

# Year in review in Asia – The major Asian trials published in 2011 on Breast Cancer

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Cancer is now burdening many countries in Asia. A rapid increase in breast cancer incidence has become a big health issue among Asians. Over the decades, breast cancer treatment paradigm has been changing as more important research results come out. Research has been widely conducted in clinics and laboratories. In the clinic, a number of international multi-center clinical trials have been initiated in Asia with bigger patient pool and fewer expenses. Several studies have shown the superior treatment response and manageable toxicity using targeted agents. As more evidence demonstrated the true benefit of adding targeted agents to conventional treatment, some of

them have already entered clinics, among which, anti-HER therapy is commonly used recently. The mortality rate for breast cancer has therefore dropped in general. However, there is still a challenge for clinicians as we started realizing ethnic differences among patients from anatomy to molecular biology. Therefore, over the time, basic research in exploring new biomarkers has started. Further to the molecular classification of breast cancer, different gene signatures for guiding treatment decision have been discovered and tested for patients of different races. In the future, more molecular studies in Asia will appear on the global stage of cancer research.

## Introduction

Breast cancer is the most common cancer among women and the incidence is rapidly increasing in many Asian countries. While mortality rate is decreasing gradually among western countries, the rate is increasing in their eastern counterparts [1]. It is of interest to note that breast cancer patients in most Asian countries are younger with peak incidence at age from 45 to 50 [1,2] and there is also a declining risk of breast cancer after menopause among Asian women [3]. The changing patterns of female breast cancer incidence and mortality in Asia may lead to consideration of a different treatment strategy thus shifting the focus of breast cancer research in the near future.

Treatment paradigm for breast cancer has been changing tremendously over the past years. The decreasing mortality is in no doubt attributed to advances of cancer treatments resulting from extensive research programs conducted in clinics and laboratories. In addition to new generations of anthracycline- and taxane-based chemotherapeutic agents, targeted treatment has further revolutionized the treatment for breast cancer, from the development of hormonal therapies such as tamoxifen [4], aromatase inhibitors [5] targeting estrogen receptors and aromatase respectively to anti-HER therapies such as trastuzumab [6], lapatinib [7] and neratinib [8]. Many of them have already successfully entered clinical practice. A number of other biologic agents such as bevacizumab [9], mammalian target of rapamycin inhibitors [10] and poly (ADP-ribose) polymerase inhibitors [11], albeit investigational, are also complementing conventional therapies to hopefully improve

the survival of breast cancer patients. Nevertheless, without clinical trials, their usefulness can hardly be unveiled. In recent years, there are increasing numbers of international multi-center clinical trials initiated in Asia. The largest number of studies published for pharmaceutical products came from randomized-controlled trials conducted in low and middle income countries among which China has the highest number of publications [12].

In clinical practice, physicians taking care of cancer patients are always facing a challenge, that is, the treatment plan effective for one patient might not offer the same outcome for another patient with similar tumor characteristics. An effective treatment for Western breast cancer patients might not have the same treatment effect for Asian counterparts. As we started to realize differences among patients of different origins, from anatomy to molecular biology, racial or ethnic disparities in breast cancer will be the next step to explore for betterment of breast cancer therapy.

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### Characteristics of Asian breast cancer

Breast cancer rate has been consistently higher in western countries than in Asian countries [13]. However, it has been increasing dramatically in Asia in the recent decades. Exposure to the western lifestyle at an early stage has been suggested to be critical in breast carcinogenesis [14]. In Asian populations, breast cancer is predominantly a premenopausal disease [15,16]. This has been supported by different observations carried out in the U.K. and U.S.A. and that they stated South Asian patients were significantly younger during the time of diagnosis [17-20]. The peak incidence age of breast cancer is about 45-50 in most Asian countries, such as China, Korea, Japan, etc [21], and that a lower level of estrogen receptor (ER) expression and a higher percentage of triple-negative breast cancer case was found in Chinese women [22,23]. In our clinical experience, there is an obvious increasing proportion of young Asian woman at first presentation in clinics. In addition to the differences in treatment between pre- and post-menopausal, young breast cancer patients have to tackle more problems than post-menopausal patients, such as pregnancy after breast cancer, marital and family issues, as well as household financial problems. Same treatment and caring plan for Western patients might not be suitable for Asian patients. Generally speaking, the geographic variation in breast cancer incidence may be caused by various biological factors, such as racial, genetic, cultural differences and environmental exposures. Thus, a better understanding of these underlying factors may advance the breast cancer care.

