cancer Conference, P-3, 2009 presented by Ishiguro H).

A proposal was made for future prospective studies. A pharmacogenomics study between ethnic backgrounds is needed, looking at differences in SNPs for CYP genes

(2D6, 19) and estrogen-metabolizing enzyme genes (UGT, etc.). PK–PD studies are needed between ethnic backgrounds, investigating aromatase inhibitors and tamoxifen (endoxifen), as well as the effects of demographic factors such as diet, concomitant medications, BMI, etc. Correlations with the clinical outcome also need to be studied with regard to adverse events (hot flashes, sweating, and joint pain) and the efficacy endpoints.

Conflict of interest statement

The author, Yasuo Ohashi, received consulting fee/honorarium from AstraZeneca.

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