Identifying patients with human epidermal receptor protein-2 (HER2) alterations is important in treatment planning because these patients may benefit from anti-HER2 agent, which is the most commonly used targeted therapy for breast cancer in recent years. The momentous change arose from the discovery of hormone-sensitive breast cancer and the quantification of hormonal receptor expression. The 'Allred' score, which ranges from 0-8 has been used widely, is sum of score for the percentage and intensity of stained cells. It was performed in Harvey et al's study on 2000 patients [24]. Results showed that the Allred score was correlated with patients' response to adjuvant endocrine therapy. The determination of receptors expression harbors the development of targeted therapy.

The prevalence of hormone receptor-positive breast cancer was found to be higher in western countries than in Asian countries. This is supported by Tea's study that less Chinese women who were over 69 years old were presented with ER-positive breast cancer than Austrian women [25]. Similarly, the prevalence of hormone receptor-positive breast cancer was found to be about 78% in the United States between 1992 and 1998 [26], compared to a prevalence of 32.6%

and 46.1% for ER-positive and PR-positive breast cancers in India, respectively. Hormonal receptor negative breast cancers are usually more aggressively resistant to chemotherapy, and also associated with reduced survival [27-28]. Nevertheless, Chinese and Japanese women are usually diagnosed with a less advanced stage of breast cancer and have a better survival than non-Hispanic whites [29]. Different socioeconomic status, cultural, and behavioral characteristics may explain these differences.

Anthracycline is the most active and widely used chemotherapy for treatment of breast cancer, but treatment failure still occurs in some patients [30]. Inter-ethnic difference is an important issue in chemotherapy responsiveness. However, different ethnic patients are usually prescribed with similar doses of chemotherapy drugs without the consideration of pharmacokinetic or pharmacodynamic among different ethnic populations. Evidence has suggested that Asian patients are more susceptible to the side effects of chemotherapy than Caucasians probably due to the pharmacokinetic or pharmacodynamic factors. According to Goh et al.'s study, Chinese ethnic group has been reported to have a lower clearance ability of docetaxel [31]. In Ma's study, 85 Chinese patients of non-metastatic breast cancer receiving doxorubicin and cyclophosphamide with or without subsequent cyclophosphamide, methotrexate and 5-FU were compared to Caucasian patients in toxicities. The Chinese patients had a higher grade 3 and 4 neutropenia incidence by 3.4% and 0.3%, respectively [32]. Similarly, a study involving 104 Asian and 68 Caucasian non-metastatic breast cancer patients found that only 19% Caucasians experienced grade 4 neutropenia, whereas 54% of Asian patients had such experience [33]. A recent study also showed a significant higher rates of hematologic toxicity of early breast cancer Asian patients than Caucasian patients who received adjuvant or neo-adjuvant FEC100 (5-fluorouracil 500 mg/m<sup>2</sup>, epirubicin 100mg/m<sup>2</sup>, and cyclophosphamide 500 mg/m<sup>2</sup>, every 21 days for 3-6 cycles [34]. Although no information about pharmacokinetic analysis or non-hematological toxicity was collected in these studies, they pointed out the chemotherapy responsiveness in racial differences, which deserves ongoing investigation.

### A blend of clinical trials and basic research

Following the surge of clinical application of anti-HER therapy for HER-2 amplified breast cancer patients, several molecular agents are emerging and some treatment regimens have been studied in neoadjuvant setting. Many targeted agents have already been used in clinical practice for treatment of hormone-sensitive and HER-2 overexpressing breast cancer for several years [4-7] and new agents are coming [8-11] on the platform of clinical trials. The success has led to prolonged

survivals of breast cancer patients such that the mortality for breast cancer is dropping in general. New anti-cancer agents have illuminated breast cancer therapeutics, but we still do not understand why some patients will respond better and survive longer than others. It is questionable whether drug resistance could be the only reason. From another point of view, considering the heterogeneity of breast cancer, the non-responders might represent another type of cancer with a higher chance of disease progression. Breast cancer, as such, possesses different biological characteristics and that racial or ethnic difference has further complicated the situation. Treatment suitable for Caucasian might not be good for Asian due to difference in toxicity profile as mentioned before. The difference in toxicity profile might influence not only the treatment completeness, but also the compliance of patients. In-depth understanding about the racial or ethnic disparities between patients will be important apart from doing an international large-scale randomized clinical trial for development of a new drug. Taking the chance that many large-scale studies have landed on Asia such as mainland China, we should utilize resources to find out the difference between patients, but not just to search for a new drug bringing a few percent point improvement in treatment responses or survival rates. More genomic studies should be done to supplement clinical studies to further maximize the efforts in making another major progress.

Gene signature has made a revolution in breast cancer research to predict the therapeutic outcome [35-38]. The gene-expression profiling provides a new direction to predict clinical outcomes and a treatment recommendation over traditional clinical and pathological approaches. The four commercial genomic assays: Oncotype Dx, MammaPrint, Theras and MapQuant Dx are now available in the market, whereas only MammaPrint cleared by FDA. Oncotype Dx was selected as “recommended for use” by the American Society of Clinical Oncology Breast Cancer Tumor Markers Update Committee, but the MammaPrint assay was classified as “under investigation” [39]. Its predictive value in neoadjuvant setting has been tested further in Asian patients [40]. In any case, the development of genomic test to predict treatment outcome is definitely a big progress in Oncology and pioneering in personalized medicine. The effectiveness of breast cancer treatments such as adjuvant chemotherapy can hardly be assessed when it is given after surgical removal of primary tumors. Some patients might be over- or under-treated. The predictive model will surely help the decision making by clinicians and patients. Nevertheless, it is still controversial to standardize the use of the genetic test. Prior to clinical application, the predictive model should be further validated since many questions remain unanswered as recommended

by Flanagan [41].

Biomarker studies are getting more and more important as translational medicine becomes more and more common in Asia. Clinical trial alone can no longer give enough clues for physicians to plan the best treatment for cancer patients. Results of a clinical trial can only give doctors and patients a reference and help predict the possible clinical outcomes. Nevertheless, a high number of responder in a clinical trial does not guarantee a high rate of treatment success when same therapy is offered to a cancer patient with similar basic tumor characteristics. The underlying tumor signaling is indeed controlling the ability of tumor progression and acquired drug resistance in respond to the therapy and therefore, a similar tumor might grow and progress very differently when underlying signals are not the same. It is essential to explore the change via translational research. In breast cancer, intense research on ER and receptor tyrosine kinase pathways has led to the development of targeted therapy [42-45]. Beyond novel therapeutic targets and new drug discovery, research has moved to predicting treatment response and overcoming treatment resistance. Comparisons in responses to novel neoadjuvant treatment between patients with different molecular subtypes were now underway. Gluck [46] has illustrated that TP53 mutational analysis was predictive of responses to docetaxel-capecitabine ± trastuzumab in operable early breast cancer patients. Our research group is now doing a translational study examining the use of mammalian target of rapamycin inhibitor to reverse drug resistance. In our previous study, adding tyrosine kinase inhibitor to aromatase inhibitor has greatly improved the clinical response to neoadjuvant endocrine therapy in postmenopausal breast cancer patients [47]. Biomarker study provides clues to development of new clinical trials which in turn generate new results for refinement of treatment paradigm. However, it is not enough if we think about to eradicate breast cancer as an ultimate goal. It is a matter of fact that, many new genetic and molecular studies on breast cancer have been doing in Asia [49-53]. Publications are numerous, but diverse. Is it enough or is it too much? Before we found breast cancer preventable and curable, we can never say “enough”. It is however good to ask if our research direction is correct or not so that we would not make a detour. Numerous novel biomarkers have now been discovered, but still we can hardly understand breast cancer from initiation to metastases completely. At present, we would like to emphasize that we are just at the starting point to cure the disease and that biomarker studies just started paving the road in Oncology from prevention to treatment. Basic science is a crucial element to betterment of clinical practice whereas clinical practice is a source of tumor codes for extensive studies on cancer biomarkers.

It is quite noticeable that racial or ethnic differences do exist among patients of different origins even under conditions of globalization. In recent years, research on investigating single nucleotide polymorphism (SNP) associated with the breast cancer risk is ongoing [54]. As more academics from Asia are involved in the association studies, differences in SNPs for breast cancer risk were observed between Asian and European Americans [55-57]. As little is known about the genomic differences between Asian and Caucasians while BRAC1 and BRCA2 gene mutation, accounting for less than 5% of breast cancer, could not justify all the familial clustering of breast cancer. Through extensive association studies, albeit partially and beginning, a novel susceptible locus might be solely found in Asian breast cancer to elucidate why the first-degree relatives of breast cancer patients have higher risk of getting the disease and earlier prevention could be done.

Investment of trials has been on the rise in Asia. According to Liu [58], running trials in Asian countries such as China, Thailand, Philippines and Malaysia save the cost of 60% when compared to running in United States. As clinical trials are more acceptable in those low and middle income countries, we expect there is still an increasing number of a clinical trial in those countries, but at the same time, competition for clinical trial participants will increase as well. To make use of the availability of tumor samples, translational research could be conducted in parallel to clinical trials. The breakthrough

in breast cancer research in Asia depends on not only the number of clinical trials to be done, but also how tumor samples could be fully utilized to decipher codes inside tumors. Shekhar [59] presented quite an interesting "Translational Cycle" which demonstrated how new scientific ideas and discoveries are transformed from "bench" findings to "bedside" and subsequently such findings will enter clinical practice and go back to "laboratory" for further investigation and refinement.

### Conclusions and future directions

Epidemiology, pathology, culture and behavior of breast cancer patients in Asia are different from that in Western countries. The focus of breast cancer research will be different in light of the racial and ethnic disparities. Large-scale multi-center clinical trials have already landed on Asia and translational research should follow. Despite a lot of randomized controlled studies for Asian breast cancer patients, translational research is lacking to pinpoint the racial or ethnic differences in breast cancer. Genetic and molecular studies have been extensively done in many Asian countries, but focus and collaboration are missing. Asia has a great potential as a trial hub for breast cancer. We believe, through cooperation between different trial groups, breast cancer research in Asia will go into another milestone. Translational research will create a new era in Asia in upcoming years.

### Author's Disclosure of Potential Conflicts of Interest

Author	Remunerations	Shareholdings	Patent Royalties	Speaking Fees	Manuscript Fees	Research Fundings	Other Remunerations (items not directly related to research, including travel/holidays, gifts, etc.)
Louis W.C. Chow	none	none	none	none	none	none	none

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### References

- Toi M, Ohashi Y, Seow A, et al. The Breast Cancer Working Group Presentation was Divided into Three Sections: The Epidemiology, Pathology and Treatment of Breast Cancer. *Jpn J Clin Oncol*. 2010;40 (Suppl 1) i13-i18.
- Seow A, Duffy SW, McGee MA, et al. Breast cancer in Singapore: trends in incidence 1968-1992. *Int J Epidemiol*. 1996;25:40-45.
- Liu L, Zhang J, Wu AH, et al. Invasive breast cancer incidence trends by detailed race/ethnicity and age. *Int. J. Cancer*. in press 2011. doi: 10.1002/ijc.26004 Early Breast Cancer Trialists' Collaborative Group
- Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: An overview of the randomised trials. *Lancet*. 2005;365 (9472) :1687-1717.
- Chumsri S, Howes T, Bao T, et al. Aromatase, aromatase inhibitors, and breast cancer. *J Steroid Biochem Mol Biol*. 2011;125 (1-2) :13-22.
- Gianni L, Dafni U, Gelber RD, et al. Treatment with trastuzumab for 1 year after adjuvant chemotherapy in patients with HER2-positive early breast cancer: a 4-year follow-up of a randomised controlled trial. *Lancet Oncol*. 2011;12 (3) :236-244.
- Yip AYS, Tse LA, Ong EYY, Chow LWC. Survival benefits from lapatinib therapy in women with HER2-overexpressing breast cancer: a systematic review. *Anticancer Drugs*. 2010;21 (5) :487-493.

8. Burstein HJ, Sun Y, Dirix LY, et al. Neratinib, an irreversible ErbB receptor tyrosine kinase inhibitor, in patients with advanced ErbB2-positive breast cancer. *J Clin Oncol.* 2010;28 (8) :1301-1307.
9. Burstein HJ. Bevacizumab for advanced breast cancer: all tied up with a RIBBON? *J Clin Oncol.* 2011;29 (10) :1232-1235.
10. O'Regan R, Hawk NN. mTOR inhibition in breast cancer: unraveling the complex mechanisms of mTOR signal transduction and its clinical implications in therapy. *Expert Opin Ther Targets.* 2011;15 (7) :859-872.
11. Telli ML, Ford JM. PARP inhibitors in breast cancer. *Clin Adv Hematol Oncol.* 2010;8 (9) :629-635.
12. Lodge M, Corbex M. Establishing an evidence-base for breast cancer control in developing countries. *Breast.* 2011;20 Suppl 2:S65-S69.
13. Parkin DM, Muir CS. Cancer incidence in five continents. Comparability and quality of data. *IARC Sci Publ.* 1992; (120) :45-173.
14. MacMahon B, Cole P, Brown J. Etiology of human breast cancer: a review. *J Natl Cancer Inst.* 1973;50 (1) :21-42
15. Waard F. Premenopausal and postmenopausal breast cancer: one disease or two? *J Natl Cancer Inst.* 1979;63 (3) :549-552.
16. Matsuno RK, Anderson WF, Yamamoto S, et al. Early- and late-onset breast cancer types among women in the United States and Japan. *Cancer Epidemiol Biomarkers Prev.* 2007;16 (7) :1437-1432.
17. Elmore JG, Mocerri VM, Carter D, et al. Breast carcinoma tumor characteristics in black and white women. *Cancer.* 1998;83 (12) :2509-2515.
18. Joslyn SA, West MM. Racial differences in breast carcinoma survival. *Cancer* 2000;88 (1) :114-123.
19. Dos Santos Silva I, Mangtani P, De Stavola BL, et al. Survival from breast cancer among South Asian and non-South Asian women resident in South East England. *Br J Cancer.* 2003;89 (3) :508-512.
20. Smith LK, Botha JL, Benghiat A, Steward WP. Latest trends in cancer incidence among UK South Asians in Leicester. *Br J Cancer.* 2003;89 (1) :70-73.
21. Chow LWC, Ho P. Hormonal receptor determination of 1,052 Chinese breast cancers. *J Surg Oncol.* 2000;75 (3) :172-175.
22. Toi M, Ohashi Y, Seow A, Moriya T, Tse G, Sasano H, Park BW, Chow LW, Laudico AV, Yip CH, Ueno E, Ishiguro H, Bando H. The Breast Cancer Working Group presentation was divided into three sections: the epidemiology, pathology and treatment of breast cancer. *Jpn J Clin Oncol.* 2010;40 (Suppl 1) :i13-18.
23. Tea MM, Fan L, Shao Z, Singer CF. Do Asian breast cancer patients younger than age 40 have more aggressive biologic characteristics than their western counterparts? A comparison between Shanghai and Vienna. *J Clin Oncol.* 2010;28 (15S) :abstr 1573.
24. Harvey JM, Clark GM, Osborne CK, et al. Estrogen receptor status by immunohistochemistry is superior to the ligand-binding assay for predicting response to adjuvant endocrine therapy in breast cancer. *J Clin Oncol.* 1999;17:1474-1481.
25. Tea MM, Tang L, Di G, Shao Z, et al. Does breast cancer in Asian geriatric patients have the same biological characteristics as in their Western counterparts? A comparison between Shanghai and Vienna. *J Clin Oncol.* 2011;29 (15S) :abstr 1550.
26. Li CI, Darling JR, Malone KE. Incidence of invasive breast cancer by hormone receptor status from 1992 to 1998. *J Clin Oncol.* 2003;21:28-34.
27. Akiyama F, Iwase H: Triple negative breast cancer: clinicopathological characteristics and treatment strategies. *Breast Cancer.* 2009;16 (4) :252-3
28. Bouchalova K, Cizkova M, Cwiertka K, Trojanec R, Hajdich M: Triple negative breast cancer--current status and prospective targeted treatment based on HER1 (EGFR) , TOP2A and C-MYC gene assessment. *Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub.* 2009;153 (1) :13-17
29. Meng L., Maskarinec G., Lee J. Ethnicity and conditional breast cancer survival in Hawaii. *J Clin Epidemiol.* 1997;50:1289-1296
30. Hortobagyi GN: Treatment of breast cancer. *N Engl J Med.* 1998;339:974-984
31. Boon-Cher Goh, Soo-Chin Lee, Ling-Zhi Wang, Lu Fan, Jia-Yi Guo, Jatinder Lamba, Erin Schuetz, Robert Lim, Hong-Liang Lim, Ai-Bee Ong, How-Sung Lee. Explaining Interindividual Variability of Docetaxel Pharmacokinetics and Pharmacodynamics in Asians Through Phenotyping and Genotyping Strategies. *J Clin Oncol.* 2002;20 (17) :3683-3690
32. Ma B, Yeo W, Hui P, et al. Acute toxicity of adjuvant doxorubicin and cyclophosphamide for early breast cancer – a retrospective review of Chinese patients and comparison with an historic Western series. *Radiother Oncol.* 2002;62 (2) :185-9
33. Jane M Beith, Boon Cher Goh, W Yeo, Anne Sullivan, S Lim, S Zhong, Laurent P Rivory. Inter-ethnic differences in the myelotoxicity of adriamycin/cyclophosphamide (AC) for adjuvant breast cancer. *Proc Am Soc Clin Oncol.* 2002;21: abstr 252.
34. Han HS, Reis I, Kuroi K, et al. Racial differences in acute toxicities of FEC 100 chemotherapy in patients with breast cancer. *J Clin Oncol.* 2009;27 (15S) : abstr e11515)
35. Glas AM, Floore A, Delahaye LJ, et al. Converting a breast cancer microarray signature into a high-throughput diagnostic test. *BMC Genomics.* 2006;7:278.
36. Buyse M, Loi S, van't Veer L, et al. Validation and clinical utility of a 70-gene prognostic signature for women with node-negative breast cancer. *J Natl Cancer Inst.* 2006;98 (17) :1183-1192.
37. Sotirio C, Pusztai L. Gene-Expression Signatures in Breast Cancer. *N Engl J Med.* 2009;360 (8) :790-800.
38. Parker JS, Mullins M, Cheang MC, et al. Supervised risk predictor of breast cancer based on intrinsic subtypes. *J Clin Oncol.* 2009;27 (8) :1160-1167.
39. Harris L, Fritsche H, Mennel R, et al. American Society of Clinical Oncology 2007 update of recommendations for the use of tumor markers in breast cancer. *J. Clin. Oncol.* 2007;25 (33) :5287-5312.
40. Masuda N, Toi M, Ueno T, et al. A study of the recurrence score by the 21-gene signature assay as a predictor of clinical response to neoadjuvant exemestane for 24 weeks in estrogen-receptor-positive breast cancer. *J Clin Oncol* 2011;29 (15S) : abstr 558.
41. Flanagan MB, Dabbs DJ, Brufsky AM, et al. Histopathologic variables predict Oncotype DX™ Recurrence Score *Modern Pathology* (2008) 21, 1255-126
42. Gutierrez C, Schiff R. HER2: biology, detection, and clinical implications. *Arch Pathol Lab Med.* 2011 Jan;135 (1) :55-62.
43. Li Y, Ye X, Tan C, et al. Axl as a potential therapeutic target in cancer: role of Axl in tumor growth, metastasis and angiogenesis. *Oncogene.* 2009;28 (39) :3442-3455.
44. Hiscox S, Nicholson RI. Src inhibitors in breast cancer therapy. *Expert Opin Ther Targets.* 2008;12 (6) :757-767.

45. Schiff R, Massarweh SA, Shou J, et al. Advanced concepts in estrogen receptor biology and breast cancer endocrine resistance: implicated role of growth factor signaling and estrogen receptor coregulators. *Cancer Chemother Pharmacol*. 2005 Nov;56 (Suppl 1) :10-20.
46. Glück S, Ross JS, Royce M, et al. TP53 genomics predict higher clinical and pathologic tumor response in operable early-stage breast cancer treated with docetaxel-capecitabine ± trastuzumab. *Breast Cancer Res Treat*. In press 2011; DOI 10.1007/s10549-011-1412-7.
47. Chow LWC, Yip AYS, Loo WTY, Toi M. Evaluation of neoadjuvant inhibition of aromatase activity and signal transduction in breast cancer. *Cancer Lett*. 2008;262 (2) :232-238.
48. Jing MX, Mao XY, Li C, et al. Estrogen receptor-alpha promoter methylation in sporadic basal-like breast cancer of Chinese women. *Tumour Biol*. In press 2011. DOI: 10.1007/s13277-011-0172-7
49. Toi M, Yasui W, Ito H, et al. Recent Progress in Carcinogenesis, Progression and Therapy of Breast Cancer: The 20th Hiroshima Cancer Seminar--the 4th Three Universities' Consortium International Symposium, October 2010: 31 October 2010, International Conference Center Hiroshima. In press 2011. DOI: 10.1093/jjco/hyr054
50. Inaki K, Hillmer AM, Ukil L, et al. Transcriptional consequences of genomic structural aberrations in breast cancer. *Genome Res*. 2011;21 (5) :676-687.
51. Kang UB, Ahn Y, Lee JW, et al. Differential profiling of breast cancer plasma proteome by isotope-coded affinity tagging method reveals biotinidase as a breast cancer biomarker. *BMC Cancer*. 2010;10:114.
52. Kuo SJ, Chien SY, Lin C, et al. Significant elevation of CLDN16 and HAPLN3 gene expression in human breast cancer. *Oncol Rep*. 2010;24 (3) :759-766.
53. Ranade KJ, Nerurkar AV, Phulpagar MD, et al. Expression of survivin and p53 proteins and their correlation with hormone receptor status in Indian breast cancer patients. *Indian J Med Sci*. 2009;63 (11) :481-490.
54. Easton DF, Pooley KA, Dunning AM, et al. Genome-wide association study identifies novel breast cancer susceptibility loci. *Nature*. 2007;447 (7148) :1087-1093.
55. Knappskog S, Lønning PE. MDM2 promoter SNP285 and SNP309; phylogeny and impact on cancer risk. *Oncotarget*. 2011;2 (3) :251-258.
56. Long J, Cai Q, Shu XO, et al. Identification of a functional genetic variant at 16q12.1 for breast cancer risk: results from the Asia Breast Cancer Consortium. *PLoS Genet*. 2010 Jun 24;6 (6) :e1001002.
57. Wang Z, Fu Y, Tang C, et al. SUL1A1 R213H polymorphism and breast cancer risk: a meta-analysis based on 8,454 cases and 11,800 controls. *Breast Cancer Res Treat*. 2010;122 (1) :193-198
58. Liu J. Demystifying the intricacies of Asian clinical trials. *Foresight*. 2011;3 (1) :1-3.
59. Shekhar A, Denne S, Tierney W, et al. A model for engaging public-private partnerships. *Clin Transl Sci*. 2011;4 (2) :80-83.